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**Summary Report of the Technical Peer Review Workshop
on the EPA Risk Assessment Forum
Draft *Framework for Cumulative Risk Assessment***

U.S. Environmental Protection Agency
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June 4-5, 2002

Risk Assessment Forum
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NOTICE

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This report was prepared by Versar, Inc., an EPA contractor (Contract No. 68-C-99-238, Task Order No. 68), as a summary of the discussion held at the Technical Peer Review Workshop on the Risk Assessment Forum Draft *Framework for Cumulative Risk Assessment* (June 4-5, 2002). This report captures the main points and highlights of the meeting. It is not a complete record of all details discussed, nor does it embellish, interpret, or enlarge upon matters that were incomplete or unclear. Statements represent the individual views of each workshop participant.

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EXECUTIVE SUMMARY

The Peer Review Workshop on the Draft *Framework for Cumulative Risk Assessment* was held on June 4 and 5, 2002, in Crystal City, VA. The purpose of the meeting was to provide comments on the current draft of the *Framework*, both generally and in response to a series of charge questions. The reviewer suggestions and recommendations will be used by EPA in finalizing the *Framework* document. In addition, the reviewers raised issues on topics related to cumulative risk assessment that may warrant additional development in issue papers or other future activities.

The meeting was opened by Versar staff, following which the Chair briefly discussed the process for the meeting. After two presentations by EPA staff providing a summary of the *Framework* and background information on the draft *Framework*, the Chair summarized premeeting comments. The reviewers then engaged in an open discussion on their general impressions of the document. Each person highlighted the issues that they felt should be discussed in greater detail during the meeting. This discussion of overarching issues was followed by responses to a series of charge questions, lasting the remainder of the first day and until noon on the second day. The last part of the meeting was devoted to a review of the document for any items that had not yet been discussed. Time was set aside on both days of the workshop for comments to be made by observers, though no observer comments were provided.

Most reviewers prepared written premeeting comments in which they presented their individual reviews of the *Framework*. During the two-day review meeting, the reviewers raised a number of important points that they wished to emphasize in the written report to EPA. The suggested changes to the *Framework* document presented in this report generally represent the opinion of multiple reviewers. Recommended revisions to the *Framework* presented in this report were considered highly significant by the Chair because they were voiced by multiple reviewers or applied broadly to most of the document. The following list summarizes some of the most significant suggested changes to the document provided by the peer reviewers.

Summary of Suggestions and Recommendations from Peer Reviewers:

- 1) EPA did a good job with the *Framework* and the reviewers generally found the document easy to read, well written, and organized. It was clear that the authors found it difficult to convey the issues and concepts related to cumulative risk assessment. In addition, the draft reflects comments made during the August 2001 peer consultation and other public meetings. The text boxes add something to the content without distracting from the flow of the text – make sure the boxes are in a readable font.
- 2) Terminology should be reviewed to make sure it is correct and does not change the use of a common term with an existing understood meaning. Reviewers found several places in which the *Framework* was unclear or created some ambiguity. The text should be consistent with the glossary; at present the two are not consistent. The glossary needs to be augmented and the number of entries greatly increased.

3) EPA should confirm that the *Framework* is consistent with existing disciplinary uses of terminology, methods, references, data, and present state of the art. EPA should use caution with terminology, to avoid revising the current use of terms and methods when they already have use and meaning in other disciplines.

Reviewers discussed the definitions of cumulative risk and stressor, along with other terms. The reviewers acknowledged that EPA should set an operational definition for cumulative risk assessment that is practical within the existing regulatory and assessment programs. Caution should also be used with the term “stressor,” because there is already a field of experts using that term and the *Framework* should reflect that existing use of the term.

4) The *Framework* should provide a window to the literature and the reviewers said that in many respects the document does accomplish this goal. However, the references cited by EPA and listed in several sections of the *Framework* are focused on EPA documents and products. EPA should provide citations to more than their own Agency documents, so the literature reflects a broad perspective and does not seem insular. The other area where the reviewers recommended that EPA broaden the literature cited pertains to ecological risk assessment, especially case studies.

5) EPA should continually answer the query – What is unique to cumulative risk assessment? Reviewers raised this point in premeeting comments, in discussion of the whole *Framework*, and in discussion of every section and charge question. The reviewers also frequently asked this question of one another.

6) Public health issues were raised in several contexts. Several reviewers said that public health needs more emphasis in the *Framework*. Others recommended that EPA use more public health data and emphasis in framing cumulative risk assessments for communities and populations. Public health data are already available to better inform such cumulative risk assessments, such as birth weight and biomarker data, which are natural integrators of multiple effects and have the potential to be used to assess the separate and combined influences of multiple stressors.

7) Both qualitative and quantitative aspects of cumulative risk assessment are applicable in many, if not all areas of the *Framework* and the document should clearly articulate this fact. The reviewers focused on the analysis phase and uncertainty analysis, but this point applies broadly.

8) The role of decision-makers and risk managers in the cumulative risk assessment process is important and should be spelled out in somewhat more detail, even for a framework document. The reviewers discussed the need for balance between the necessity to inform the process with management goals and objectives, and the requirement to prevent management from dictating the assessment outcome.

9) Several reviewers raised issues of how this *Framework* document will fit into the process of developing guidelines for cumulative risk assessment. EPA did address this issue on pages 5-6, where the *Framework* discussed this point, but reviewers felt that more information would be

useful. Maybe EPA could insert a text box that includes the other major steps in the whole process, such as issue papers and case studies leading to development of guidelines.

10) Some aspects of the conduct of a cumulative risk assessment need to be highlighted in the initial steps of planning, scoping, and problem formulation. These aspects include population (or ecosystem) identification or selection, vulnerability, uncertainty analysis, data collection and analysis, statistical analysis, and statutory constraints. These steps are not unique to cumulative risk assessment, but are particularly important because the entire risk assessment depends on these first steps. Raising certain issues at the outset also serves to highlight them to the risk assessment team and the interested and affected stakeholders.

11) The reviewers recommended addition of examples and references in some key parts of the *Framework*. The additions are intended to accomplish two purposes: (1) add ecological cases and perspectives in areas that are now exclusively human health discussions and (2) broaden the base, geographic range, or types of studies presented.

12) The reviewers supported the use of indices or other methods to combine, analyze, and present data in a cumulative risk assessment. However, they had some concerns that data and qualitative information could be lost or otherwise obscured in moving from conceptual model to analysis phase, in analysis, in moving from analysis to characterization, in uncertainty or sensitivity analysis, etc. It is important to preserve data throughout the process of assessing risks in cumulative risk situations, in no small part because of the number and complexity of stresses and agents, endpoints, and methods.

13) EPA should acknowledge and incorporate more of the international efforts on cumulative risk assessment. Some of these international efforts are noted in the present version of the *Framework*, but more notation would be an important enhancement.

14) EPA should consider producing issue papers or background materials on the following:

- Background conditions, especially compared with ambient, control etc.
- Precautionary Principle
- Uncertainty analysis
- Vulnerability (defined and parsed)
- Biomarkers of exposure and of effects
- Single metrics in cumulative risk assessment (including combining chemical and non-chemical stressors)
- A database of literature on case studies and methods.

Summary of Responses to Charge Questions

Question #1. Comment on whether the Framework adequately captures, describes, and reasonably organizes the key issues for cumulative risk assessment so as to serve as an adequate foundation for the development of future guidance. Does the Framework provide adequate coverage of: terminology, structure, and methods?

The reviewers were largely satisfied that EPA had covered the subjects of terminology and methods in the *Framework*, with a discussion of the meaning of cumulative risk and the nature and scope of a framework document. Several suggestions were made for improving the treatment of these aspects of the *Framework*. The reviewers discussed the definitions of “cumulative risk” and “stressor” at some length, with some recommendations for EPA. The main improvements suggested by the reviewers were in: identifying and describing the issues that are unique for cumulative risk assessment, clarifying terminology in the context of related disciplines that use the same terms, and providing the reader with a clearer sense of what constitutes cumulative risk assessment and when such assessments may be required. Reviewers suggested that EPA use more examples of ecological risk cases and provide more references in the text.

Question #2. Does the Framework document include any scientific or technical inaccuracies in its presentation of terminology, assessment structure, and methods? Please identify any problem areas and propose revisions or other actions that will result in a scientifically sound and supportable discussion. With respect to methods, comment on whether the Framework adequately conveys the state of the science with respect to currently available cumulative risk assessment methods/approaches and the areas that are in need of further research and development.

The reviewers were satisfied that there were few scientific inaccuracies, but did make recommendations to clear up some ambiguities. The methods for cumulative risk assessment are mostly those developed for other risk assessment applications, so EPA does not have much to cover here, but should note the fact that new tools are required.

Question #3. Comment on whether the Framework adequately characterizes the importance of uncertainty analysis in cumulative risk assessment. What additional discussions of uncertainty should be included in the Framework (and in what sections of the document)?

The reviewers thought that the *Framework* covered the subject of uncertainty analysis sufficiently and suggested some changes to improve the document. One of these recommendations was to insert consideration of uncertainty analysis into the planning phase, so that much like statistical analysis, the preparation of the risk assessment will be done with the uncertainty analysis in mind. The reviewers also recommended that the process begin with qualitative uncertainty analysis and move into more quantitative aspects.

Question #4. Comment on the adequacy and accuracy of the Framework's presentation in each of these areas: vulnerability, chemical vs non-chemical stressors, and different types of risk.

There was an extended discussion of vulnerability and most reviewers agreed that it is a critical issue in cumulative risk assessment, warranting introduction earlier in the *Framework*. Reviewers initially felt that the topic could be arranged in a manner that was different from how EPA had presented it in the draft *Framework*. During this discussion, a few reviewers introduced some alternate schemes for organizing vulnerability, but these did not differ substantially from the approach presented in the document. The issue of non-chemical stressors raised the incorporation of disease predictions and exotic species introductions, for which the reviewers had some recommendations for EPA. The topic of types of risk is one of the most complex areas of cumulative risk assessment and it seemed to have been adequately covered in the *Framework*, but the reviewers provided some feedback on possible improvements.

1.0 INTRODUCTION

1.1 Workshop Purpose

The Technical Peer Review Workshop on the Risk Assessment Forum Draft *Framework for Cumulative Risk Assessment* was held on June 4-5, 2002, in Arlington, VA. The workshop was sponsored by the U.S. Environmental Protection Agency's (EPA's) Risk Assessment Forum and was convened and facilitated by Versar, Inc. The purpose of the meeting was to provide a scientific peer review of the draft *Framework* document.

1.2 Workshop Participants

A group of 13 experts, from different disciplines and types of organizations, was assembled by Versar to peer review EPA's Draft *Framework for Cumulative Risk Assessment*. Twelve of these experts attended the June 4-5 workshop (one of the reviewers were unable to attend). Versar selected experts with experience related to cumulative risk assessment from a variety of perspectives: academia, consulting, industry, environmental groups, and community advocates. In addition, the experts were selected such that the following topic areas would be covered: aggregate exposure, risk assessment for chemical mixtures, accident and transportation risks, epidemiology, community-based risk assessments, socioeconomic issues, uncertainty analysis, and other topics of importance in cumulative risk assessment. Versar identified more than 50 candidate reviewers, from which the final group of experts were selected. The list of peer reviewers is presented in Appendix A. In addition to these reviewers, about 20 observers attended the workshop. The list of observers is presented in Appendix B.

1.3 Charge Questions

A list of charge questions, presented in Appendix C, was prepared by EPA in advance of the peer review and was distributed to the reviewers to stimulate feedback on technical issues related to the draft *Framework* document. These charge questions addressed the document's technical

content, accuracy, and clarity, as well as: (1) overall presentation of an assessment structure as well as information, terminology, and methods for cumulative risk assessment, (2) presence of any scientific or technical inaccuracies, (3) handling of uncertainty analysis in cumulative risk assessment, and (4) other technical challenges which have been under deliberation within the EPA Risk Assessment Forum Technical Panel, such as vulnerability, chemical and non-chemical stressors, and different types of risk. The charge questions were a starting point for the dialogue and participants were encouraged to raise other issues or topics. However, regulatory and policy issues were beyond the scope of the peer review.

1.4 Agenda

The workshop agenda is presented in Appendix D. The meeting began with opening remarks from Versar and the Chair including an overview of the agenda for the two-day meeting and a review of the objectives and process for the meeting. This was followed by presentations from EPA staff on the background of the draft *Framework* document. The agenda was organized around the four charge questions. After the morning presentations, most of the remainder of the first day was devoted to raising over-arching issues and then responding to the first two charge questions. Discussion on the second day focused on third and fourth charge questions, which addressed technical issues such as vulnerability, uncertainty, and combining different types of risks. The end of the second day included a chapter-by-chapter review of the document and comments on specific sections. Time was set aside on both days of the workshop for observer comment, though no observer comments were provided.

1.5 Workshop Summary Report

This report summarizes the workshop presentations and discussion, with appendices that provide handouts, materials used in presentations, and written comments from the peer reviewers. The remainder of the report is organized as follows:

- Section 2 of this report summarizes the opening presentations. Overheads used by the presenters are provided in Appendix E.

- Section 3 provides summaries of the reviewers' suggested changes to the document. Overarching comments are provided first, followed by the suggestions and recommendations made by the reviewers in response to the four main charge questions.
- Section 4 summarizes the document review and lists the chapter- and page-specific comments that were raised at the end of the meeting.
- The appendices to this report present the handouts from the meeting (e.g., lists of peer reviewers and observers, agenda, charge questions, and presentation materials/slides) as well as written comments from the peer reviewers.

2.0 SUMMARY OF OPENING REMARKS

2.1 Welcome

David Bottimore of Versar, Inc., opened the meeting by welcoming participants and observers. He presented an overview of the agenda, introduced the participants, and described the goals and intended outcome of the workshop. During his opening remarks, he emphasized that the meeting was intended to promote dialogue and provide input on technical issues associated with the draft *Framework*. Mr. Bottimore talked about the effort to assemble a group of experts with diverse backgrounds and expertise to contribute suggestions and recommendations on ways to improve the draft *Framework* report. He also noted that in addition to the main discussion sessions, time would be set aside each day for comments from observers. His opening remarks were concluded by introducing the peer reviewers, including the Chair, Peter deFur.

2.2 Chair's Introduction

Peter deFur, from Environmental Stewardship Concepts, was the Chair for the peer review workshop and served as facilitator. He started by describing the peer review process and setting the ground rules for the two-day workshop. The goal of the meeting was restated to emphasize that technical input was sought from each reviewer, noting that there would be no attempt to achieve consensus through this meeting. Rather, the discussion should bring out the diverse perspectives of individual experts in the group. He introduced ground rules and guides to keep the discussion focused on technical issues related to the draft *Framework* document. Finally, he talked about post meeting activities to prepare a workshop report that summarizes the discussion and made the request that each participant's individual comments be represented by either pre- or post-meeting comments, which will be appended to the workshop report.

2.3 Background on Risk Assessment Forum and Framework Development

Steve Knott, from EPA's Risk Assessment Forum (RAF), provided a short overview of the RAF and its activities working toward developing cumulative risk assessment guidelines. He stated that comments and recommendations from this peer review will be used by the Cumulative Risk Assessment Technical Panel in finalizing the *Framework*. His presentation began with background on the RAF, explaining that their mission is to promote consensus across the Agency and apply the best-available science in risk assessments. They usually are called upon to address difficult, precedent-setting scientific issues that are relevant to programs across the Agency. As a result, the RAF, and technical panels assembled to address particular issues, are composed of scientists from the Agency's program, regional, and research offices. The RAF provides guidance to EPA risk assessors through three principal types of products (1) agency guidelines, (2) guidance documents, and (3) technical issue papers. Major previous efforts include the exposure assessment guidelines and the ecological risk assessment guidelines.

Development of the *Framework* was initiated in 1999 in response to a request from the EPA Science Policy Council that the RAF begin developing guidance on cumulative risk assessment. The draft *Framework* document has been developed by a Technical Panel composed of scientists from more than ten Agency offices and regions. They have been working over the last two years, consulting twice with the Executive Committee of the Science Advisory Board (SAB) and meeting with Federal and State government scientists, to obtain input for the *Framework*. In addition, a peer consultation workshop was held in August 2001 to provide interested stakeholders with an opportunity to see an early draft of the *Framework* and to obtain input from 12 experts in various fields related to cumulative risk assessment. Steve Knott emphasized that the *Framework* is the first step in the overall process of developing guidelines on cumulative risk assessment, and as such, is different than guidelines. He also noted that this process is similar to that used by other Agency efforts, most notably the ecological risk assessment guidelines.

The *Framework* document is intended to provide a flexible structure, capable of evolving with experience, that captures the basic elements of cumulative risk assessment. It should serve as a basis for developing guidelines by defining key terms and concepts to promote a common language and furthering development of the approaches. He stressed that the *Framework* is not intended to present detailed technical guidance, but rather provide a general overview of issues, topics, and approaches that can be considered in conducting a cumulative risk assessment. Future guideline development efforts will build on the *Framework*, including case studies and issue papers on certain cumulative risk assessment topics.

2.4 Presentation of the Draft *Framework for Cumulative Risk Assessment*

Mike Callahan, from EPA Region 6 and Chair of the RAF's Cumulative Risk Assessment Technical Panel, provided a more detailed presentation on the *Framework* document. He opened his talk by stating that the *Framework* is an information document, presenting what cumulative risk assessment is, rather than describing how to do it, which is the purpose of future guidelines. The *Framework* is intended to be a brief, 50 to 75 page document that introduces scientific concepts, presents definitions, and describes available approaches for cumulative risk assessment. It is not a protocol or a guideline on how to perform such an assessment. EPA will be developing guidelines over the next several years, building on the *Framework* and other subsequent efforts. Furthermore, cumulative risk assessment is not a replacement for traditional risk assessment techniques. Rather, it is an evolution in risk assessment that responds to the growing need to focus on populations or communities, rather than on sources of pollution. Mike Callahan pointed out that several EPA offices are already doing cumulative risk assessments, such as the Office of Pesticide Programs (under the Food Quality Protection Act) and the Office of Air (as part of the National Scale Air Toxics Assessment), the Dioxin Reassessment, and city-specific assessments in Chicago and Baltimore.

The *Framework for Cumulative Risk Assessment* presents information that can be considered in planning and performing such an assessment. Included in the document are working definitions and descriptions of the overall process, organized into the three main phases: (1) planning,

scoping, and problem formulation, (2) analysis, and (3) risk characterization. Cumulative risk assessment is not appropriate for every task, but it is a tool available to help risk assessors and decision makers address situations involving cumulative risks (e.g., multiples chemicals or other stressors, multiple exposure routes, etc.). It is particularly applicable to community-based studies. It is also important to recognize what a cumulative risk assessment can and cannot do, so people have realistic expectations of the possible outcomes. This is something that groups performing assessments should discuss during the planning and scoping of a project, so all stakeholders come to a common understanding that a cumulative risk assessment can only answer certain types of questions. The science behind such efforts is still being developed, particularly to meet needs of the analysis and risk characterization phases. He acknowledged the scientific challenges in cumulative risk assessment related to integrating different stressors and types of risks, incorporating vulnerability, and evaluating uncertainty. The *Framework* describes methods that the Agency is aware of, recognizing the strengths and limitations of the approaches. He pointed out that there are qualitative aspects to such assessments, in addition to the quantitative analyses, so the results will be more meaningful to decision makers. Mike Callahan's presentation introduced the definition of cumulative risk assessment and he described the many considerations that went into the definition, such as the language from the Food Quality Protection Act and usage from other Agency efforts.

Mike Callahan concluded his presentation by reiterating that while EPA is already performing cumulative risk assessments in certain situations, more studies are needed to develop, test, and improve methods. The *Framework* should be completed in the fall of 2002 following revisions after the peer review and approval by the Science Policy Council. He again stated that policy issues will not be part of the *Framework* and are being addressed separately from the Technical Panel's efforts. Mike Callahan described EPA's plans for developing guidelines for cumulative risk assessment; the Agency is following a process similar to Ecological Risk Assessment Guidelines. This process includes preparing a series of case studies on cumulative risk assessments that have been performed, some of which are in initial stages of planning now. EPA will also prepare issue papers on topics that need additional consideration before finalizing the guidelines. Although EPA is already starting or planning these, the full process will require

several years to complete, and guidelines are expected in 2005.

2.5 Discussion on Opening Presentations

During the opening presentations by Steve Knott and Mike Callahan, several peer reviewers asked questions about the draft *Framework*. Many of the issues raised were related to definitions, the need for the Framework to reflect information in the scientific literature, and challenges in performing cumulative risk assessments involving chemical/non-chemical “stressors” and other types of risks. Peter deFur noted that these topics would be the focus of discussion later in the workshop, in response to the charge questions.

3.0 SUMMARY OF COMMENTS AND RECOMMENDATIONS

The peer reviewers met over two days and evaluated EPA's draft *Framework for Cumulative Risk Assessment* generally and in light of the charge questions. Most, but not all reviewers provided premeeting written comments in which they commented on the overall quality of the *Framework* and on the charge questions. During the two-day review meeting, the reviewers raised a number of important points that they wished to emphasize in the written report to EPA.

The summary below begins with the major suggestions and recommendations for changes to the *Framework*, followed by responses to the charge questions. Charge questions #1 and 2 were addressed simultaneously and are presented together in Section 3.1. Subsequent subsections detail the responses on the remaining questions, followed by a list of topics that reviewers believed warrant further development by EPA, possibly in issue papers.

The Chair and Versar staff who took notes consulted on these topics and agreed that these issues were the most important and encompassing issues raised during the two-day meeting. The suggested changes to the document presented in this report generally represent the opinion of multiple reviewers. Recommended revisions to the *Framework* were considered highly significant by the Chair because they were voiced by multiple reviewers or applied broadly to most of the document. The following list summarizes some of the most significant suggested changes to the document provided by the peer reviewers.

- 1) EPA did a good job with the *Framework* and the reviewers generally found the document easy to read, well written, and organized. It was clear that the authors found it difficult to convey the issues and concepts related to cumulative risk assessment.

In addition, the draft reflects comments made during the August 2001 peer consultation and other public meetings. The text boxes add something to the content without distracting from the flow of the text – make sure the boxes are in a readable font.

2) Terminology must be correct and not change the use of a common term with an existing understood meaning. Reviewers found several places in which the *Framework* was unclear or created some ambiguity. The text should be consistent with the glossary; at present the two are not consistent. The glossary needs to be augmented and the number of entries greatly increased.

3) EPA should confirm that the *Framework* is consistent with existing disciplinary uses of terminology, methods, references, data, and present state of the art. The reviewers realized that cumulative risk assessment demands the use of expertise and methods from other fields, including epidemiology, public health, toxicology, etc. This point was raised several times in the discussions of charge questions and in the overall evaluation of the *Framework*. EPA should use caution with terminology, to avoid revising the current use of terms and methods when they already have use and meaning in other disciplines.

Reviewers discussed the definitions of cumulative risk and stressor, along with several other terms. The reviewers acknowledged that EPA should set an operational definition for cumulative risk assessment that is practical within the existing regulatory and assessment programs. Caution should be used with the term “stressor,” because there is already a field of experts using that term.

4) The *Framework* should provide a window to the literature and the reviewers said that in many respects the document does accomplish this goal. However, the references cited by EPA and listed in several sections of the *Framework* are focused on EPA documents and products. EPA should provide citations to more than their own Agency documents, so the literature reflects a broad perspective and does not seem insular. The other area where the reviewers suggested that EPA broaden the literature cited pertains to ecological risk assessment, especially case studies. EPA is referred to their own work on watershed assessments (Waquoit Bay, Clinch River, etc.) and the peer-reviewed literature associated with those efforts. Other examples were brought up during the discussion, including Pacific Northwest forests, Green Bay, WI, Fox River, WI, Florida Everglades, Coastal Louisiana, and gypsy moths in eastern forests.

5) EPA should continually answer the query – What is unique to cumulative risk assessment? Reviewers raised this point in premeeting comments, in discussion of the whole *Framework*, and in discussion of every section and charge question. The reviewers also frequently asked this question of one another. EPA was cautioned to not needlessly repeat text, material, or other information that is in existing EPA guidance on risk assessment, but rather to focus on the aspects of risk assessment that are unique or special in cumulative risk assessment. If this *Framework* is supposed to serve both human health and ecological assessments, then this effort is new, and if implemented in such a way, will be unique.

6) Public health issues were raised in several contexts. Some reviewers said that public health needs more emphasis in the *Framework*. Others recommended that EPA use more public health data and emphasis in framing cumulative risk assessments for communities and populations. Public health data are already available to better inform such cumulative risk assessments, such as birth weight and biomarker data, which are natural integrators of multiple effects and have the potential to be used to assess the separate and combined influences of multiple stressors.

7) Both qualitative and quantitative aspects of cumulative risk assessment are applicable in many if not all areas of the *Framework* and the document should clearly articulate this fact. The reviewers focused on the analysis phase and uncertainty analysis, but this point applies broadly. Important qualitative methods and approaches can and must be used in cumulative risk assessment. Some qualitative analyses should/could be done before initiating the quantitative procedures, particularly in the case of uncertainty analysis.

8) The role of decision-makers and risk managers in the cumulative risk assessment process is important and should be spelled out in somewhat more detail, even for a framework document. The reviewers discussed the need for balance between the necessity to inform the process with management goals and objectives, and the requirement to prevent management from dictating

the assessment outcome. In regard to cumulative risk uniquely, when these assessments focus on a community, a specific population, etc., these groups are the decision-makers and participate actively in risk management, thus defining and clarifying their role is key in the initial phases (planning, scoping, etc).

9) Several reviewers raised issues of how this *Framework* document will fit into the process of developing guidelines for cumulative risk assessment. They wanted to know how EPA will deal with this document, develop the subsequent issue papers and case studies, and whether EPA will make this a living document. The introduction to the *Framework* seems to be the place to spell out to the reader what the next steps are, and how the process will proceed. EPA did address this issue on pages 5-6, where the *Framework* discussed this point, but reviewers felt that more information would be useful. Maybe EPA could insert a text box that includes the other major steps in the whole process, such as development of issue papers and case studies.

10) Some aspects of the conduct of a cumulative risk assessment need to be highlighted in the initial steps of planning, scoping, and problem formulation. These aspects include population (or ecosystem) identification or selection, vulnerability, uncertainty analysis, data collection and analysis, statistical analysis, and statutory constraints. These steps are not unique to cumulative risk assessment, but are particularly important because the entire risk assessment depends on these first steps. Once the risk assessment has started, usually it is not possible to start over again with another modified process because of an error or omission. If a community partner has been omitted at the outset, this partner may be alienated and no longer trust the assessment no matter what transpires. If the statistical and uncertainty analysis are not considered when the data acquisition is planned, it may not be possible to conduct the necessary analyses.

Raising certain issues at the outset also serves to highlight them to the risk assessment team and the interested and affected parties.

11) The reviewers recommended addition of examples and references in some key parts of the *Framework*. The additions are intended to accomplish two purposes: (1) add ecological cases and perspectives in areas that are now exclusively human health discussions and (2) broaden the base, geographic range, or types of studies that are presented. Several examples served to illustrate the point. Cumulative risk assessment is most difficult for cases that apply to understudied and “hard to reach” populations, such as homeless individuals or some minority communities. These same individuals and communities may often be the most vulnerable or sensitive. The same trend is true for ecosystems and wildlife populations- Arctic and desert ecosystems are notoriously understudied and turn out to be fragile.

12) The reviewers supported the use of indices or other methods to combine, analyze, and present data in a cumulative risk assessment. However, they had some concerns that data and qualitative information could be lost or otherwise obscured in moving from conceptual model to analysis phase, in analysis, in moving from analysis to characterization, in uncertainty or sensitivity analysis, etc. It is important to preserve data throughout the process of assessing risks in cumulative risk situations, in no small part because of the number and complexity of stresses and agents, endpoints and methods. For example, the method of creating a matrix was selected by some previous researchers because it did not collapse data to the extent that other methods did, yet there is still distillation of data into a more condensed form. The reviewers cautioned that cumulative risk assessment has inherently more information and data than assessments with single chemicals, single endpoints, etc. As users seek to collapse and simplify the presentation of the results of a cumulative risk assessment, data should not be lost, but preserved.

13) EPA should acknowledge and incorporate more of the international efforts on cumulative risk assessment. Some of these international efforts are noted in the present version of the *Framework*, but more notation would be an important enhancement. Several reviewers pointed out that other countries have efforts specifically in cumulative risk assessment or related fields. EPA could/should do their best to note those, as in the box on page 63 that uses the European report on environmental cases and decisions.

14) The Chair and Versar staff kept a running list of topics that might warrant further examination outside the context of the Framework, such as in issue papers. These topics, specifically as each applies to the process of conducting cumulative risk assessments, included:

- Background conditions, especially compared with ambient, control etc.
- Precautionary Principle
- Uncertainty analysis
- Vulnerability (defined and parsed)
- Biomarkers of exposure and of effects
- Single metrics in cumulative risk assessment (including combining chemical and non-chemical stressors)

The reviewers also recommended that EPA prepare and compile materials that would enhance the field of cumulative risk assessment or promote further work in the area. Foremost among these was the suggestion that EPA post on a web site a database of literature on cumulative risk assessment case studies and methods.

3.1 Charge Questions #1 and #2

Question #1. Comment on whether the Framework adequately captures, describes, and reasonably organizes the key issues for cumulative risk assessment so as to serve as an adequate foundation for the development of future guidance. Does the Framework provide adequate coverage of: terminology, structure, and methods?

Question #2. Does the Framework document include any scientific or technical inaccuracies in its presentation of terminology, assessment structure, and methods? Please identify any problem areas and propose revisions or other actions that will result in a scientifically sound and supportable discussion. With respect to methods, comment on whether the Framework adequately conveys the state of the science with respect to currently available cumulative risk assessment methods/approaches and the areas that are in need of further research and

development.

In general, most reviewers felt that EPA had done an admirable job at introducing the main topics for cumulative risk assessment and that the document had few errors and omissions. The *Framework* provides a broad, flexible assessment structure that is not only appropriate but required for the complex scientific and policy needs that call for cumulative risk assessment. The main improvements suggested by the reviewers were in: identifying and describing the issues that are unique for cumulative risk assessment, clarifying terminology, and providing the reader with a clearer sense of what cumulative risk assessment is (and isn't) as well as when such assessments may be required. With respect to methods, reviewers recognized that cumulative risk assessment is a rapidly developing field that will benefit greatly from anticipated advancements in the supporting scientific fields. Much of the discussion on methods could be expanded and improved, particularly on biomarkers, biomonitoring, and drawing analogies between human health and ecological risk assessment. Because the *Framework* is applicable for both human health and ecological assessments, it should provide a better balance in the discussion of both topics, including examples.

3.1.1 Terminology

With respect to terminology, most reviewers felt that the *Framework* does a good job at introducing terms and concepts. The main suggestions were to make sure that terms are clearly defined, consistent with the glossary, and reflective of usage in the numerous disciplines related to cumulative risk assessment. Several reviewers recommended that the *Framework* present additional examples and illustrations that portray the terms in ways that help the reader to understand the relationships among cumulative risk assessment and “traditional” human health and ecological risk assessment. Additional references that might be highlighted for this purpose are the ILSI (1999) report, as well as international documents, to better reflect what other organizations are doing with respect to cumulative risk assessment.

During the discussion, several terms were raised that were either unclear or their usage might

cause confusion. Some of these terms included:

- Background (includes: ambient, baseline, control, etc.)
- Stressor (issues related to its use to encompass toxic chemicals, non-chemical agents, risk factors and other types of “stressors”)
- Adverse
- Cumulative vs. aggregate risk assessment
- Mechanism and mode of action
- Ecological (differentiating between usage in epidemiology and “natural resource” contexts)
- Toxicology (in reference to human health vs. ecological effects)

The reviewers provided suggestions on ways to improve and clarify use of these terms in the *Framework*. These recommendations included adding text boxes (to distinguish terms and provide examples), using the most specific term(s) possible, and making sure the glossary defines all terms that might be unclear (vulnerability, susceptibility, etc.). EPA was encouraged to look at how different scientific disciplines use these terms and to be aware of the challenges inherent in interdisciplinary fields such as cumulative risk assessment.

3.1.2 Structure for Cumulative Risk Assessment

On the issue of the *Framework* providing an adequate assessment structure, most reviewers voiced their opinions that the document is very well done and that the structure meets the needs for cumulative risk assessment. It was recognized by one reviewer that this structure diverges from the one shown in the SAB (2000) report *Toward Integrated Environmental Decision-Making*, while another reviewer stated that it does follow the three steps used in the ecological risk assessment guidelines. Some discussion should be added to explain the rationale for the proposed *Framework*. Most reviewers supported the idea that having a broad, flexible structure is beneficial for responding to the many types of situations that might be encountered and anticipated in the future. This is true for EPA’s use of the document as well as the needs of

stakeholder groups.

Throughout the discussion, the need for clarification on what is unique about cumulative risk assessment was voiced many times by the reviewers. Specifically, reviewers suggested that the document call attention to the issues that are particularly different for cumulative risk assessment and provide references for the reader to consult on more general aspects of those topics (e.g., importance of stakeholder involvement, uncertainty analysis, etc.).

The *Framework* document should also provide more examples, illustrations, and criteria for circumstances where cumulative risk assessment is appropriate/required. These examples should include figures that display how cumulative risk assessment differs from traditional risk assessments, but may interact with other efforts. It is important that readers and practitioners be able to identify the characteristics of a situation that might call for a cumulative risk assessment. Similarly, the document should also help stakeholders to understand what such an assessment can and cannot do. Reviewers also felt that the document needs to provide information on what guidelines will look like, which would help to differentiate the *Framework* from the guidelines, while providing a clearer picture of the “how to” aspects that should be included in the future guidelines.

The focus on populations, identified in the *Framework* as one of the distinguishing characteristics of cumulative risk assessment, should receive even more emphasis (for both human health and ecological populations). Rewording of select sections can provide this emphasis and readers should also be reminded of the potential difficulties in characterizing subpopulations, particularly minority groups in urban areas, which are often undercounted in the Census. Similarly, ecological risk assessment uses the population as the focus for assessment. Therefore the ecological risk assessment guidelines should be reviewed for applicable text to be added in the context of identifying populations. Introducing the need to consider vulnerabilities of subpopulations early in the process was suggested by several reviewers. Vulnerability in subpopulations should be raised earlier as part of the planning, scoping, and problem formulation

phase (possibly as Section 2.2.4). Similarly, in the analysis phase, mention should be made of the needs for data collection and use of existing data (e.g., public health statistics and exposure data).

Several reviewers stated that cumulative risk assessment should be decision-driven, providing answers to questions posed by risk managers, communities, and other stakeholders. As such, the *Framework* should provide focus on the types of questions that decision makers need to answer, such as those about (1) general human health risks, (2) priority-setting, and (3) policy options. Similarly, the *Framework* should help risk assessors to respond to complex situations where the science calls for a cumulative risk analysis. Balancing these needs is difficult and reviewers had various suggestions, such as presentation of qualitative information before more quantitative analysis and results and planning for public involvement prior to beginning the process. One reviewer suggested that two cumulative risk assessment documents be prepared, one for stakeholders and another separate document for scientists. Reviewers generally agreed that the *Framework* should point out the benefits of transparency and retaining as much data as possible through the cumulative risk assessment phases.

Finally, many reviewers agreed that the figures depicting the three phases of cumulative risk assessment need to be improved. First, figures should distinguish cumulative risk from other types of risk assessments. Also, the flow diagrams should be sure to show forward motion, while recognizing the need for feedback to accommodate the iterative nature of assessments. Suggestions were made to use large arrows going forward and smaller arrows backwards, representing feedback/iteration or the need to do screening prior to the actual cumulative risk assessment. The overall message to EPA was to be cautious to avoid two headed arrows, which might result in “paralysis by analysis.”

3.1.3 Methods

The reviewers acknowledged EPA's efforts to introduce some of the major approaches used for cumulative risk assessment, recognizing that the *Framework* would not be the place for extensive description of the applicable methods. Many reviewers felt that the document could be improved with respect to information on biomarkers, biomonitoring, mixtures risk assessment, and alternative methods to address the need to integrate chemical, non-chemical, and other types of risks. Suggestions were also made by several reviewers to improve the figures (particularly Figure 1-2) to better depict the differences between approaches used in cumulative risk assessment and the more linear portrayal of traditional risk assessments. Reviewers felt that the *Framework* can encourage development of alternative methods to improve the cumulative risk assessment process.

The discussion on methods began with several reviewers distinguishing between methods and approaches. Approaches are seen to be more general, while methods are more specific. These reviewers felt that what the *Framework* provides are introductions to approaches and that the terminology should be distinguished. One reviewer raised the potential to use either "top down" or "bottom up" approaches for cumulative risk assessment. The *Framework* tends to include more bottom up examples, such as the use of relative potency factors (RPFs) or toxicity equivalency factors (TEFs) to "accumulate" risks from chemical mixtures. Some of the strengths and weaknesses of these approaches were reviewed. Top down approaches that estimate overall risks and then apportion them among populations, according to different measures, may also be useful for cumulative risk assessments.

Several reviewers advocated the utility of biomarkers in the context of cumulative risk assessment and they thought the presentation in the document should be enhanced and expanded, with caveats on what they can and cannot do. Discussion on biomarkers focused on their potential use as time-based integrators of exposure and effects, which could be used to provide an overall picture of environmental health in a community. Selection of biomarkers was recognized to be a complicated issue, as there are limitations in their ability to identify specific

exposures or effects. Furthermore, some biomarkers can require invasive studies that call for individuals to consent to providing samples, which could lead to environmental justice issues. In other cases (such as birth weights and other aspects of birth records) the data are routinely collected but precautions need to be taken to prevent inappropriate disclosure of data on specific individuals. This topic migrated into a more general discussion of biomonitoring, which, like biomarkers, can be very informative. Some reviewers recommended that the *Framework* discuss these issues and provide additional references on existing biomarker and biomonitoring efforts and data (e.g., CDC National Exposure Project and NIEHS studies) that could be used in cumulative risk assessments. Other valuable public health surveillance data sources include state registries on cancer, birth defects, and other diseases. Similarly, other sources of human health baseline data, such as Healthy People 2010, can be used in general ways for cumulative risk assessments. Reviewers pointed out that the fields of biomarkers and molecular epidemiology will be producing many more tools that can be used in the future. The desire to link science on the public health side with the ecological side will give the *Framework* more weight, which will result in it being used more extensively. Furthermore, the *Framework* can help to identify the needs and stimulate more research to develop these types of methods.

Methods for addressing multiple chemical, non-chemical, and other stressors are widely recognized as one of the most significant challenges for cumulative risk assessment.

Aggregating and integrating risks from these disparate types of stressors to human health is not as advanced as analogous techniques used for ecosystem-level ecological risk assessments. The *Framework* introduces some methods, such as using a matrix to array data and facilitate comparing and contrasting different types of stressors or risks, but the document should try to expand the envelope in this area. EPA is encouraged to consult the ecological risk assessment literature on single metrics, indices, and other measures of ecological health (e.g., IBI, EMAP benthic index, USDA APHIS approach, etc) to determine their applicability to human health assessments. A particularly good resource on these issues is the SETAC Press 1999 document *Multiple Stressors in Ecological Risk Assessment*.

3.2 Charge Question #3

Question #3. Comment on whether the Framework adequately characterizes the importance of uncertainty analysis in cumulative risk assessment. What additional discussions of uncertainty should be included in the Framework (and in what sections of the document)?

The reviewers acknowledged that uncertainty analysis, a complicated issue, is even more complex in a cumulative risk assessment. The *Framework* does a good job of conveying the general concepts and issues of uncertainty analysis, however, the reviewers suggested that EPA focus on those elements that are unique to cumulative risk assessment, rather than try to provide an overview on the subject. Uncertainty analysis should be used not only in the risk characterization phase, but also as part of the planning of an assessment, to guide data collection (value of information analysis), scoping of a study, and communicating to stakeholders the possible outcomes of an assessment. For example, use of sensitivity analysis in the early phases can be helpful in planning a cumulative assessment. However, it is the communication aspects that reviewers felt would be most critical to a cumulative risk assessment and they emphasized the importance of communicating both qualitative and quantitative information on the confidence of an assessment. These communication challenges exist because uncertainty analysis tends to be very complex and quantitative, using language that is not easily conveyed to other audiences, which may result in conceptual and language barriers and miscommunication. As a result, it is important that qualitative uncertainty analyses be given emphasis in a cumulative risk assessment document, which will be useful to decision makers and other stakeholders. This type of open and honest communication should clearly state not only the uncertainties, but also the unknowns.

Discussion on uncertainty addressed one of the unique aspects of a cumulative risk assessment, evaluating chemical mixtures. One reviewer felt that the *Framework* could be enhanced by the addition of text describing some of the uncertainties that result from approaches for chemical mixtures risk assessment, particularly (1) dose-response relationships, (2) relative potency, and (3) considering biological activity from other modes of action. This discussion highlighted the

need for the *Framework* to introduce quantitative techniques to analyze uncertainty resulting from these mixtures assessment techniques (e.g., relative potency factors, toxicity equivalency factors, etc.). Several reviewers noted that many existing cumulative risk assessments assume that chemicals can be grouped together based on the assumption of common modes of action, but they pointed out that this assumption does not account for all toxic effects. Similarly, statements should be made in the narrative that certain approaches can over- or under-estimate the toxicity of actual mixtures and that the different approaches make basic assumptions relative to additivity, synergy, and other effects.

Other suggestions on uncertainty analysis were provided by the reviewers, including the need to differentiate between uncertainty and variability (adding definitions in the glossary would be a good start) and discussing some of the major tools available to risk assessors. Several reviewers stated that the *Framework* would benefit from introduction of Bayesian statistics tools, but others cautioned against overconfidence with such tools. Discussion returned to the communication challenges and the recognition that the *Framework* should not be an uncertainty analysis primer. As such, reviewers noted that the *Framework* should point readers toward additional references (e.g., the SETAC document *Uncertainty Analysis in Ecological Risk Assessment* by Warren-Hicks and Moore) for more background and explanatory material on the subject. Additionally, reviewers believed that uncertainty analysis is a topic that may be a good candidate for an issue paper, where expanded discussion could be presented on the advantages/disadvantages of available tools, the balance between qualitative and quantitative presentation, and related topics that warrant further development specifically for cumulative risk assessment.

Finally, a few reviewers acknowledged that even though cumulative risk assessments may have large uncertainties, they can be powerful tools for reporting on general environmental health, ranking risks for priority setting, and making decisions affecting public health. In cumulative risk assessment, a concerted effort should be made to gather and analyze large amounts of data; however, it is critical that such assessments do not get “bogged down” because uncertainties cannot get resolved. Reference was made to the precautionary principle and the need for an adequate margin of safety to be provided, while avoiding long delays to determine cause and

effect and analyze the uncertainties. The precautionary principle, placed in the context of cumulative risk assessment, may be a suitable topic for an issue paper. Part of this discussion referred back to general public health principles as well as the need to build the capacity among stakeholders to consider uncertainty issues as parts of the analysis and decision making processes.

3.3 Charge Question #4

Question #4. Comment on the adequacy and accuracy of the Framework's presentation in each of these areas: vulnerability, chemical vs non-chemical stressors, and different types of risk.

The comments and recommendations in response to charge question #4 were provided according to the three subparts below.

3.3.1 Vulnerability

The issue of vulnerability is critical in cumulative risk assessment and the reviewers were pleased that EPA had provided extensive attention to the topic. Reviewers discussed at length the following: possible alternate structures/terminology for classifying vulnerability; expanding the discussion with additional examples from public health, medical, and ecological fields; and the need for vulnerability considerations to be introduced earlier in the document, in the planning and scoping phase as part of identifying populations. Like other topics, reviewers suggested that the *Framework* focus the vulnerability discussion on those aspects that are unique to cumulative risk assessment. Furthermore, vulnerability is a topic that should receive increased attention, possibly via an issue paper. In addition to the issues of classifying types of vulnerability, reviewers pointed out the difficulty in characterizing vulnerable populations. In both human

health and ecological contexts, there are “hard to reach” populations that are understudied, and therefore, difficult to account for in cumulative risk assessments. As such, it was recognized that vulnerability is both a technical and policy challenge for cumulative risk assessment.

Several reviewers raised questions about the four categories of vulnerability presented in the *Framework*, particularly with respect to terminology and being able to differentiate among the types. Reviewers also introduced possible alternate structures for considering vulnerability issues. One such structure would consist of two major categories (1) differential susceptibility and (2) differential exposure. The differential susceptibility category could encompass issues related to ability to withstand initial exposure as well as the ability to recover from effects. Another approach is based on dependencies where susceptibility is viewed as the difference in the dose required to produce the same effect, essentially a shift in the starting position on the dose-response curve. A few reviewers felt that this approach might be less confusing and easier to communicate, though the reviewers did not resolve many of the issues introduced. Subsequent clarification by EPA indicated that the reviewers’ suggestions were very close to the existing scheme presented in the draft *Framework*.

Discussion also focused on existing vulnerability terminology used in other disciplines, such as those in public health, medicine, and ecological risk assessment fields. It was suggested that EPA consult the literature from those (and other) fields to see how vulnerability and related terms (e.g., susceptibility, sensitivity, resistance, resilience, dependency, etc.) are used. Examples could be added to the *Framework* to illustrate the similarities and differences. However, one reviewer suggested waiting on a vulnerability definition as the field of vulnerability is still developing. These conceptual definitions may not be helpful once better methods for vulnerability assessment become available. Regardless of the terminology that EPA chooses to use, it is important that the way that vulnerability is factored into an assessment be transparent and involve stakeholders in the process.

In the context of classifying vulnerability and related issues, reviewers pointed out that one of the biggest challenges is in characterizing vulnerabilities of populations, in both human health and ecological contexts. One reviewer stated that particularly in urban areas the most vulnerable populations may be under represented in census counts and therefore may not be adequately addressed in an assessment. This situation is analogous to remote ecosystems (e.g., arctic and desert resources) which are not extensively studied. As such, some of the most vulnerable populations may be among the ones that are most unknown. This becomes an issue on a site-specific analysis where the variability range may become statistically indefensible. The *Framework's* discussion of differences in race and gender vulnerabilities should be revisited because there are references that show that these populations do have differential exposures as well as different responses to the same exposures. While most reviewers recognized the potential for increased risks among certain populations, some examples were provided where select subpopulations often exhibit lower risks from similar exposures, such as the “healthy worker.” A related issue was raised by one reviewer that concerns risk perception and the different areas of concern of different races and genders, which is important as these perceptions can be "drivers" for community participation. The literature (e.g., paper by Paul Slovic) contains more information on risk perception factors. These vulnerability considerations should be recognized in the scoping process and also in communicating the results of a cumulative risk assessment.

3.3.2 Chemical and Non-Chemical Stressors

Reviewers stated that EPA deserves credit for the narrative in the current draft of the *Framework* because the issue of combining chemical and non-chemical stressors is one of the most challenging aspects of cumulative risk assessment. Several suggestions, as in previous discussions, were made for EPA to acknowledge the literature from other countries (e.g., Canada, Europe) for information on how they deal with integrating multiple exposures of disparate types of stressors. Similarly, public health approaches can be used to evaluate the impacts of chemical and non-chemical stressors, though there are limitations in their utility. Furthermore, the ecological risk assessment literature should also be consulted for analogues that

might be applicable to human health approaches. It was noted that there is a rich summary of what is currently out there; however, discussion should be expanded to figure out what can be defined with qualitative and quantitative techniques. As with other complex technical issues in cumulative risk assessment, this topic may be worthy of additional development in an issue paper.

Suggestions provided by several reviewers were to use a “top down” approach that relies on public health approaches, such as ecological epidemiology, to help to examine risks from chemical and non-chemical stressors. Such approaches, advocated by some of the reviewers, use biomarkers or other biomonitoring data (e.g., birth weight) as indicators that integrate the effects of different exposures, and which can also be used to predict future health outcomes. One reviewer, however, voiced reservations that ecological epidemiology studies would not be very useful because they will not identify specific causes of problems, they are time and resource intensive, and often raise more questions than they answer. Several reviewers felt that EPA should expand the discussion of ecological epidemiology to inform the reader of the possible advantages and disadvantages of such an approach. Also, a definition for ecological epidemiology should be added to the document and glossary (also distinguishing use of the term ecological in the context of epidemiology from the more widespread use). The issue of interactions (synergy and antagonism) was raised in this context such that approaches to combine different types of stressors should be done so with the recognition of such interactions. Several reviewers felt that the *Framework* should clearly state the default assumptions on combining stressors relative to additivity and related interactions, as a point of comparison. This discussion concluded with the recognition that these types of public health approaches have limitations, but can be helpful in developing hypotheses for future focused studies. This is similar to approaches used in ecological risk assessment and wildlife experimental science, where survey data can identify ecosystem level effects, but not causal relationships. Such information is then used to develop hypotheses for more intense monitoring and research, which are focused on isolating particular combinations of stressors and responses in resource health.

Similar to the discussion of vulnerability, one reviewer emphasized the importance of social

sciences in evaluating the significance of non-chemical stressors. Sociocultural aspects, such as limited access to health care, risk perception, and other risk factors, should be recognized by risk assessors in this context. Several papers are available in the literature on approaches to consider these factors in qualitative analyses. Another reviewer revisited one of the major themes from the workshop; the need for the *Framework* to provide more references and possibly a “document clearinghouse” for readers to consult for more background information on assessment approaches and methods. Such a central repository (or web site) of information on cumulative risk assessment will not only help practitioners, but it may promote further research to improve available methods.

3.3.3 Different “Types” of Risks

Discussion among the reviewers on approaches for assessing different types of risks was similar to that on previous topics; EPA had done a good job introducing the subject and providing available information, but more could be added to improve the *Framework*. Reviewers recognized that this is among the most complex aspects of a cumulative risk assessment, where the goal is to evaluate disparate types of exposures and effects. Suggestions for improving the document focused on issues that were similar to those on previous challenging topics, such as the importance of acknowledging the literature, the need to retain data and transparency when aggregating data, and the utility of ecological risk assessment approaches as possible models for human health assessments of different types of risks. This topic, particularly the use of single metrics for cumulative risk assessment, might be another good candidate for an issue paper.

Reviewers discussed approaches such as comparative risk ranking, matrix-type approaches, and single metrics, recognizing that all of these options diverge from purely scientific analyses into areas of policy, risk management, sociology, economics, and related subjects that rely on judgments to be made on the relative weight to be placed on different types of risks. The “translation of disparate types of risks into different units” was seen as the core of these approaches, with the clearly stated drawbacks that judgments have to be made and information can be lost in the process. Reviewers cited the QALY and DALY discussion presented in the

Framework as examples where health effects and other types of impacts (e.g., economics) are combined into metrics, with recognized limitations. One reviewer voiced the opinion that indices based on economic values or quality of life are useful because communities can relate to such topics, often better than environmental indicators.

Comparative or relative risk assessment was seen by several reviewers as one of the more useful tools in the context of cumulative risk assessment, where communities are often trying to prioritize risk reduction efforts. Such risk ranking exercises have been conducted for years in both human health and ecological risk assessment fields, particularly by the Europeans. The difficulty of weighing different endpoints was pointed out as a possible drawback, but reviewers felt that tradeoffs are often made in these types of risk ranking procedures. One example was provided by a reviewer which had been developed by USDA to evaluate exotic species using a high, medium, low scale (see OSTP document *Ecological Risk Assessment in the Federal Government*). Other examples of approaches used in ecological assessments, such as energy flow measures, trophic level indices, and other diversity indices, are used in similar ways, but with limitations. While reviewers generally felt that such approaches can be useful, they also acknowledged the struggle with the types of judgment calls to be made. Several reviewers also reiterated the need to retain data (present the disaggregated data too) and provide transparency in the process (such as for future re-analysis), as is advised in the draft *Framework*.

Reviewers voiced the opinion that the *Framework* should remain neutral and not advocate any particular approach for addressing different types of risks. Rather, the document should present available options and criteria for use, and let the risk assessors and stakeholders decide on the method that is most appropriate for the particular situation. This discussion again raised the importance of involving stakeholders in these types of decisions. Community participation is important in considering socioeconomic and sociocultural options and making the types of choices involved in deriving or using a metric. The priorities and values of stakeholders should be incorporated into the metric(s), which will increase understanding of the metric and acceptance of the results. Reviewers recognized overall that in the future, there are scientific improvements to be made as well as in the other factors, that should be considered as these

approaches are applied in cumulative risk assessments.

3.4 Summary List of Suggested Topics for Issue Papers

During the course of the peer review workshop, reviewers raised issues for discussion, several of which are particularly challenging topics in the context of cumulative risk assessment. These topics may warrant more attention, possibly in issue papers. Below is a summary list of those topics that the reviewers felt were worthy of additional development:

- Background - issues related to the use of the term and distinguishing among background, ambient, baseline, etc. while recognizing the discipline-based meanings.
- Vulnerability
- Uncertainty
- Precautionary Principle
- Biomarkers and Biomonitoring
- Single Metrics in Cumulative Risk Assessment (including combining chemical and non-chemical stressors and decision indices)

4.0 DOCUMENT REVIEW

For the last part of the workshop, the Chair opened the discussion for a section-by-section review of the document, to address any issues that had not been raised in either individual written comments or during the response to charge questions. He asked the experts to address major issues, such as reorganizing sections or clarifying the presentation of technical content, rather than providing editorial comments. The lists below summarize the comments and suggestions made by individual reviewers during this final document review, organized by the section of the *Framework* document.

4.1 Section 1

Incorporate more text in Section 1 on what cumulative risk assessment is as well as what it can and cannot do (much like EPA's introductory presentations). Address issues with definitions and consider adding more examples to illustrate definitions. Add a figure that illustrates where cumulative risk assessment fits into the larger picture and what inputs are provided to the process from other exposure and risk assessment efforts.

Discuss EPA's statutory constraints and issues that may need to be overcome when conducting a cumulative risk assessment (e.g., integrating across programs and agencies). That discussion could be presented in Section 1 or in the planning and scoping phase. It is also important to note that despite EPA's limitations that may result from statutory requirements, communities may want to use this approach.

The examples on environmental justice issues, presented on page 3 (line 23-39), are outdated and could be brought up to date.

Figures 1-1 through 1-3 should be revised and improved. Make Figures 1-1 and 1-2 different, perhaps changing Figure 1-1 to a more linear presentation.

The text on page 9, lines 16-24 should be reworded to put the emphasis on populations as the starting point for many cumulative risk assessments. This is similar to ecological risk assessments, which are often triggered by an impacted resource or the desire to protect a resource of value.

Add a text box on the scientific disciplines that are relevant to cumulative risk assessment and how they interact in the process.

Make sure the glossary definitions are consistent with the text, as well as with accepted usage in fields of human health and ecological risk assessment.

Expand the discussion of when a cumulative risk assessment should be done, on page 11. The existing text is a good start, but it could be elaborated upon. Possibly discuss post September 11 issues as they pertain to cumulative risk assessment.

4.2 Section 2

Text could be added discussing the influence of land use decisions and the need for their consideration in the planning and scoping phase.

Add some introductory discussion on consideration of vulnerability and uncertainty in the planning and scoping phase.

Figure 2-1 should show a forward arrow through the phases.

Wording in the paragraph at the bottom of page 16 on balancing stakeholder participation should be checked to make sure the meaning is clear. Several reviewers agreed with the intent of the

text, but had slightly different interpretations. A suggestion was made for EPA to consult discussion from the 1996 “Understanding Risk” report by the NRC, which emphasizes that every decision does not require the same type and degree of public participation.

As stated in comments on Section 1, the focus on populations should be emphasized in the planning and scoping phase. A specific example was noted, on page 17, line 39, where the sentence could be reworded to put identifying the population as the first step in the process. In addition, this discussion should be expanded and broadened to emphasize not only human populations but also ecosystems, as starting points for planning a cumulative risk assessment (reference back to Figure 1-2).

Text could be added to put community involvement into the larger perspective of the American democratic process.

Some text could be added to Section 2.1 in planning and scoping about risk cascades (e.g., echo cancer) and solutions that cause another risk.

Discussion could be added on data collection and use of existing data, as part of the planning and scoping phase. Section 2.1.4 may be a place to present that text.

Mention the need to retain information in development of conceptual models so that information is not lost (transparency) in the move to the analysis phase (on page 26-27, Sections 2.2.3 to 2.3).

Add more examples on page 27-28 of cumulative risk assessments that have been performed, preferably with a broader geographic range, such as examples of projects from the west coast. Also, add a text box describing the Baltimore study, similar to the one for Chicago. Clarify the discussion of the importance of stakeholder involvement in Chicago, even if the project ended up not taking a cumulative risk assessment approach.

Consider having two documents for cumulative risk assessments, a document that is oriented for

community stakeholders and a technical assessment report. This might also be helpful for decision makers who can consult both resources.

4.3 Section 3

Section 3 could benefit from a slight reorganization to make the discussion clearer, which would include renaming section headers and improving transition sentences. The suggested reorganization was as follows:

- 3.0 Analysis Phase
- 3.1 General Process
- 3.2 Available Methods and Approaches
 - 3.2.1 Estimating Exposures (with a sentence linking to traditional risk assessment terms)
 - 3.2.1.1 Exposure Issues in Cumulative Risk Assessment (move part of vulnerability discussion)
 - 3.2.2 Enhancing the Dose-Response Step (cause and effect)
 - 3.2.3 Decision Indices

One reaction to the above reorganization stated that 3.2.1.1 might not be needed and could be presented as a text box. Subsequent discussion questioned having decision indices appear in the analysis section and a suggestion was made that it would be more appropriate to present that in the risk characterization section. A suggestion made was to change the wording from decision to synthesis. Further discussion did not resolve the issue on where this material should appear, but comments were added that it would be desirable to have qualitative information presented before the quantitative results from the analysis phase.

Consider the references that are called out in the document and the need to provide a “window to the literature” to help the reader to obtain key background information on topics related to cumulative risk assessment (uncertainty analysis being just one example). Emphasis may be placed on documents published by the NRC or similar groups, which carry influence in the scientific community. Consider having a list or text boxes that list the most relevant and useful

references, organized by topic.

The sentence on page 35, line 25 was questioned as to its accuracy and a comment was made that published data are available on different susceptibilities and sensitivities among races and genders. A suggestion was made to strike the beginning of the sentence and add references to back up this point.

A reviewer questioned the accuracy of the statement on page 43, line 26 about “dose addition” being the default assumption for mixtures risk assessment.

A recommendation was made to add a text box on page 50 describing comparative risk assessment and possibly providing some examples.

4.4 Section 4

On page 57 consider having a different title for the text box.

In Section 4.2.3 on page 59 consider rewording the paragraph and adding references on the caution that should be taken in combining risks and the possibility for underestimation as well as overestimation. Several examples were provided, recognizing the frequent overestimation of risks, but others pointed out that risk assessments also underestimate risks because of unknown contributors.

Make sure the document states somewhere that while all stakeholder constituents need to be heard in the process, “they don’t necessarily get their way.”

Section 4.3.2 (page 61) the use of public health statistics should be expanded with references and possibly reworded to better present the relationships between health endpoints and what answers cumulative risk assessment can provide. Specifically, the text on page 61, lines 37-39, could be reworded as: Cumulative risk assessments are unlikely to match exactly with community health

statistics, but they should be considered together where possible as a reality check for the risk estimates.

In Section 4.4 on page 62, there are some terms that are not presented that would be expected to appear in the discussion on using the results of a risk assessment, such as: risk management, public health protection, cleanup, mitigation, siting, etc. Two other issues that could be discussed in this context are communication of the results of the assessment and the need for long term monitoring and follow up. In addition to these uses of the assessment, communities can also negotiate for mitigation options as part of projects that move forward.

Several reviewers discussed the issue of cause and effect and the ability for cumulative risk assessment to answer questions about public health (causes of diseases, cancer clusters, etc). The document should mention that while cumulative risk assessment may not be able to identify causal links, it can help to yield useful results that can be used for decision making and informing communities.

Appendix A
List of Peer Reviewers

**Technical Peer Review Workshop
On The EPA Risk Assessment Forum
Draft Framework For Cumulative Risk Assessment**

June 4-5, 2002

| PEER REVIEWERS | |
|-----------------------|---|
| Charnley, Gail | HealthRisk Strategies |
| Collin, Robert | University of Oregon |
| deFur, Peter | Environmental Stewardship Concepts |
| Goldsmith, David | George Washington University |
| Hattis, Dale | Clark University |
| Held, Joann | New Jersey Department of Environmental Protection |
| Locke, Paul | Johns Hopkins University |
| MacDonell, Margaret | Argonne National Laboratory |
| Muller, Pavel | ToxProbe, Inc. |
| Ryan, Barry | Emory University |
| Sass, Jennifer | Natural Resources Defense Council |
| Schlosser, Paul | CIIT Centers for Health Research |
| Travis, Curtis | Quest Technologies |

Appendix B
List of Observers

**Technical Peer Review Workshop
On The EPA Risk Assessment Forum
Draft Framework For Cumulative Risk Assessment**

June 4-5, 2002

| OBSERVER ATTENDEES | |
|---------------------------|---|
| Bender, Ed | U.S. EPA - Office of Science Policy |
| Boa, Elizabeth | American Chemistry Council |
| Bober, Timothy | U.S. General Accounting Office |
| Byrd, Daniel | LSRO |
| Callahan, Michael | U.S. EPA - Region VI |
| Crawford, David | U.S. EPA - OERR |
| Dellarco, Vicki | U.S. EPA - OPP |
| Halper, Marty | U.S. EPA - Office of Environmental Justice |
| Hoddinott, Keith | U.S. Army |
| Hofmann, Lee | U.S. EPA - OERR |
| King, Marva | U.S. EPA - Office of Environmental Justice |
| Knott, Steve | U.S. EPA - Risk Assessment Forum |
| Lee, Charles | U.S. EPA - Office of Environmental Justice |
| Levin, Leonard | EPRI |
| Margosches, Elizabeth | U.S. EPA |
| McBride, Alexander | U.S. EPA - Office of Solid Wastes |
| Murphy, Deirdre | U.S. EPA - Office of Air Quality Planning & Standards |
| Putzrath, Resha | Georgetown Risk Group |
| Semeiks, Ilga | U.S. General Accounting Office |
| Utterback, Dennis | U.S. EPA - ORD |
| Zahodikin, Phil | Pesticide and Toxic Chemical News |

Appendix C

Charge Questions

The Risk Assessment Forum

Draft Framework for Cumulative Risk Assessment

Peer Review Charge

June 4 and 5, 2002

The following background and questions are provided to help guide the peer review of the draft EPA Framework for Cumulative Risk assessment. The peer review is intended to provide input on the technical issues associated with cumulative risk assessment and how to capture these issues in a broad, flexible framework that will inform the development of future guidance. The focus of the peer review discussions will be on technical issues. Regulatory policy issues and specific program management concerns will not be addressed through this review.

Background

Several recent reports have highlighted the importance of understanding the accumulation of risks from multiple environmental stressors via multiple exposure pathways. These include the National Research Council's (NRC) 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, recent legislation, such as the *Food Quality Protection Act of 1996* (FQPA), directed the Environmental Protection Agency (EPA) to move beyond single chemical assessments and to focus, in part, on the cumulative effects of chemical exposures.

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. More recently, the Office of Pesticide Programs has developed cumulative risk assessment guidance focused on implementing certain provisions of FQPA. The Office of Air Quality Planning and Standards has recently assessed inhalation health risks associated with cumulative exposure to air toxics in its National Scale Assessment.

The EPA Science Policy Council has asked the Risk Assessment Forum (RAF) to begin developing Agency-wide cumulative risk assessment guidance that builds from these ongoing activities. The RAF is a standing committee of EPA senior scientists established to promote Agency-wide consensus on difficult and controversial risk assessment issues and to ensure that this consensus is incorporated into appropriate Agency risk assessment guidance. As a first step, a technical panel convened under the RAF has been working to develop a Framework for Cumulative Risk Assessment. Building from the Agency's growing experiences, the 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. Earlier drafts of the framework were presented during meetings

with other Federal and State scientists and during a peer consultation workshop with experts representing environmental and community groups, academia, and industry. The framework was revised based, in part, on discussions during these meetings. A new draft of the Framework for Cumulative Risk Assessment is being made available at this time for the purpose of peer review. At the completion of the peer review process, the document will be revised and then finalized for publication. The final framework document will reflect the peer review comments and will require review and approval by the Agency's Science Policy Council.

Charge Questions

The following questions are provided to help guide the peer review and associated discussions during the peer review workshop. When considering these topics, keep in mind that the purpose of a framework is to identify and "frame" key issues for a broad audience of readers. Therefore a balance must be struck between adequately characterizing the issues and providing a detailed, comprehensive technical discussion.

1. Comment on whether the Framework adequately captures, describes, and reasonably organizes the key issues for cumulative risk assessment so as to serve as an adequate foundation for the development of future guidance. In your comments, please address each of the following questions. In answering each question, provide a supporting discussion that highlights any areas of the Framework that may need to be clarified and relevant topics that may be missing from the current Framework document. Include references to any published literature that could help improve the completeness and clarity of the Framework.
 - a) Does the Framework document capture the relevant terminology?
 - b) Does the Framework document provide an adequate assessment structure?
 - c) Does the Framework document outline the relevant methods for cumulative risk?
2. Does the Framework document include any scientific or technical inaccuracies in its presentation of terminology, assessment structure, and methods? Please identify any problem areas and propose revisions or other actions that will result in a scientifically sound and supportable discussion. With respect to methods, comment on whether the Framework adequately conveys the state of the science with respect to currently available cumulative risk assessment methods/approaches and the areas that are in need of further research and development.
3. Uncertainty analysis is an important aspect of risk assessment (and policy analysis in general). However, historically, dealing with uncertainty has been a shortcoming of many assessments. Cumulative risk assessments present new challenges for uncertainty analysis. For example, assessing cumulative risks will involve combining data of varying quality. Perhaps more important, assessing cumulative risks will involve the use of

“soft” assumptions. These are assumptions which may have a high degree of uncertainty that is difficult (or not possible) to quantify. Comment on whether the *Framework* adequately characterizes the importance of uncertainty analysis in cumulative risk assessment. What additional discussions of uncertainty should be included in the *Framework* (and in what sections of the document)?

4. The following topics have been identified by the RAF technical panel as technically difficult areas that will pose challenges to cumulative risk assessment. Comment on the adequacy and accuracy of the Framework’s presentation in each of these areas.

- a. *Vulnerability*

As applied to cumulative risk assessment, it is useful to think of four components to vulnerability: the susceptibility or sensitivity of the human or ecological receptors; the differential exposures of the receptors; the differential preparedness of the receptor to withstand the insult from exposure; and the differential ability to recover from the effects. The issue for cumulative risk assessment is how to consider these aspects of vulnerability and their potential impacts on risk. This is highlighted in the Framework as an issue in need of further research and development. Comment on the discussion of vulnerability in the draft Framework. Has the state of the science been captured in this discussion? How can the discussion of this issue be improved?

- b. *Cumulative Risk Assessment Involving Chemical and non-Chemical Stressors*

Viewing cumulative risk assessment as an evaluation of the accumulation of stressors presents many challenges. These may be seen when attempting to combine, in some meaningful way, the risks from multiple chemicals that may act as synergistic, antagonistic, or additive doses leading to a single effect. The situation is exacerbated when non-chemical stressors (e.g., radiation, biological agents, and psychological stress) are considered. Comment on the Framework’s discussion concerning the combining of disparate environmental stressors. In commenting, consider the state of the science with respect to understanding the effects of different stressors acting together (e.g., chemical exposure and viral infection). What can be added to the Framework to adequately convey the state of the science in this area?

- c. *Cumulative Risk Assessment Involving Different “Types” of Risk*

Conveying the combined risks from multiple chemical and non-chemical stressors, in a meaningful way, is the ultimate challenge for cumulative risk assessment. Experience in this area is extremely limited. Indices, common metrics (e.g., Disability Adjusted Life Years - DALYs) and graphical (e.g., GIS) approaches have been explored but much methods development work remains to be completed. Cumulative risk assessment can be a valuable part of the decision making process, but only if the results are conveyed in a meaningful way. Comment on the Framework’s discussion concerning the combining of

disparate measures of risk. Do the example approaches discussed capture the state of the science in this area? In particular, consider the role of valuation (i.e., the assignment of societal values to disparate health outcomes) implicit in some of the approaches. Suggest changes or additions that may improve this discussion.

Appendix D

Agenda

United States
Environmental Protection Agency
Risk Assessment Forum

Technical Peer Review Workshop on the EPA Risk Assessment Forum Draft Framework for Cumulative Risk Assessment

Courtyard Crystal City Hotel
2899 Jefferson Davis Highway
Arlington, VA
June 4-5, 2002

Agenda

Workshop Chair: **Peter de Fur**
Environmental Stewardship Concepts

T U E S D A Y , J u n e 4 , 2 0 0 2

| | |
|---------|--|
| 8:30AM | Registration |
| 9:00AM | Welcome & Introductions <i>David Bottimore, Versar, Inc.</i> |
| 9:15AM | Chair's Introduction <i>Peter deFur, Workshop Chair</i> |
| 9:30AM | Background <i>Steven Knott, Risk Assessment Forum (RAF), U.S. Environmental Protection Agency (U.S. EPA)</i> |
| 9:45AM | Presentation on the Draft Framework for Cumulative Risk Assessment <i>Michael Callahan, U.S. EPA, Region VI</i> |
| 10:15AM | B r e a k |
| 10:30AM | Summary of Premeeting Comments <i>Peter deFur, Workshop Chair</i> |
| 10:45AM | Initial Round Table Discussion |
| 12:00PM | L u n c h |

T U E S D A Y , J U N E 4 , 2 0 0 2 (continued)

1:15PM **Discussion Session**

- **Charge Question #1** - Comment on whether the Framework adequately captures, describes, and reasonably organizes the key issues for cumulative risk assessment so as to serve as an adequate foundation for the development of future guidance.

a) Does the Framework document capture the relevant terminology?

b) Does the Framework document provide an adequate assessment structure?

c) Does the Framework document outline the relevant methods for cumulative risk?

2:45PM Break

3:00PM **Discussion Session (cont'd)**

- **Charge Question #2** - Does the Framework document include any scientific or technical inaccuracies in its presentation of terminology, assessment structure, and methods? Please identify any problem areas and propose revisions or other actions that will result in a scientifically sound and supportable discussion. With respect to methods, comment on whether the Framework adequately conveys the state of the science with respect to currently available cumulative risk assessment methods/approaches and the areas that are in need of further research and development.

4:15PM **Observer Comments**

4:45PM Wrap-Up

5:00PM A d j o u r n

W E D N E S D A Y , J u n e 5 , 2 0 0 2

8:30AM Discussion Session

- **Charge Question #3** - Uncertainty analysis is an important aspect of risk assessment (and policy analysis in general). However, historically, dealing with uncertainty has been a shortcoming of many assessments. Cumulative risk assessments present new challenges for uncertainty analysis. For example, assessing cumulative risks will involve combining data of varying quality. Perhaps more important, assessing cumulative risks will involve the use of “soft” assumptions. These are assumptions which may have a high degree of uncertainty that is difficult (or not possible) to quantify. Comment on whether the *Framework* adequately characterizes the importance of uncertainty analysis in cumulative risk assessment. What additional discussions of uncertainty should be included in the *Framework* (and in what sections of the document)?

9:30AM Discussion Session (cont'd) - Charge Question #4

The following topics have been identified by the RAF technical panel as technically difficult areas that will pose challenges to cumulative risk assessment. Comment on the adequacy and accuracy of the Framework's presentation in each of these areas.

- *Vulnerability* - As applied to cumulative risk assessment, it is useful to think of four components to vulnerability: the susceptibility or sensitivity of the human or ecological receptors; the differential exposures of the receptors; the differential preparedness of the receptor to withstand the insult from exposure; and the differential ability to recover from the effects. The issue for cumulative risk assessment is how to consider these aspects of vulnerability and their potential impacts on risk. This is highlighted in the Framework as an issue in need of further research and development. Comment on the discussion of vulnerability in the draft Framework. Has the state of the science been captured in this discussion? How can the discussion of this issue be improved?

10:30AM Break

WEDNESDAY, June 5, 2002

10:45AM **Discussion Session - Charge Question #4 (cont'd)**

- *Cumulative Risk Assessment Involving Chemical and non-Chemical Stressors* - Viewing cumulative risk assessment as an evaluation of the accumulation of stressors presents many challenges. These may be seen when attempting to combine, in some meaningful way, the risks from multiple chemicals that may act as synergistic, antagonistic, or additive doses leading to a single effect. The situation is exacerbated when non-chemical stressors (e.g., radiation, biological agents, and psychological stress) are considered. Comment on the Framework's discussion concerning the combining of disparate environmental stressors. In commenting, consider the state of the science with respect to understanding the effects of different stressors acting together (e.g., chemical exposure and viral infection). What can be added to the Framework to adequately convey the state of the science in this area?

11:45AM Lunch

1:00PM **Discussion Session - Charge Question #4 (cont'd)**

- *Cumulative Risk Assessment Involving Different "Types" of Risk* - Conveying the combined risks from multiple chemical and non-chemical stressors, in a meaningful way, is the ultimate challenge for cumulative risk assessment. Experience in this area is extremely limited. Indices, common metrics (e.g., Disability Adjusted Life Years - DALYs) and graphical (e.g., GIS) approaches have been explored but much methods development work remains to be completed. Cumulative risk assessment can be a valuable part of the decision making process, but only if the results are conveyed in a meaningful way. Comment on the Framework's discussion concerning the combining of disparate measures of risk. Do the example approaches discussed capture the state of the science in this area? In particular, consider the role of valuation (i.e., the assignment of societal values to disparate health outcomes) implicit in some of the approaches. Suggest changes or additions that may improve this discussion.

2:00PM B r e a k

2:15PM **Observer Comments**

2:45PM **Wrap-Up, Summary of Comments, and Next Steps**

4:00PM A d j o u r n

Appendix E
Presenter Overheads

**Technical Peer Review Workshop
on the
Draft Framework for Cumulative Risk Assessment**

June 4-5, 2002

**David Bottimore
Versar, Inc.**

**Courtyard Crystal City
2899 Jefferson Davis Highway
Arlington, VA 22202**

Overview of Peer Consultation Workshop

Welcome

Review of Agenda

Introduction of Participants

EPA Presentations

Chair - Peter deFur - groundrules, summary of comments, and discussion topics

Observer Comments

Post Meeting Activities – Workshop Report

**Technical Peer Review Workshop
on the
Draft Framework for Cumulative Risk
Assessment**

June 4-5, 2002

Peter deFur - Chair

Chair's Opening Remarks

Goals for Meeting – Provide input to EPA on technical issues related to the Draft Framework for Cumulative Risk Assessment

Ground Rules – Process issues, do's and don'ts

Peer Review Process

- Obtaining input on technical issues from experts in diverse specialties and from broad perspectives**
- Focus on technical issues (not regulatory or policy)**
- Not a consensus building process**
- Documentation of comments and recommendations**
- Role of EPA in peer review meeting**

Post Meeting Activities – Workshop report that summarizes discussion and comments on Framework

Ground Rules and Operating Guidelines

- We are here as individuals**
- Consensus is not necessary and will not be actively sought**
- Everyone participates**
- Keep to the logistics of time, subject, scope**
- Keep to the topics and the task (we will keep side lists)**
- Peer review among ourselves is the activity - not a conversation with EPA**
- No EPA bashing - or other attacks**
- Mutual respect**
- Factually based comments**
- Distinguish fact and opinion**

Ground Rules and Operating Guidelines (cont'd)

- Everyone speaks for themselves**
- No ad hominum or organizational attacks**
- Speak up when it is needed**
- Hold side conversations during breaks etc.**
- You will be working with these people again in your careers**

Charge Questions

- 1. Comment on whether the Framework adequately captures, describes, and reasonably organizes the key issues for cumulative risk assessment so as to serve as an adequate foundation for the development of future guidance. In your comments, please address each of the following questions. In answering each question, provide a supporting discussion that highlights any areas of the Framework that may need to be clarified and relevant topics that may be missing from the current Framework document. Include references to any published literature that could help improve the completeness and clarity of the Framework.**
 - a) Does the Framework document capture the relevant terminology?**
 - b) Does the Framework document provide an adequate assessment structure?**
 - c) Does the Framework document outline the relevant methods for cumulative risk?**

Charge Questions (cont'd)

- 2. Does the Framework document include any scientific or technical inaccuracies in its presentation of terminology, assessment structure, and methods? Please identify any problem areas and propose revisions or other actions that will result in a scientifically sound and supportable discussion. With respect to methods, comment on whether the Framework adequately conveys the state of the science with respect to currently available cumulative risk assessment methods/approaches and the areas that are in need of further research and development.**

Charge Questions (cont'd)

- 3. Uncertainty analysis is an important aspect of risk assessment (and policy analysis in general). However, historically, dealing with uncertainty has been a shortcoming of many assessments. Cumulative risk assessments present new challenges for uncertainty analysis. For example, assessing cumulative risks will involve combining data of varying quality. Perhaps more important, assessing cumulative risks will involve the use of “soft” assumptions. These are assumptions which may have a high degree of uncertainty that is difficult (or not possible) to quantify. Comment on whether the *Framework* adequately characterizes the importance of uncertainty analysis in cumulative risk assessment. What additional discussions of uncertainty should be included in the *Framework* (and in what sections of the document)?**

Charge Questions (cont'd)

- 4. The following topics have been identified by the RAF technical panel as technically difficult areas that will pose challenges to cumulative risk assessment. Comment on the adequacy and accuracy of the Framework's presentation in each of these areas.**

- a. *Vulnerability***

As applied to cumulative risk assessment, it is useful to think of four components to vulnerability: the susceptibility or sensitivity of the human or ecological receptors; the differential exposures of the receptors; the differential preparedness of the receptor to withstand the insult from exposure; and the differential ability to recover from the effects. The issue for cumulative risk assessment is how to consider these aspects of vulnerability and their potential impacts on risk. This is highlighted in the Framework as an issue in need of further research and development. Comment on the discussion of vulnerability in the draft Framework. Has the state of the science been captured in

this discussion? How can the discussion of this issue be improved?

Charge Questions (cont'd)

4b. *Cumulative Risk Assessment Involving Chemical and non-Chemical Stressors*

Viewing cumulative risk assessment as an evaluation of the accumulation of stressors presents many challenges. These may be seen when attempting to combine, in some meaningful way, the risks from multiple chemicals that may act as synergistic, antagonistic, or additive doses leading to a single effect. The situation is exacerbated when non-chemical stressors (e.g., radiation, biological agents, and psychological stress) are considered. Comment on the Framework's discussion concerning the combining of disparate environmental stressors. In commenting, consider the state of the science with respect to understanding the effects of different stressors acting together (e.g., chemical exposure and viral infection). What can be added to the Framework to adequately convey the state of the science in this area?

Charge Questions (cont'd)

4c. *Cumulative Risk Assessment Involving Different “Types” of Risk*

Conveying the combined risks from multiple chemical and non-chemical stressors, in a meaningful way, is the ultimate challenge for cumulative risk assessment. Experience in this area is extremely limited. Indices, common metrics (e.g., Disability Adjusted Life Years - DALYs) and graphical (e.g., GIS) approaches have been explored but much methods development work remains to be completed. Cumulative risk assessment can be a valuable part of the decision making process, but only if the results are conveyed in a meaningful way. Comment on the Framework's discussion concerning the combining of disparate measures of risk. Do the example approaches discussed capture the state of the science in this area? In particular, consider the role of valuation (i.e., the assignment of societal values to disparate health outcomes) implicit in some of the approaches. Suggest changes or additions that may improve this discussion.



Risk Assessment Forum

Framework for Cumulative Risk Assessment



Steven M. Knott

Exposure Science Coordinator
Risk Assessment Forum Staff





Risk Assessment Forum

Risk Assessment Forum's Mission:

To promote Agency-wide consensus on difficult risk assessment issues and to ensure that this consensus is incorporated into appropriate Agency risk assessment guidance.



Risk Assessment Forum

Characteristics of Forum Projects:

They represent difficult or precedent setting scientific questions for the Agency

They are intended to guide the Agency as a whole rather than any specific program

They are designed to be regulation neutral



Risk Assessment Forum

Forum Products Provide Guidance to EPA Risk Assessors:

Agency Guidelines (e.g., Guidelines for Ecological Risk Assessment)

Guidance Documents (e.g., Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures)

Technical Papers (e.g., Special Report on Environmental Endocrine Disruption: An Effects Assessment and Analysis)

Visit the Forum Web Page at:

www.epa.gov/ncea/raf



Risk Assessment Forum

Cumulative Risk Assessment Guidance Development

SPC Requests that the Forum Begin Developing
Cumulative Risk Assessment Guidance

Risk Assessment Forum Technical Panel Convened.



Risk Assessment Forum

Programs Participating in the Risk Assessment Forum Cumulative Risk Assessment Technical Panel

EPA Region VI, Michael Callahan, Panel Chair
Office of Science Policy
Office of Pesticide Programs
Office of Pollution Prevention and Toxics
Office of Environmental Justice
Office of Emergency and Remedial Response
Chemical Emergency Preparedness and Prevention Office
Office of Solid Waste
Office of Air Quality Planning and Standards
National Center for Environmental Assessment
Regions V, VI, and IX



Risk Assessment Forum

Guidance Development Process

- **Develop Framework**
- Extract lessons learned/experiences from ongoing case studies to illustrate aspects of the Framework
- Develop technical issue papers on selected cumulative risk topics
- Develop Proposed Guidelines for Cumulative Risk Assessment



Risk Assessment Forum

The Framework

Building from ongoing cumulative risk assessment experiences within the Agency, the *Framework* is intended to capture the basic elements of the cumulative risk assessment process. The *Framework*:

- 1) provides a flexible structure for cumulative risk assessment issues (capable of evolving with experience)
- 2) defines key terms, and basic concepts, to promote a common language on cumulative risk assessment



Risk Assessment Forum

The Framework cont'd

- 3) does not provide substantive technical guidance; but rather
- 4) serves as a basis for the development of future issue papers and cumulative risk assessment guidelines;



Risk Assessment Forum

Milestones in the Development of the Draft Framework for Cumulative Risk Assessment

Consultations with Science Advisory Board (FY'00 and FY' 01)

Meetings with Federal and State Government Scientists (May 2001)

Public Peer Consultation Workshop (August 2001)

External Peer Review (June 4 and 5, 2002)

Goal: Complete the Framework for Cumulative Risk Assessment by the End of FY'02.

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Framework for Cumulative Risk Assessment



Peer Review Meeting
June 4-5, 2002

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Framework vs. Guidelines

- Framework: General description of the topic. An *information document* laying out scope of the subject and how various parts fit together. (This document)
- Guidelines: Description of how it's done, including *boundaries* (e.g., limits of “good science”) not to be exceeded. (To be completed later)

⋮

Framework Definitions

- **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.

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Key Definition Points

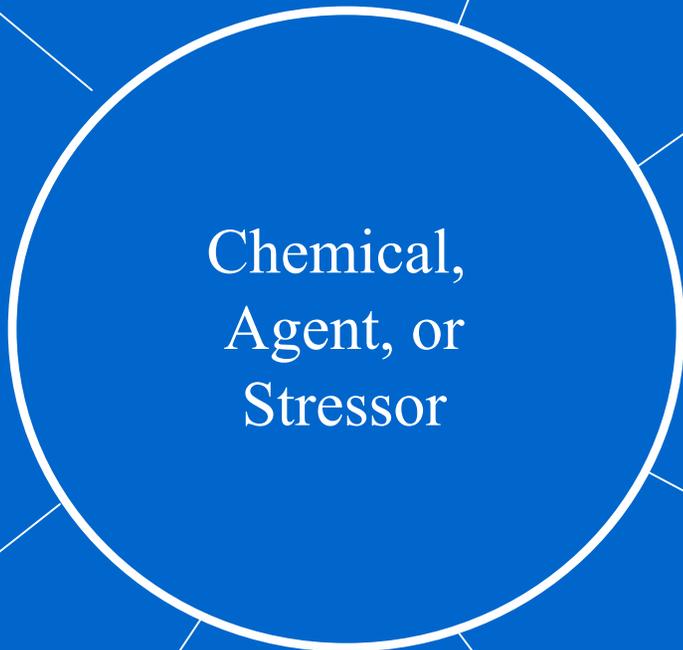
- Multiple stressors or chemicals
- Combined risks
- Can be qualitative

Goal of Cumulative Risk Assessment

- Using the commonly accepted definition of risk as “probability of harm”, the goal of a cumulative risk assessment is:
 - To address and hopefully answer questions related to the probability of harm, to human health or the environment, from multiple stressors acting together.

Cumulative Risk Assessment

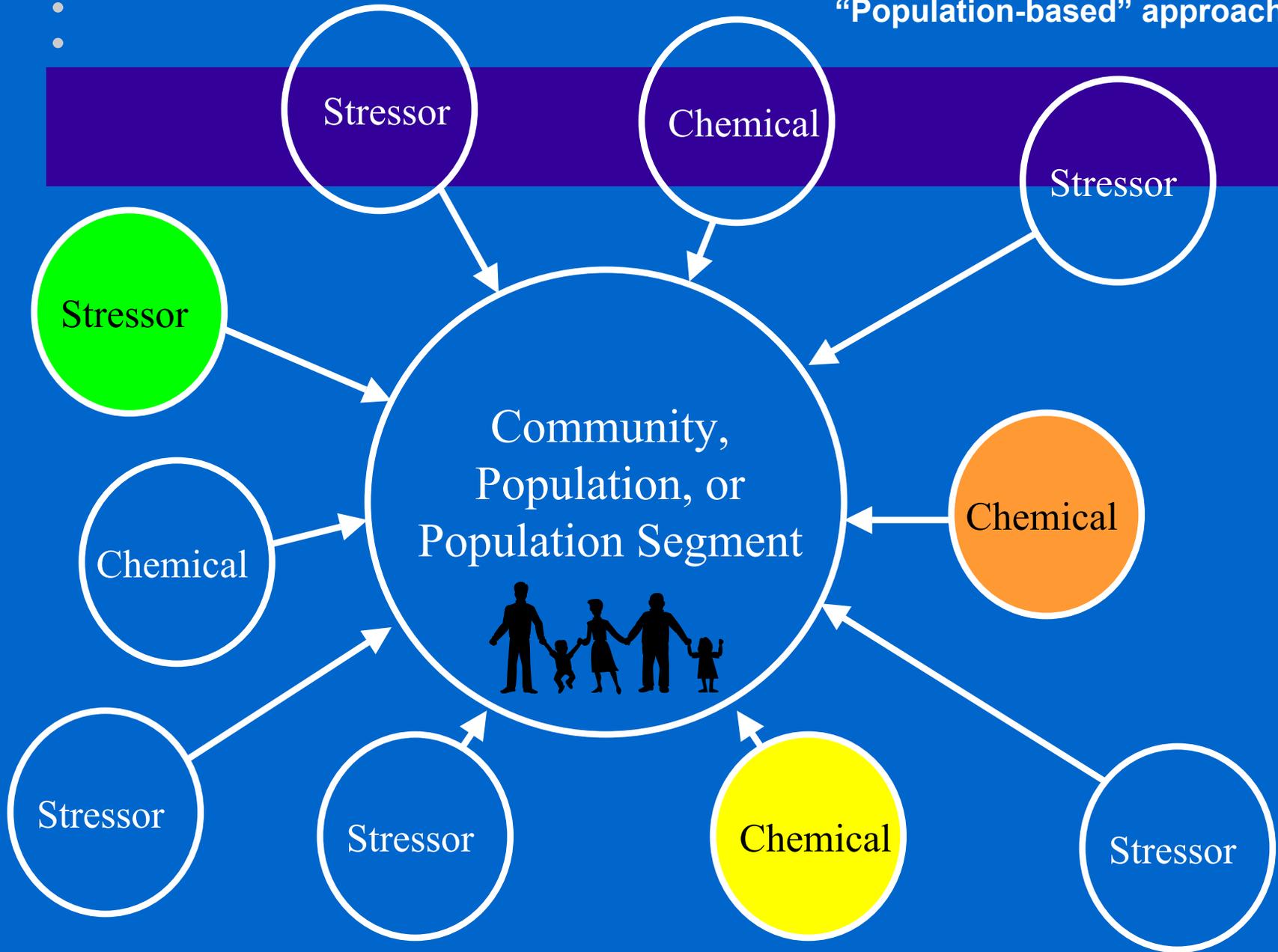
- “Traditional” Risk Assessment:
 - Where we’ve been
- Cumulative Risk Assessment :
 - Why change?
- Ongoing Agency efforts
- Policy issues
- State of the science



“Traditional” approach



“Population-based” approach



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Current Agency Efforts

- OP pesticides
- National Air Toxics Assessment
- Dioxin reassessment
- City-specific studies

-
-
-

Policy Issues

- Not part of this peer review
- Agency is talking internally about various policy issues

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Current State of the Science?

- Cumulative risk assessments will be most useful in situations where questions need to be addressed concerning the impacts of multiple stressors acting together
- Cumulative risk assessment is a tool
- It is not appropriate for every task
- Currently, there are methods limitations, and research and development is needed

•
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Organization of Report

1. Introduction
2. Planning, Scoping, and Problem Formulation Phase
3. Analysis Phase
4. Risk Characterization Phase
5. Glossary
6. References
7. Appendices

•
•
•

Planning/Scoping, Problem Formulation

- Public participation description in Chapter 2 reflects recent Agency trend.
- Conceptual model and analysis plan
- Discussion of possible outcomes

•
•
•

Analysis Phase

- Can different types of risk be combined?
- Toxicologic similarity vs. toxicologic independence
- Influences
- Common metric approach
- Index approach

•
•
•

Analysis Phase: Vulnerability

- Susceptibility/Sensitivity
- Differential exposure
- Differential preparedness
- Differential ability to recover

- Sexton (1997): Issue is not “are these important?”, but how much do these factors change bottom-line risk?

•
•
•

Risk Characterization: Uncertainty

- Few good examples of uncertainty analysis for Cumulative Risk Assessments
- New GIS-based technology poses new challenges in uncertainty analysis
- What type of analysis would be useful to a decision-maker?

-
-
-

Schedule

- Framework currently in peer review
- Science Policy Council final signoff
- Framework final by Fall, 2002?
- Case studies developed 2002?
- Guidelines development *starts* 2002-3?

Appendix F
Written Comments

Written Comments from Peer Reviewers

Gail Charnley - HealthRisk Strategies
Robert Collin - University of Oregon
Peter deFur - Environmental Stewardship Concepts
David Goldsmith - George Washington University
Dale Hattis - Clark University
Joann Held - New Jersey Department of Environmental Protection
Paul Locke - Johns Hopkins University
Margaret MacDonell – Argonne National Lab
Pavel Muller - ToxProbe Inc.
Barry Ryan - Emory University
Jennifer Sass - Natural Resources Defense Council (NRDC)
Paul Schlosser – CIIT Centers for Health Research
Curtis Travis - Quest Technologies

**Review by
Gail Charnley - HealthRisk Strategies**

PRE-MEETING COMMENTS
Gail Charnley

General Impressions

1. Including risk managers in the problem formulation phase is an important step towards the development of risk assessments that are focused on solving problems instead of creating them.
2. It is notable that the examples of cumulative risk assessments currently underway at EPA (executive summary) are confined to individual programs and offices. Risks from cumulative exposures are seldom cognizant of statutory constraints. One of the goals of this document should be to help move the agency forward in an attempt to, if not overcome, at least start to integrate the requirements of its various legislative mandates. Mentioning such a goal and providing a couple of examples of possible cross-program assessments would be useful.
3. The introduction is a useful overview of the evolution of risk-based decision-making at EPA, first towards single-chemical-based assessments and now towards cumulative analyses. It also provides a clear description of the nature and purpose of the framework

Charge Questions

1. The document does a very good job of articulating the relevant terminology and providing an adequate assessment structure. However, it does not describe the relevant methods for cumulative risk so much as describe the relevant process and approaches, mentioning methods to the extent they have been developed while pointing out that the methods and data are still challenging and evolving.
2. I have not yet detected any scientific or technical inaccuracies.
3. The document does not appear to over-sell its approach to cumulative risk assessment. It provides a balanced discussion of what we know and what is still uncertain (much) about performing a cumulative risk assessment. It does not over-emphasize quantitative analysis and appropriately promotes qualitative analysis.

Details

1. Page 27; The Baltimore Community Environmental Partnership Air Committee experience is referred to briefly as an example of a community-based cumulative risk attempt that contains valuable lessons. I agree and suggest that it be described more fully in an accompanying box similar to that for the Cook and Lake Counties Cumulative Risk Initiative on page 29.
2. Page 61; The discussion of cumulative risk in a public health context could use some expansion and possibly relocation. I will bring suggested additional text to the meeting.

**Review by
Robert Collin - University of Oregon**

This was prepared in response to Versar’s request. It is a preliminary reaction designed to assist Versar in arranging a 2 day meeting.

1. Framework

A. Captures- yes, in this context.

B. Describes - yes generally, but see page 36, line 43 -44; need more on exposure and vulnerability.

C. Reasonably organizes - yes

key issues in context of foundation for future guidance.*[EPA policy I presume?]*

A. Capture relevant words -

It seems to capture most of terminology. Possible exception - regional cumulative risk management; a broader discussion of the different meanings of the word “inert” in Chemistry and in consumer marketing. If the cumulative risk assessment reaches all stressors and close pathways, then chemicals under the sink and in the cleaning closet need to be fully disclosed to users [like MSDS].

B. Provide adequate assessment structure.

If adequate means a fair start, then yes. If adequate means actually measuring accumulating chemicals and their interactions dynamically, then no. If adequate means something that meets the minimum legislative and intellectual goals of NEPA, then generally yes. If adequate means application to urban areas, then a general, but hopeful, no.

C. Outline methods of cumulative risk; especially valuation [assignment of societal values to disparate health outcomes]. Public health is both a societal value, and presumed aspect of citizenship. It is also a Context. P 61, line 21 ; s 4.3.2 Cumulative Risk Assessments in a Public Health Context.

2. Inaccuracies

Problem areas revised only with “scientifically sound and supportable discussion.” The recently formed Canadian Cumulative Risk Association accepts both sciences as part of their organizational mission.

State of science and areas in need of further research and development *[also, how to do this research in controlled application]*

3. Uncertainty as “shortcoming”. Additional discussions of “uncertainty” in which section of the document. This discussion was interesting and useful. I would add epistemological uncertainty - roughly meaning not even knowing the questions to ask, yet. As to where to add this term and its explanation, its application to communities will be seen as a need for precaution.

4. Adequacy and accuracy of Framework's presentation of

a. Vulnerability - did not see much about generation skipping chemical effects. Did not see much of the research on "coping" mechanisms; treatment of childhood cancers causing secondary cancers; preventative health measures in environmental decisions and their effects on cumulative risk assessments; or assessment of migratory and immigrant populations. The Demographics can get complicated with dynamic urban issues like ethnic churning and inaccurate Census counts of particularly vulnerable populations.

b. Chemical and non chemical stressors - did not see much discussion of so called "inert" chemicals that are part of the everyday exposure paths of households, hospitals, and armies.

c. Different "types" of risk - did not see much on how perception of industrial hazard risk alone increases risk of heart attacks, stroke, and hypertension. In s 3.3.1 Interaction Between Stressors and Other Factors, issues like the lack of health care access and the lack of trust of Physicians may increase risk, and will increase uncertainty. The biomarker discussion was interesting. Metals that bioaccumulate remain metals for a detectable amount of time in tissue. They may be adverse, as defined here, or not. It raises a common environmental issue, from an Environmental Justice perspective, of some communities being required to scientifically prove harm to themselves; and other communities simply preferring not to have the same exposure. Here, in the Biomarker discussion, people may be part of your baseline as well as the implementing stakeholder. People can create risk to each other from vehicles, waste, etc. and would seem to be a necessary component of a good cumulative risk assessment. Also, is there any discussion of how these factors can synergize/antagonize other factors? [besides neurotoxicants]

5. Post Meeting Addendum

Here is my list of references, in no particular order. I have them if copies are difficult to get. I have given pinpoint cites where applicable, and can discuss any of these with you if you wish. I have included 3 forthcoming references.

1. Institute of Medicine, Research, Education and Health Policy Needs, ENVIRONMENTAL JUSTICE (National Academy Press, Washington, DC 1999) . ISBN # 0-309-06407-4

2. Adam M. Finkel & Domenic Golding, eds. WORST THINGS FIRST:THE DEBATE OVER RISK BASED NATIONAL ENVIRONMENTAL PRIORITIES (Resources for the Future, Washington, DC1994) isbn # 0-915707-74-8), pp. 237 -324 - The Environmental Justice Paradigm.

3. Sheldon Krimsky & Domenic Golding, eds, SOCIAL THEORIES OF RISK, Praeger Publishers, Westport, CT 1992) ISBN # 0-275-94168-X. pp 83 - 196 - Social, Cultural, and Psychological Paradigms; pp. 215 - 300 The Role of Science in Risk Assessment.

4. This is an international journal that EPA should review. Here are 2 recent articles. In the

first they discuss the principles of the Canadian Cumulative Risk organization. Steve Bonnell & Keith Story, ADDRESSING CUMULATIVE EFFECTS THROUGH STRATEGIC ENVIRONMENTAL ASSESSMENT; A CASE STUDY OF SMALL HYDRO DEVELOPMENT IN NEWFOUNDLAND, CANADA, vol. 2, no. 4 12/2000, pp. 477 - 500. Same journal volume - Harry Spaling, et al, MANAGING REGIONAL CUMULATIVE EFFECTS IN OIL SANDS DEVELOPMENT IN ALBERTA, CANADA, pp. 501 - 528. ISSN 1464 - 3332, Imperial College Press, London.

5. Robert Bullard, ed. CONFRONTING ENVIRONMENTAL RACISM: VOICES FROM THE GRASSROOTS (South End Press, Boston, MA 1993) ISBN# 0-89608-446-9.

6. National Academy of Public Administration, MODELS FOR CHANGE: EFFORTS BY FOUR STATES TO ADDRESS ENVIRONMENTAL JUSTICE, (June 2002) EQ-82906401-0.

7. James Flynn, Paul Slovic, and Howard Kunreuther, RISK, MEDIA, AND STIGMA: UNDERSTANDING PUBLIC CHALLENGES TO MODERN SCIENCE AND TECHNOLOGY (Earthscan Publications WWW.EARTHSCAN.CO.UK, 2001) ISBN3 1 85383 700 8. This includes a perspective from industry.

The following are books that are FORTHCOMING.

1. Robert Riddell, SUSTAINABLE URBAN PLANNING: THE DELIVERY OF CONSERVATION WITH DEVELOPMENT (Blackwell Publishers, London 2003).

2. R & R Collin, FOREVER WILD, FOREVER FREE: ENVIRONMENTAL JUSTICE AND SUSTAINABILITY, (Georgia University Press, Athens, GA, 2003).

3. Robert Bullard, ed. UNEQUAL PROTECTION REVISITED, (Sierra Club Publications, San Francisco, CA 2003).

I have many other International, EJ, Sustainability, and Law references that a Professor would think relate to cumulative risk assessment. Footnotes, literature reviews, and research generally are some of my favorite things. However, my goal was to give a window to the literature approach to this document at this stage of development. This is based on my hope that the issue papers develop strong reference and research foundations. This is also based on my hope that some type of national clearinghouse, per this meeting, will be developed.

**Review by
Peter deFur - Environmental Stewardship Concepts**

Comments on
"Framework for Cumulative Risk Assessment"
EPA/630/P-02/001A
April 23, 2002 Draft

These comments were prepared in advance of the peer review of the Framework to be held June 4-5, 2002 in Crystal City, VA and conducted by Versar, Inc. under contract to EPA. These comments are arranged as follows: general comments on the Framework; reply to charge questions provided by Versar; page specific comments, including editorial comments.

I. General Comments:

This Framework document is the initial step in the Agency effort to draft guidelines for conducting Cumulative Risk Assessments. The document has been carefully prepared and drafted by staff who are familiar with a wide array of Agency risk assessment efforts and reports. The relationships with other EPA Frameworks and risk assessments are clear and the intent of this Framework is explained by the authors. Some issues warrant a fuller discussion and the peer review should be one context in which to hold some of those discussions.

The Framework has the simultaneous benefit and curse of many authors. The benefit of many authors is the greater expertise and experience; the curse is the different styles of each in such a short document. Editorial attention is needed to overcome the differences in style. Some sections, not all, are written with long sentences (approaching and reaching run-on status); see specific comments, e.g. page 49. The passive voice is used too often in my estimation and more so in some chapters than others. Complex sentences and dependent clauses are also something that could be evened out to improve the readability and flow. Also, EPA needs to be very cautious about writing this for a knowledgeable v naive audience; it is now written for the former.

The Framework uses the term "background" to mean both "background" and "ambient". The word ambient is a better term for what is meant in this Framework as the present conditions that exist now- to which people and ecological units are exposed. I prefer ambient for these applications and actually think background has both explicit and implicit meaning that is not applicable.

The Framework needs more ecological examples and explanation. My specific comments indicate in some places where these might be used, references, and in some cases the text. This document seems to be the first EPA effort to integrate human health and ecological risk and as such needs to use language and references from both fields.

Several differences between ecological and human health risk assessment are worth noting and I have been thinking about whether or not these warrant a section in the front of the Framework. Clearly the authors recognized differences and sought to use the best and most appropriate features of each in developing the Framework.

Some of the major differences between human health and ecological are;

- 1) Eco RA uses a problem formulation phase
- 2) Ecological systems are not as well known biologically as are human health systems, both at the population and the individual level.

- 3) For this reason, and because biological communities and ecosystems are inherently more complex, EcoRA requires more preliminary analysis and deliberation regarding endpoints and protective standards
- 4) Ecosystems, habitats and ecological communities have traits and properties that individuals do not or that are not applicable to individuals or populations
- 5) Eco RA has been generally applied to populations, not individuals, a situation reversed for human health.
- 6) Ecological risk assessment must assess risk at multiple levels of organization, i.e. molecule, cell, organism, population, community, ecosystem.

This Framework follows the form of the Ecological Risk Assessment Framework and it would seem EPA is following a similar guideline development process here. This point needs to be made more clearly and explicitly in the Framework, with specific references to both substance and process similarities.

The initial step proposed here is planning scoping and problem formulation; the last step coming from the Eco Risk Guidelines. EPA should separate these into two steps in order to distinguish management and assessment as originally recommended by NRC in 1983 (Risk Assessment in the Federal Government). NRC did not say to remove the risk managers from the process, but NRC did recommend that the management and assessment process be kept separate and for good reason. Managers have a propensity to become closely involved in the risk assessment process unless specifically removed. The NRC was concerned that managers will tell assessment teams what sort of outcomes are acceptable or not. EPA heard a similar concern when preparing the Eco Risk Guidelines (Peer Review Report from Dec 1995 review).

The figures all show double headed arrows that more than imply a reversible flow of information, results, and data. While there is an important iterative step that must remain a part of the approach to conducting risk assessment (RA), this feature creates an endless loop that will lead to paralysis by analysis. The Framework needs a change to eliminate this option. The RA is a decision-based, outcome driven process, and is not an open-ended investigation.

Is this intended to be used in combined human health/ecological risk assessments? (see Suter). If so, then some groundwork needs to be inserted here.

II. Reply to Charge Questions:

1. key issues, terminology, structure and methods

The general answer to this question is "Yes, but." The general Framework is good, and builds on the Ecological Risk Assessment (RA) Guidelines, with which I am familiar. This Framework also indicates that it is the first step in a longer process, but this point needs to be repeated in the beginning of each chapter. The big missing element is an explanation up front that the difference between single chemical and cumulative risk means that the entire approach is altered and the conduct of the resulting assessment will shift accordingly. Compare the TCDD national assessment, any of the EPA watershed assessments and some single chemical/single source assessment. Basic assumptions differ, data handling, equations differ, etc.

Terminology is mostly correct except that I do not agree that background is the correct term here- it should be ambient.

Methods- See the Warren-Hicks and Moore (1999) book on uncertainty analysis, Stahl et al (2001) on Risk Management v RA; Foran and Ferenc provide methods for multiple stressors that come from Harris et al (see Foran and Ference) and others.

2. State of the Science:

In my opinion, the difference between "ambient" and "background" is a scientific one as well as terminology. Ambient really is meant to refer to local current conditions as influenced by whatever factors are on-going. "Background" at least implies some untouched, even pristine state or condition. Background has the meaning of some reference state or location.

The double arrows in the figures are important substantive issues for analysis that EPA needs to address here and now rather than wait for later. RA must not be an endless loop of analysis and measurement.

Numerous methods exist for uncertainty analysis and I refer to the Warren-Hicks and Moore (1999) publication.

The matrix approach of Harris et al and explained in greater detail in Foran and Ferenc is an important method for assessing multiple stressors that can be explained in greater detail here.

3. Uncertainty analysis:

The Framework section on uncertainty analysis could be enhanced, but this field is now getting more attention than even 5 years ago, so it is going to be hard. But there are methods of quantitative analysis that should be noted: Probability bounds, Bayesian analysis, point estimation, etc.

4. Vulnerability, chemical and non-chemical stresses; types of risk:

The text on vulnerability is quite good in explaining what is meant by vulnerability and why it matters. But the context for considering vulnerable targets is not clear to me. It feels awkward coming in to the discussion. Vulnerability is an aspect of analysis that has to be considered in the problem formulation B what are the vulnerable targets- either humans or ecological units? And then the analysis needs to be conducted to account for these vulnerable targets.

There is not much written in the area of combining chemical and non-chemical stresses in the RA literature, but I suggest that the pure literature in pathology and toxicology has some information on this matter. EPA can and should get some information on how these combine by getting some literature work done in specific areas, such as comparing disease in exposed and non-exposed groups, comparing response to second exposures, etc.

Measures of risk is another area that has not much literature, and I doubt that the non-expert reader will really understand the nature of the discussion. I am not especially impressed with the discussion on different valuations of risk - unless of course EPA is ready to insert a good discussion of the Precautionary Principle into the document. Such text would help a lot, especially in the area of valuation of risk. My reading of the literature is that the public is fairly

risk-averse in the environmental area. Citizens do not want to have even low risk in water, air, food, soil, which they believe should not be degraded as a matter of course by the fact of humans living on the planet. So, the socially acceptable risk business leads down the slippery slope of accepting basically unacceptable situations simply because someone says the situation cannot be fixed.

I am not sure to which sections of the Framework this question applies. And that comment in itself is a comment on the labels or structure, or both. Issues of this nature are in section 3.3.3.1, and that text is interesting, but I am not sure how necessary it is. I have to read it another time to address that question specifically. But one aspect I do not agree with is the appearance of economic issues in several places outside the context of management.

III. Page specific comments:

Page 1 Figure 1-1 does not do the trick. I recommend making it linear, and proceed from left to right

Page 2 This figure does not cover the subject well either, although it is better than fig 1.

Page 6-7 The definitions of aggregate and cumulative risk need some attention in order to address the difference between those two terms. I am not sure that all of the readers and intended audience will appreciate the distinctions as they are now expressed.

In addition, the document should make an explicit comment that cumulative risk refers to time, space and method or route of exposure. In single stressor risk assessments for human health, the focus on identifying the pathway and the effect drives the entire process. Now, that approach has to be replaced with one that essentially does that opposite and intentionally includes time, space, media exposures.

Page 13 Figure 1-3 makes a single step out of the two steps of Assessment- Manager discussion and problem Formulation that comes from Ecological Risk Assessment. I do think these steps are sufficiently different that they should be specifically identified as not one step.

Page 15 section 2.1 Planning and Scoping – 2nd and 4th paragraphs need language changes to require the legal mandates and community participants in the processes. These are not optional elements and if they are not addressed at the beginning will likely bog down the RA.

Page 18 Line 13- make this “ambient”, not background. See previous comment and discussions.

Page 19 Section 2.1.2 that starts on p 17 must refer to the analytical and deliberative methods and processes. Perhaps the specific equations are unclear until more data are gathered, but the expected form of analysis should be spelled out initially. Also, as noted by NRC (1996, Understanding Risk), this step needs to specifically indicate both analysis and deliberation are required.

Section 2.1.3 needs to include language on how this participation will work for ecological resources and evaluations. There are plenty of possible groups, but let's see a list here: outdoors clubs, American Indians, community groups, state and local and national resource NGO's, commercial and recreational fishers, etc.

Page 21 Lines 14 et seq. B We need some participant programs like the TAG Superfund program. Some states have this idea, but some national leadership would be great.

Page 23, line 11 Start by identifying all the system components and the relationships among them.

Page 26, line 37 The economics is NOT an RA issue - it is risk management and policy. This analysis is later and separate. See Stahl et al 2001 (SETAC book Ecological Risk Management).

Page 31, line 1 et seq. Somewhere in this section the Framework needs to acknowledge that the dose-response and risk characterization are placed in different sections of the RA process in Eco, and Human Health RA and why it does or does not matter.

Line 11, Section 3.1 The whole process should begin with a status assessment of either the population or habitat or both.

Page 42, line 10-11 please explain this in simpler terms- many readers will not understand this as written

In this section, please give an example from an exotic species introduction, and an exotic in combination with chemicals B see the excellent risk assessment by USDA for the control of Gypsy Moth in the eastern US.

Page 46, line 6 Remove the economic language or relegate it to indirect or secondary at best. Economics is part of the management analysis.

Page 48, line 9 Explain that "the use of biomarkers is based on the concept that the biological unit is an effective and accurate element to integrate the aggregate/cumulative risks or exposures."

Line 25- 31 I don't know the purpose of this language - it is apologetic and dismissive of biomarkers. Biomarkers are merely measures of exposure and not effect, and include all that the animal has experienced. Furthermore, body burdens are certainly effective estimates that can and have been, and are used to estimate total risk to individuals (NB Pb, Hg, TCDD, PCB's, etc.), even if these do not provide sufficient information on specific exposures or sources, or periods of sensitivity. DDT residues certainly do provide information on total lifetime exposures, but not on whether exposure during puberty was greater and caused greater risk for one disease or another.

Lines 39- 42 Please reword to make it more clear- it reads like weasel words as it is now written.

Page 49, lines 9-16 This paragraph is an example of editorial needs in the document B with apologies to the original author. This paragraph is two sentences that are both run-on and indirect.

Page 50, lines 8, 10 Explain how you get HQ here- it is not clear how RfD comes to or from HQ unless the reader knows the stuff well.

Page 52, line 42 See the USDA (APHIS) approach to risk assessment for exotic species (also NRC 2001 on Exotic Species and Agricultural Resources).

Page 53 figure 4.1 has the double arrows that create a do-loop.

Page 58 Section 4.2.2 See Warren-Hicks and Moore, 1999 (SETAC book- Uncertainty Analysis in Ecological Risk Assessment).

Page 61 line 23 et seq is another run-on.

Page 62 line 23 et seq. This section needs to note that the following are essential in the "use of the assessment:" Risk Management; Public Health; Clean-up or mitigation; Siting; Communication; Long-term monitoring.

Page 63, line 33 Somewhere in here the text must acknowledge religious, cultural, aesthetic and social values issues. Some decisions are based on the facts that these other issues are the overriding reasons for decision-making. We, as a society, once restored and now protect the bald eagles because they are an important national symbol. The Corps rejected a project because 10 years of abuse of American Indian rights could not be undone by new analysis or procedures.

Page 64 please give the source

Page 89 please distinguish background and ambient. In this section, give a list of stressors/agents for which this issue applies now: TCDD, Hg, Pb, As, *E. coli*, *Salmonella*, etc.

Page 91 None of these have conceptual models.

**Review by
David Goldsmith - George Washington University**

The draft seems to mash concepts together in order to talk about "Cumulative Risk Assessment"

I see three areas that we must try to address and make distinct:

- 1) Risks from multiple pesticide exposures
- 2) Additive mixtures of toxic risks
- 3) Ecological risk.

In order to make things distinct, I believe we need to try to think critically and make the draft recognize that threats to health are NOT all stressors.

A pesticide is a chemical with both beneficial and risky attributes, while stressors are much broader concepts of potential change in status, which can result in temporary or permanent health.

For example, a fishery can come under stress when temperature rises, when larger predatory fish attack, or when a bolus of pesticide is illegally dumped in it. But when a human is exposed or overexposed to either multiple chemicals or multiple OP insecticides, that is a risk to health (increase in the likelihood of disease related to that specific exposure), not simply a "stressor."

We need to be thinking about measuring dose or exposure for use in epidemiology or in toxicology, while in ecological risk assessment, we may not be equally able to define when a watershed is at risk, simply that it no longer functions to recharge groundwater, or to provide aquatic habitat, and thus the 'exposure and response' parameters will need better definition. This scenario also means we need new definitions of thresholds.

**Review by
Dale Hattis - Clark University**

Premeeting Comments on the 4/23/02 Draft *Framework for Cumulative Risk Assessment* (Risk Assessment Forum, U.S. Environmental Protection Agency)

General Impressions

The EPA authors of this document have struggled diligently with a very amorphous problem. In consultation with a wide array of participants, they have included a wide variety of analytical enterprises that various stakeholders may wish to find shelter and respectability under the rubric of “Cumulative Risk Assessment”. For example the things that are cumulated in a cumulative assessment may share a common biological mode of action (as for organophosphate insecticides) or they may not have the slightest commonality in this respect. The object of the exercise may be to produce some coherent quantitative assessment of a problem, or no risk quantification may be done. The assessment must focus on some set of effects of multiple stressors, but the only other thing that evidently needs to be shared in order to be cumulatively assessed, is the population exposed or affected (see box on page 9). In seeking this inclusiveness, and in parallel striving to avoid giving offense to various stakeholders with knowledge and experience with past analyses, the EPA authors have produced a document that is structured in very general terms. This unfortunately leads to a relatively small ratio of helpful methodological “meat” to definitional rhetoric. I think that diligent analysts trying to approach cumulative risk problems in the future will be better served by a document that gives them considerably more in the way of specific do’s and don’ts, and unobvious insights into ways to structure and illuminate their problems. I will elaborate on this general suggestion in my responses to the charge questions and the specific comments below.

Response to Charge Questions

- 1. Does the Framework adequately capture, describe and reasonably organize the key issues for cumulative risk assessment so as to serve as an adequate foundation for the development of future guidance?**
 - a) Does the Framework document capture the relevant terminology?
 - b) Does the Framework document provide an adequate assessment structure?
 - c) Does the Framework document outline the relevant methods for cumulative risk?

Each of the parts a, b, and c above begs the question “relevant” to what, or “adequate” for what? Broadly, the document seems to envision that the cumulative risk assessments covered are

intended to be helpful for some kinds of public policy/decision-making.¹ But certainly not all kinds of public policy decisions on environmental health and ecological risk issues are well served by the kind of cumulative risk assessment covered by the document. The document needs to address up front under what circumstances a cumulative risk assessment is in order, and under what circumstances the community of stakeholders and governmental actors should undertake some different kind of policy analysis. It is in failing to draw the contrast between cumulative risk assessments and other policy analysis alternatives that I think the current draft document fails to “capture relevant terminology,” “provide an adequate assessment structure,” and “outline the relevant methods.”

The other kinds of policy analysis I think need to be at least briefly covered in a revised introduction include traditional cost-benefit analysis (Office of Management and Budget, 2000; Freeman, 1997), trade-off analyses (Ashford et al., 1981), priority-setting analyses (Hattis and Goble, 1994), or various kinds of cost-effectiveness analyses. In general, these kinds of efforts address more directly the needs for information helpful in decision-making whenever it is possible to define a coherent set of options for a decision-maker for comparative analysis of likely good and bad outcomes. By contrast, I would say that one might prefer to do a cumulative risk assessment only as a predecessor to later framing of possible options to make changes in emissions/exposures, and only then when the community is really unclear as to which types of community exposures are responsible for the greatest portion of risks of concern, and which present the most promising opportunities for beneficial interventions. (It is not necessarily true that the greatest drivers of risk will provide the most promising opportunities for intervention to produce public health and/or ecological benefits.)

¹ We learn early on in the introduction (p. 2) that the particular virtue of population-based cumulative assessments (in contrast to the single-chemical or single-stressor assessments designed to serve the needs of “command-and-control” regulatory decision-making in the benighted days before the enlightenment of the 1980s) is that they “were much more useful to decision-makers who were dealing with public health or ecological health questions, rather than controlling sources of pollution.”

References for Charge Question 1

Ashford, N. A., D. Hattis, E.M. Zolt, J.I. Katz, G.R. Heaton, and W.C. Priest. 1981. Evaluating Chemical Regulations: Trade-Off Analysis and Impact Assessment for Environmental Decision-Making. Final Report to the Council on Environmental Quality under Contract No. EQ4ACA35. Cambridge, Massachusetts: Massachusetts Institute of Technology, Center for Policy Alternatives Report No. CPA-80-13, Washington, D.C.: National Technical Information Service # PB81-195067.

Freeman, M. III. 1997. Economics, Incentives, and Environmental Regulation. Chapter 9 In: Environmental Policy in the 1990s. Reform or Reaction? Third Edition, Edited by Norman J. Vig and Michael E. Kraft, Congressional Quarterly Press, Washington, D.C.

Hattis, D., and Goble, R. L. 1994. "Current Priority-Setting Methodology: Too Little Rationality or Too Much?" Chapter 7 in: Worst Things First? The Debate over Risk-Based National Environmental Priorities, A. M. Finkel and D. Golding, eds., Resources for the Future, Washington, D.C. pp. 107-131.

Office of Management and Budget. 2000. Guidelines to Standardize Measures of Costs and Benefits and the Format of Accounting Statements. Memo from Jacob J. Lew, Director, OMB, for the Heads of Departments and Agencies, March 22, 2000.

2. Does the Framework document include any scientific or technical inaccuracies in its presentation of terminology, assessment structure, and methods? Does it adequately convey the state of the science with respect to currently available methods/approaches and the areas that are in need of further research and development?

I think the document can do better in this respect. For example on page 8 the document mixes together a discussion of what might be called "bottom up" assessments—in which a combined effect is estimated as the predicted aggregation of the effects of several different stressors—with "a physician's use of a model, derived empirically from epidemiological studies, to estimate the probability of a woman's developing breast cancer over the next ten years." For convenience, I will call the second kind of analysis "top down" because it derives the influence of various stressors/"risk factors" from actual observations of a "top" effect of concern—often in careful prospective studies with extensive opportunities to statistically control for a variety of potential confounding factors in addition to those factors that can be affected by environmental health policy interventions.

The methodology for this latter type of cumulative assessment is very different from the “bottom up” assessments, and deserves extensive separate treatment. Indeed, many of the most important current analyses of environmental effects take the form of such empirical epidemiological studies using multiple regression techniques for analysis—including the mortality and morbidity effects of airborne particulates, among other air pollutants, to name only the most prominent example. The versatility of the technique to tease apart contributions of different sources of environmental exposures of interest is illustrated by a recent paper by Harvard researchers on the association of particulates from different sources for short term mortality changes.²

There are also some notable pitfalls of the “top down” assessments. These are most importantly in the form of the equations used to represent the influences of various factors on the measured outcome variable(s). These of course need to be causal predictive models, however the tradition of the field is simply to derive the most parsimonious “best fit” equations that satisfy prevailing statistical criteria. One example that I noticed over twenty years ago was that the multiple logistic risk equations used to analyze the chronic prospective heart disease studies such as Framingham used an equation that made no distinction between possible contributions of risk factors (e.g., blood pressure, diabetes, etc.) to the chronic process of atherosclerosis, vs the acute events that are responsible for precipitating observed clinical events such as heart attacks and strokes. The foundational paper for these analyses (Truett et al., 1967) goes into extensive detail to address statistical issues, but says not one word about why one should believe that their generic multiple logistic risk equation is a good causal model of the processes leading to adverse cardiovascular outcomes, and the interactions of different risk factors in contributing to the adverse events (e.g. contributions of diabetes and smoking to myocardial infarctions), let alone give analysts a way to distinguish between contributions to acute precipitating events vs chronic causal processes.

This subject is worthy of further treatment in the document. This is an important mode of analysis for some of the major environmental health hazards known at present. And in addition it has considerable potential to be applied in combination with new biomarkers of early response to help sort out and quantify the contributions and interactions of multiple stressors. Biomarkers represent natural integrators of the influence of multiple environmental and background factors on adverse outcomes. Such continuous biomarkers that I think are useful as dependent variables for use in future study include birth weights (Hattis, 1998), sperm count and other sperm quality parameters (Hattis, 1998), heart rate variability parameters (Pope et al., 1999), measures of lung function, and blood coagulation parameters such as fibrinogen (Schwartz, 2001).

References for the Question 2 Response

Hattis, D. “Strategies For Assessing Human Variability In Susceptibility, And Using Variability To Infer Human Risks” In Human Variability in Response to Chemical Exposure: Measures,

² They find that a 10 $\mu\text{g}/\text{m}^3$ exposure to mobile source $\text{PM}_{2.5}$ is associated with a 3.4% increase in daily mortality (95% confidence interval 1.7-5.2%), in contrast to the smaller 1.1% response indicated for coal combustion $\text{PM}_{2.5}$ particles particulates (95% confidence interval 0.3% - 2.0%) and no detected response to $\text{PM}_{2.5}$ of crustal origin. If confirmed, this is of considerable importance in directing efforts to control the particles from sources with the greatest health impacts.

Modeling, and Risk Assessment, D. A. Neumann and C. A. Kimmel, eds., CRC Press, Boca Raton, FL, pp. 27-57, 1998.

Laden, F., Neas, L. M., Dockery, D. W., and Schwartz, J. (2000) Association of fine particulate matter from different sources with daily mortality in six U.S. Cities. *Environmental Health Perspectives* 108: 941-947.

Pope, C. A. 3rd, Verrier, R. L., Lovett, E. G., Larson, A. C., Raizenne, M. E., Kanner, R. E., Schwartz, J., Villegas, G. M., Gold, D. R., and Dockery, D. W. (1999). "Heart rate variability associated with particulate air pollution. *Am Heart J* 138:890-899.

Schwartz, J. (2001) Air pollution and blood markers of cardiovascular risk. *Environ Health Perspect.* 109 Suppl 3: 405-409.

Truett, J., Cornfield, J., and Kannel, W..1967. A multivariate analysis of the risk of coronary heart disease in Framingham. *J. Chron. Dis.* 20: 511-524.

3. Does the Framework adequately characterize the importance of uncertainty analysis in cumulative risk assessment? What additional discussions of uncertainty should be included, and where in the document?

It seems to me that the document provides only the most cursory treatment of uncertainty analysis. There is considerable that could be said about the specific uncertainties that arise in cumulative risk analyses, for example the uncertainties that arise in estimating "relative potency factors," for organophosphates or TEFs for agents thought to act via the dioxin receptors. Some of these uncertainties can be usefully partitioned between (1) the basic uncertainty in the dose response relationship for the reference chemical, and (2) the uncertainty in estimating the relative potencies of the other chemicals in the common mechanism group in relation to the reference chemical, and (3) the uncertainties arising from the fact that members of the common mechanism group may have other modes of action that are not fully captured via the common-mechanism potency calculation.

4. Comment on the adequacy and accuracy of the Framework's presentation in each of these technically difficult areas:

a) Vulnerability

Of the four components mentioned, I think only two are really needed—susceptibility or sensitivity, and exposure. The third, preparedness to withstand the stressor is I think completely redundant with susceptibility, and the fourth—differential ability to recover—I think should be treated by having multiple endpoints (some perhaps downstream of each other) to capture the duration and secondary consequences of any initially induced effects.

b) Cumulative Risk Assessment Involving Chemical and Non-Chemical Stressors

The “top down” biomarkers methodology discussed in my response to question 2 I think is a useful addition to the current discussion of this issue in the document. Biomarkers like birth weight naturally integrate the effects of all kinds of conditions—including individual medical conditions; differences in exposures and other factors associated with prevailing racial categories; socioeconomic factors, etc. I have recently done an analysis of this kind in the context of a community military facility (Hattis, 2001):

Hattis, D. (2001) “How have Birthweights in Massachusetts Changed from 1990-1997 and Why?” Appendix C in Ryan, L., Schwartz, J., Goble, R., and Hattis, D. Technical Advisors’ 3rd Report (2000-2001). Research on Health and Environmental Exposures. Massachusetts Military Reservation Harvard University and Clark University, 2001.

c) Cumulative Risk Assessment Involving Different “Types” of Risk

I think uses of common metrics can have some value but only when it is accompanied by (1) accommodating those people who may not completely buy the relative tradeoff valuations used in the common index by providing the disaggregated effects (e.g., mortality, various kinds of morbidity, disability and/or loss work days and days of restricted activity, and (2) good attention to equity issues by breaking down the relative burdens on different subpopulations if there are appreciable differential effects.

Specific Observations (other than those covered in the comments above)

p. ci, 3rd par, 2nd line. The goal is stated here as “reducing” uncertainty. I think that as a general matter, a good analysis will “clarify” uncertainties but not generally “reduce” stated uncertainties from naïve statistical calculations.

p. 8—here is where a strong distinction needs to be made between “bottom-up” and “top down” analyses of cumulative effects (see above discussion).

p. 9, last paragraph. Some more detailed description of the Bogen (2001) would be helpful, perhaps as an appendix. The document repeatedly refers to this work, but it is not readily available, so the reader has very little clue to what exactly is being cited.

p. 10, line 28—I would refer to risk “analysis” rather than risk “assessment” here, in order to preserve “assessment” as a relatively technical exercise.

p. 16 (bottom)- p. 17—here is where I would describe an important goal as to identify options for control/abatement of hazards/risks. This also deserves emphasis in the box on page 23

p. 31 (box) I would say that distributions of hazard index values are not the only option for non-cancer effects. Analyses for criteria air pollutants, for example, have done extensive quantification of non-cancer effects, largely from epidemiological data. In addition, I have recently proposed an alternative to the standard RFD procedure that I think provides a feasible

starting point for quantitative risk assessment for more general non-cancer effects. See, for example:

Hattis, D., Baird, S., and Goble, R. "A Straw Man Proposal for a Quantitative Definition of the RfD," in Final Technical Report, U.S. Environmental Protection Agency STAR grant # R825360, "Human Variability in Parameters Potentially Related to Susceptibility for Noncancer Risks," Paper presented 4/24/01 at the U.S. EPA/DoD symposium on Issues and Applications in Toxicology And Risk Assessment, Fairborn, Ohio. Full version available on the web at <http://www2.clarku.edu/faculty/dhattis>; shortened version Drug and Chemical Toxicology, in press.

Hattis, D., Banati, P., and Goble, R. "Distributions of Individual Susceptibility Among Humans for Toxic Effects--For What Fraction of Which Kinds of Chemicals and Effects Does the Traditional 10-Fold Factor Provide How Much Protection?" Annals of the New York Academy of Sciences, Volume 895, pp. 286-316, December, 1999.

Hattis, D. "Strategies For Assessing Human Variability In Susceptibility, And Using Variability To Infer Human Risks" In Human Variability in Response to Chemical Exposure: Measures, Modeling, and Risk Assessment, D. A. Neumann and C. A. Kimmel, eds., CRC Press, Boca Raton, FL, pp. 27-57, 1998.

These references could also be cited and/or discussed at the top of page 36. Also because the first two are examples of the simultaneous treatment of uncertainty and variability, they could be mentioned on p. 45 lines 14-19.

p. 38, line 32. The document needs to distinguish the concepts of individual threshold doses (doses that will not affect a single person in a particular way) and population thresholds (doses that will not affect anyone in a large mixed population of people with different individual thresholds.)

p. 45, lines 35-36. I don't agree that it is generally adequate to characterize only risks to people who are "reasonably maximally exposed". A population approach is generally much better because helps managers face the societal aggregate consequences of their actions while also illuminating the full distribution of expected risks among diverse people.

p. 48, line 22. I disagree that the state-of-the science is not yet advanced enough to allow biomarkers such as birth weight and some others a place in current risk analyses.

p. 59, lines 14-18. You should also give other examples of the simultaneous treatment of variability and uncertainty, such as my work on cancer risks from genetically acting agents:

Hattis, D. and Barlow, K. "Human Interindividual Variability In Cancer Risks--Technical And Management Challenges" Human and Ecological Risk Assessment, Vol. 2, pp. 194-220, 1996.

p. 59, line 36. "most probable estimates" of cancer risks are almost never of primary interest. Even if you want to do cost benefit analysis it preferable to use arithmetic mean population "expected value" estimates, which can differ from "most probable" estimates by many fold. See:

Hattis, D., and Goble, R., "Expected Values for Projected Cancer Risks from Putative Genetically-Acting Agents," Risk Analysis, Vol. 11, pp. 359-363, 1991.

Review by
Joann Held - New Jersey Department of Environmental Protection

Written Comments on the Draft Framework for Cumulative Risk Assessment Submitted by Joann Held, NJDEP

General Impressions

The draft document is well written and thorough (with the exceptions described below). I intend to make it required reading for all members of the workgroup that my Agency is presently forming to oversee a cumulative risk assessment in South Camden, NJ.

The introductory section does a good job of saying what the Framework is and is not intended to be. There should also be a discussion of the future of the Framework. Is it a living document? Will there be future editions and/or updates?

The example boxes have been well chosen to illustrate the points being made in the text and should be especially helpful to nontechnical readers.

Breaking down the Risk Assessment into 3 phases (Planning, Scoping & Problem Formulation; Analysis; Risk Characterization) is a useful way to organize the document. And representing the phases with a logo is an interesting approach. However, you never explain why the arrow in the logo flows in both directions. Is this to indicate some type of iterative approach, where you could get to the Risk Characterization and then find that you need to reformulate the problem? Or is it simply to imply that the 3 phases are interrelated and you need to keep the other phases in mind as you work on each one?

Appendix A regarding Research and Development Needs is helpful, but there should be a discussion in the Introductory Chapter or at the end of each of the Phase Chapters regarding development of these new tools. Who is responsible for doing this? How will we learn about them? Will there be a series of follow-up reports after this Framework document that tell us how EPA, et al are doing at filling in the gaps?

Some discussion regarding the following topics should be included in the Analysis Phase discussion in the Framework document.

1. The times when using an iterative approach might be helpful, e.g. screening risk assessment to focus on a smaller set of chemicals of concern followed by a more refined risk assessment using the shorter list.
2. The complimentary role of monitoring and modeling data, especially the complexities of using data derived by both means in the same analysis.
3. Special problems related to ecological risk assessment.

Response to Charge Questions

Scoping Phase: The terms “Routes” and “Pathways” are used often in this part of the report. The distinction between the two is not completely clear from the way they are used in the text. They should be defined more completely somewhere in this section and also added to the Glossary.

Analysis Phase: General Comments

1. There should be a step built into the early part of this phase for data collection. Where are the data coming from? Do they already exist? Will there be literature searches? Ambient air monitoring? Blood testing? Adequate time must be set aside in the analysis plan to collect this information.
2. The Analysis Plan should also include a schedule showing how long each step will take and what efforts can be carried out concurrently.
3. Would it be reasonable to add pregnant women to the list of susceptible populations (p. 35st paragraph)? This group would be especially important when stressors in the assessment are likely to result in adverse developmental effects. In my program we often shorten the exposure timeframe of interest if we are concerned about the pregnant population.

Analysis Phase: Available Methods & Approaches

I have seen an approach suggested for predicting risk of exposure to multiple noncarcinogenic chemicals which might be of use here, but I have never seen it used in a final assessment. I wonder if any of the other Peer Reviewers have seen it and might recommend that it be described in the Framework. The basic idea is that although Reference Concentrations have been set for a single endpoint or critical effect, many times the substance in question will have evidence of less critical effects at higher concentrations. For these less critical effects, something like a Reference Concentration (call it a pseudo RfC) could be developed. Then when Hazard Quotients are being added to get a Hazard Index for each target organ or critical endpoint, these additional health endpoints could be considered. For example, the RfC for methyl ethyl ketone is based on fetotoxicity. However, it also has irritant effects. If it is included in a cumulative risk assessment with a number of other irritants, a pseudo RfC for MEK could be developed so that this effect would not be lost in the analysis.

Analysis Phase: Decision Indices

On p. 44, it is noted that the actual value of HI is not that informative all by itself. It might be helpful to elaborate by giving as an example Reference Concentrations (or Reference Doses). These health benchmarks have uncertainty factors (UF) that can vary from about 3 to 1000. If the UF is only 3, then an exposure prediction that is just a little bit above the RfC is more interesting than it would be for a pollutant with a UF of 1000.

Analysis Phase: Areas of Complexity

The discussion of Qualitative Approaches for comparing across stressors in Section 3.3.4 is very helpful. Without this section, the full scope of cumulative risk assessment envisioned by the framework could not be achieved; we would be limited to evaluating only those risks that we can quantify.

Risk Characterization Phase: Uncertainty

1. It is important not to let the Uncertainty Analysis overwhelm the Risk Characterization Phase. Some balance must be maintained in preparing the risk characterization in order to keep the uncertainty analysis from paralyzing the project (as per the EEA lesson “Avoid paralysis by analysis...”)
2. Discuss the acceptability of an uncertainty analysis that simply identifies the assumptions that would lead to an overestimate of risk and those that would lead to an underestimate, and

- tries to draw conclusions about which side of the scale the risk assessment is likely to be on.
3. The Framework might recommend that some standard statements of uncertainty be developed as a starter set for use in cumulative risk assessment. For example, the uncertainty associated with Unit Risk Factors (or slope factors) for known human carcinogens vs probable carcinogens vs possible carcinogens could be described in general terms in one place that we could all access and then it could be elaborated on as necessary within a given risk assessment.
 4. For Reference Concentrations (and Reference Doses) is it sufficient for the uncertainty analysis to simply review the uncertainty factors that were selected for each RfC?

Risk Characterization: Risk Description

Could there be a clearinghouse of studies related to combined risk of exposure to two or more substances such as those described by Kodell and Chen (1994) and referenced in section 4.2.3? Perhaps this could be a recommendation of the Framework or could be added to Appendix A.

Specific Observations

Chapter 3

In addition to the changes to the Section headings that I suggested during the Peer Review session, it would be helpful to have some transitional sentences at the beginning of each subsection introduces the content of that section. For example, at the beginning of Section 3.2.1.1, it could be stated that some aspects of estimating risk could be more complex in the context of a Cumulative Risk Assessment. These aspects include: variation of exposure with time, vulnerability related to differential exposure, and subpopulations with special exposures.

Page 34, Text Box: Some Examples of Exposure Models Which Consider Time Aspects
There is a typo in the second to last line. I believe that the acronym for the American Crop Protection Association should be ACPA.

Section 3.2.2.3 Decision Indices

- a) Could you define “high dimensional matrix” and “high dimensional graphical presentation” or replace them with a term that is more commonly used? By high dimension I assume that you mean more than two. Is that correct?
- b) The discussion of severity categories (p. 44, 3rd paragraph) is not clear. Is this the same as ranking exposures as High/Medium/Low and then doing a statistical analysis of all rankings for all the stressors in the analysis?

Section 4.2 Uncertainty Analysis

Three of the Morgan & Henrion “Ten Commandments” are highlighted in this section, but the numbering in the text doesn’t seem to match the numbering in the box. As I read it the discussion is about:

- #4. Identify all significant assumptions
 - #6. Be explicit about uncertainties
 - #7. Perform systematic sensitivity...
- The text, however, refers to # 6, 7, and 8.

Page 60, Line 30: There is a word missing. The line should probably read: “it should be transparent...” or “it must be transparent.”

6. REFERENCES

USEPA (2001d): The web address is wrong. I think it should be the following. Note that watershed is singular. <http://www.epa.gov/owow/watershed/lessons/top10.pdf>

APPENDIX D: EXAMPLES OF ANALYSIS PLANS

The Framework should make it clear that these are outlines of analysis plans.

**Review by
Paul Locke - John Hopkins University**

**EPA's Draft Framework for Cumulative Risk Assessment
Pre-Meeting Comments**

Paul A. Locke
Visiting Scholar
Johns Hopkins Bloomberg School of Public Health
Baltimore, Maryland
30 May 2002

General Impressions

- The Framework would be strengthened if it contained a comprehensive discussion of when and how Cumulative Risk Assessment (CRA) should be used.
- It would be helpful to include additional information about how to integrate traditional health risk assessment (as outlined in the 1983 Red Book) and ecological risk assessment (as set out in EPA's guidance documents) with CRA.
- The population focused approach described in the Framework seems to be appropriate for CRA and has the potential to provide focus to the CRA process. It would be very useful to include additional guidance about how to choose the "right" population(s).
- The Framework document should more fully explain the differences between the CRA called for in the Food Quality Protection Act (FQPA) (with mode of action as the trigger) and the CRA outlined in the Framework (which is broader in approach and scope).
- It appears that the conceptual model building exercise is central to the CRA. It will define the scope of the RA and drive the questions that are pursued. Accordingly, it is probably worthwhile to expand the discussion of this step.
- Throughout the Framework, but especially in the analysis phase, there is a need to spell out when default assumptions could be applied and how to apply them.
- The section about combining risks should be substantially redrafted. It now begins with a focused discussion about some of the methods available for cumulating risk metrics and methods to measure the impact of chronic disease. Instead, it should first cover the threshold question of whether it is even feasible to attempt such a combination. In other words, a preliminary, broader discussion should first examine the question of whether risks can even be combined in such a fashion. This discussion should be followed by an analysis of ways in which qualitative approaches can be applied to combining risk. Finally, quantitative approaches (such as HQ and TEF) should be discussed followed by an introduction to QALYs and DALYs. Given what precedes this section, it seems important to recognize that quantitative approaches may not be available, and that qualitative risk combination might be the most appropriate method of thinking about risks.
- Throughout the document it would be useful to emphasize that it is sometimes better to lay out the information descriptively in a narrative form and recognize that, because of analytical limitations, it may not be amenable to quantification.

- The risk characterization section should emphasize transparency and full disclosure. In other words, items should not be dropped from the conceptual model merely because they cannot easily be reduced to a summary risk metric. The Framework indicates that the CRA document is a decision-making document and it is therefore important that all relevant information be provided to the decision makers.
- The Framework should include a fuller discussion about public health surveillance, epidemiology, chronic disease endpoints and health tracking, and encourage the use of available human disease endpoint data.

Response to Charge Questions

1. *Comment on whether the Framework adequately captures, describes, and reasonably organizes the key issues for cumulative risk assessment so as to serve as an adequate foundation for the development of future guidance. In your comments, please address each of the following questions. In answering each question, provide a supporting discussion that highlights any areas of the Framework that may need to be clarified and relevant topics that may be missing from the current Framework document. Include references to any published literature that could help improve the completeness and clarity of the Framework.*

I think the Framework is a good start and incorporates a useful approach to cumulating risks. It is heavily slanted to human health risks, and could benefit from a fuller discussion of ecological risks and the ecological risk assessment paradigm.

a. Does the Framework document capture the relevant terminology?

As far as I can tell, the Framework seems to capture a substantial body of the relevant terminology. It could benefit from a fuller discussion of biomarkers (one that covered the full range of biomarkers, including biomarkers of susceptibility and markers of early disease) and an expanded section on public health surveillance, epidemiology and chronic disease tracking.

b. Does the Framework document capture an adequate assessment structure?

Although there are pieces of the structure that require clarification, I believe that the structure presented in the framework is adequate. I think two of the strengths of the Framework are its flexibility and its broad scope.

c. *Does the Framework document outline the relevant methods for cumulative risk?*

The Framework presents a workable context for CRA, and allows flexibility so that a number of relevant methodologies can be applied. In some places, additional guidance and discussion would be useful. For example, I think the Framework should include a fuller discussion regarding the application and use of default assumptions, and qualitative methods for combining or cumulating risk.

2. *Does the Framework document include any scientific or technical inaccuracies in its presentation of terminology, assessment structure, and methods? Please identify any problem areas and propose revisions or other actions that will result in a scientifically sound and supportable discussion. With respect to methods, comment on whether the Framework adequately covers the state of the science with respect to currently available cumulative risk assessment methods/approaches and the areas that are in need of further research and development.*

As discussed above, there are certain parts of the Framework that I feel would benefit from an expanded discussion and sharper focus. For example, it would be useful to include a fuller description of biomonitoring and biomarkers, human health surveillance data (chronic disease tracking), epidemiology and ecological stressors. (Please refer to the specific comments contained in this document).

3. *Uncertainty analysis is an important aspect of risk assessment (and policy analysis in general). However, historically, dealing with uncertainty has been a shortcoming of many assessments. Cumulative risk assessments present new challenges for uncertainty analysis. For example, assessing cumulative risks will involve combining data of varying quality. Perhaps more important, assessing cumulative risks will involve the use of “soft” assumptions. These are assumptions which may have a high degree of uncertainty that is difficult (or not possible) to quantify. Comment on whether the Framework adequately characterizes the importance of uncertainty analysis in cumulative risk assessment. What additional discussions of uncertainty should be included in the Framework (and in what sections of the document)?*

I think that the issue of uncertainty is most effectively examined in the context of the specific CRA. Methods exist for describing certain uncertainties in traditional, single substance risk assessments; it would be useful to reference them in the Framework in a text box. (The text box on page 59 provides an example of where uncertainty analysis was applied, but it does not talk about uncertainty methodology.) These should be applied, if possible.

In some situations, it is likely that uncertainty will be amenable only to a narrative description. I believe that the Framework should explicitly acknowledge that some uncertainty in the CRA process is likely to be unquantifiable, but can nevertheless be described in narrative form. The Framework should acknowledge that in such cases it

is still appropriate to move forward with the CRA, as long as these uncertainties are transparent to the decision makers. Information should not be lost or abandoned because a quantitative methodology to explain attendant uncertainty is not available.

4. *The following topics have been identified by the RAF technical panel as technically difficult areas that will pose challenges to cumulative risk assessment. Comment on the adequacy and accuracy of the Framework's presentation in each of these areas.*
 - a. *Vulnerability – As applied to cumulative risk assessment, it is useful to think of four components to vulnerability: the susceptibility or sensitivity of the human or ecological receptors; the differential exposures of the receptors; the differential preparedness of the receptor to withstand the insult from exposure; and the differential ability to recover from these effects. The issue for cumulative risk assessment is how to consider these aspects of vulnerability and their potential impacts on risk. This is highlighted in the Framework as an issue in need of further research and development. Comment on the discussion of vulnerability in the draft Framework. Has the state of the science been captured in this discussion? How can the discussion of the issue be improved?*

I think that the Framework would benefit if at least a portion of the vulnerability discussion were put in the context of choosing the target population. For example, assume that a CRA was carried out for a target population that was made up of a significant portion of children, or of the infirm elderly, or of immune compromised individuals. In these cases, the vulnerability question is “built into” the choice of the target population. The Framework might benefit from a text box that addresses the question “Should populations with specific vulnerabilities be targeted for CRAs?”

- b. *Cumulative Risk Assessment Involving Chemical and non-Chemical Stressors – Viewing cumulative risk assessment as an evaluation of the accumulation of stressors presents many challenges. These may be seen when attempting to combine, in some meaningful way, the risks from multiple chemicals that may act as synergistic, antagonistic, or additive doses leading to a single effect. The situation is exacerbated when non-chemical stressors (e.g., radiation, biological agents, and psychological stress) are considered. Comment on the Framework's discussion concerning the combining of disparate environmental stressors. In commenting, consider the state of the science with respect to understanding the effects of different stressors acting together (e.g., chemical exposure and viral infection). What can be added to the Framework to adequately convey the state of the science in this area?*

As I mentioned earlier in this document, one of the strengths of the Framework is its flexibility. The Framework can also be seen as a “technology forcing” approach, in that it will encourage the asking of scientific and policy questions for which we do not yet have answers. The aspect of cumulating disparate risks – the topic of this question

and the next one – is one place where the Framework is likely to stimulate the posing of hard questions that will push risk assessment methodology (and data collection) forward. We must not forget that this could be a very good thing.

Although the approach taken in the Framework is a good start, I think that the Framework should address the issues of cumulating and combining risks in a broader fashion, as I explained above. Two threshold questions -- (1) Whether risks should be cumulated and (2) How best to combine and cumulate them -- should be addressed first.

- c. *Cumulative Risk Assessment Involving Different “Types” of Risk – Conveying the combined risks from multiple chemical and non-chemical stressors, in a meaningful way, is the ultimate challenge for cumulative risk assessment. Experience in this area is extremely limited. Indices, common metrics (e.g., Disability Adjusted Life Years – DALYs) and graphical (e.g., GIS) approaches have been explored but much methods development work remains to be completed. Cumulative risk assessment can be a valuable part of the decision making process, but only if the results are conveyed in a meaningful way. Comment on the Framework’s discussion concerning the combining of disparate measures of risk. Do the example approaches discussed capture the state of the science in this area? In particular, consider the role of valuation (i.e., the assignment of societal values to disparate health outcomes) implicit in some of the approaches. Suggest changes that may improve this discussion.*

Please refer to my comments set out above under question 4(b).

Specific Observations

- The biomarkers and biomonitoring section should be strengthened. A fuller discussion of biomarkers and biomonitoring needs to be added (beyond the discussion of markers of exposure). In addition, a discussion of CDC’s NHANES program and NIEHS efforts in this area should be added.
- The discussion on page 48, and citations that accompany it, should be updated. The Pew Environmental Health Commission reports and materials are now available at the website of Trust for America’s Health (healthyamericans.org). In addition, this discussion should expand upon the potential uses of chronic disease tracking information, epidemiology and public health surveillance in CRA.
- The Framework should make it clear when it is appropriate to reduce a series of risks or risk measures to a common metric. (See §3 generally, especially §§3.3.3 and 3.3.3.1). The Framework should add a detailed discussion about when combining risks using a quantitative method is appropriate and inappropriate. In every case, the underlying data should be provided.
- In Section 4.3.2, a much broader discussion of the public health context should be provided. It could include an examination of the precautionary principle. Some users of CRA might also want to adopt the precautionary principle as a

- guidepost for decision making.
- The appendix on background exposures should examine the policy implications of how such exposures are addressed. One default approach could be to assume that any risks posed by background should be added to, or cumulated with, similar risks and that human-made exposure risks should be controlled first. For example, if a person is exposed to naturally occurring radiation such as radon in her home, and also receives radon exposure from a source in her community, such as a uranium mill tailings pile, one approach would be to “add” the radiation risks from these two sources and focus on controlling the risks from the human-made source first. Similarly, it could be acknowledged that human created “background” risks, if they are significant, need to be reduced.

**EPA's Draft Framework for Cumulative Risk Assessment
Post-Meeting Comments**

***Paul A. Locke
Visiting Scholar
Johns Hopkins Bloomberg School of Public Health
Baltimore, Maryland
2 August 2002***

Overview

I am submitting these post-meeting comments to supplement the pre-meeting comments (dated 30 May 2002) that I submitted previously.

References

I have provided an annotated bibliography along with these comments. I hope that EPA can consider these sources in re-drafting and amending the Cumulative Risk Assessment (CRA) framework.

General Impressions

I concur with the definition, approach and scope of the CRA framework that EPA introduced at the meeting. I believe that the most important points are:

- The CRA framework is a document that seeks to learn from on-gong EPA experiences and offer a flexible strategy for carrying out a CRA. It is not a guidance document in that it does not provide detailed technical guidance. Nevertheless, it will serve as the basis for developing future guidelines.
- The goal of a CRA is to formulate, address and hopefully answer questions about multiple harms acting together.
- The CRA approach is a “community-first” approach in that it starts by identifying an impacted or potentially impacted population or community, its public health problems and health status. It then looks at the risks the community confronts that may be related to its health status. I think that this is one of the most important points to emphasize in the CRA framework.
- CRA has methodologic limitations, and it is important to identify them and discuss them transparently. Still, limitations in methodology should not be seen as reason for ignoring or not posing questions for which communities seek answers.

Additional Specific Comments (organized by CRA Framework section)

Section 2.2.2 -- Conceptual Model. This section of the report could be expanded to include additional information about ecosystems and ecosystem stressors. (I believe that other commenters will discuss this issue in more detail.)

New section 2.4 – From Scoping to Analysis. Consider adding a new section here that discusses the transition between these two areas, and focuses in particular on any questions posed in the scoping phase that cannot be addressed in the analysis phase. (Lack of an appropriate methodology is one reason that certain questions cannot be addressed.)

Section 3.3.3.1 – Creating a Common Metric. In this section, and in other parts of chapter three, it would be very useful to describe qualitative as well as quantitative ways of cumulating or bundling risks.

Section 3.3.2 -- Biomonitoring and Biomarkers. This is an area where some additional work needs to be done. In particular, the CRA Framework should discuss the ENTIRE SPECTRUM of biomarkers, including biomarkers of exposure, effect and susceptibility. As it currently stands, the CRA Framework focuses on biomarkers of exposure. As discussed at the meeting, the CRA Framework should also discuss the limitations of biomarkers and biomonitoring.

Section 4.2.3 – Uncertainty and Risk Addition. This section is incomplete because it only discusses the possible issues associated with over estimating risks. It should begin with an explanation of why we use conservative risk estimates (to be public health protective) and the possible ways that we can underestimate risk. Risk addition should be presented more fully. It is possible that it can overestimate risk; it is also possible that it underestimates or mischaracterizes risk.

Section 4.3.2 – Cumulative Risk Assessment in a Public Health Context. This section should be written from the perspective of the population at risk. It should emphasize that public health protection is a key feature of cumulative risk. As currently drafted, it is overly negative. It should focus on the potential of cumulative risk assessment in improving the public health information that will be available to communities.

New Section 4.5 – Communicating Results of the Assessment. Communities will vary substantially, and have different communication needs. As one commenter pointed out, it is essential that EPA use culturally appropriate language and methods. This new section should describe some of the “basics” of risk communication, and also provide information about the need to be sensitive to cultural and ethnic differences.

Annotated Bibliography

1. CDC NHANES – <http://www.cdc.gov/nchs/nhanes.htm>. The NHANES data and its uses and limitations should be discussed in the CRA Framework. One of the purposes of NHANES is to collect appropriate biomonitoring data to develop reference ranges of compounds. These reference ranges could be useful for communities concerned about their exposure to certain compounds, and could help answer the question “Is my exposure ‘normal?’”
2. Environment and Human Health, Inc. Children’s Exposure to Diesel Exhaust on School Buses (2002). This report is available for downloading at www.ehhi.org. The report summarizes the results of an ambitious study (undertaken in connection with Yale University) that looks at children’s exposure to diesel fuel on and from school buses. I think it is a good example of an aggregate exposure analysis and the type of study that communities interested in asthma and impaired lung function would find compelling.
3. American Lung Association. Urban Air Pollution and Health Inequities: A Workshop Report. Environmental Health Perspectives 109 (Suppl. 3) June 2001 (available on-line (if you subscribe to ehp on-line) at <http://ehp.niehs.nih.gov/>). This workshop focuses on the disproportionate impact of air pollution on certain populations, and is useful in showing why and how a population-based approach is important.
4. Hulka, Barbara S., Wilcosky, Timothy, and Griffin, Jack. Biological Markers in Epidemiology. (Oxford University Press, 1990). This is a somewhat old, but still useful, fundamental text on biomarkers. It is written from the perspective of molecular epidemiology, and explains different types of biomarkers and how biomarkers can be used. More recent texts (such as the one written by John Groopman) are also useful.
5. Institute of Medicine. The Future of Public Health (National Academy Press, 1988). This is an essential text in public health and is useful for the CRA framework in at least two ways. First, it discusses the bifurcation of public health and environmental protection (and health) (see pages 110 – 111), a problem that the CRA framework can directly address. Second, it sets out the core functions of the government in public health (pages 43 – 47), which should be referenced in the CRA Framework’s discussion of public health.
6. Michael Siegel and Lynne Doner. Marketing Public Health (Aspen Publishers, Inc. 1998). This is a useful text, especially for formulating a strategy for communicating public health messages such as the information produced in a CRA.

7. Chris F. Wilkinson. Cumulative Risk Assessment: The State of the Science (Draft). Paper presented at the ILSI Cumulative Risk Assessment Workshop, September, 1998. This paper could be valuable in helping to describe common metrics and risk additivity. It goes through a series of examples using the TEF, MOE and HI, showing their similarities and differences. (I don't know if this paper was ever finalized. I would be glad to provide a copy to interested parties.)

**Review by
Margaret MacDonell – Argonne National Lab**

U.S. Environmental Protection Agency, Risk Assessment Forum
Framework for Cumulative Risk Assessment
EPA/630/P-02/001A, External Review Draft, April 23, 2002

Peer Review
Margaret MacDonell
Argonne National Laboratory, Environmental Assessment Division

General Impressions

This document represents a major step forward for the field of environmental risk analysis, which until now has been rooted in single-chemical approaches that have ineffectively addressed real-world conditions and community concerns. The report provides an excellent overview of the key challenges involved in assessing cumulative risks and lays out a sound framework for addressing those challenges. It is very well organized and well written, and it answers a critical need at a time of increasing public attention on multiple sources, stressors, exposures, and effects. It is also noteworthy for the many complex topics discussed and inclusion of illustrative examples. The report is impressive for its broad-based flexibility designed to accommodate a variety of applications, including those extending beyond the regulatory purview of the agency. Through this general umbrella communities will have a means of filling in the gaps created by the piecemeal coverage of existing legislation, to incorporate in their risk assessments those elements with potentially significant impact that could otherwise fall through the cracks.

This framework represents a remarkable achievement not just for its advancement of the technical risk assessment field, but for the extensive input that has been solicited during its development from a wide range of parties with various perspectives. The product has clearly been enhanced by this open process. The further value of this framework is that it provides a coherent basis for much closer integration among currently distinct (and sometimes inconsistent) programs and approaches for evaluating multiple hazards. Such a basis has been sorely needed to guide the explosion of new research in this area, made possible by technology developments unimaginable until recently that have allowed us to study the human body and impacts of our environment with an ever finer eye, moving from the system and organ levels to proteins and genes, in pursuing better understanding of the cumulative effects of multiple stressors by multiple routes over our lifetimes. It also provides a structure within which we can integrate analyses across different risk types, from human health and ecological risks to economic and sociocultural risks, as we continue to better understand the interconnections among these different areas.

A comprehensive framework such as this can guide the more realistic assessments and predictions of cumulative risks that are essential to effective human health and environmental protection programs. The authors are to be strongly commended for the high quality of the report and the sustained dedication required by this complex task. I look forward to implementing the framework as it is filled in with specific methods and information over the coming years.

Charge Questions

1. *Does the Framework adequately capture, describe, and reasonably organize the key issues for cumulative risk assessment so as to serve as an adequate foundation for the development of future guidance?*

Yes, the key issues have been capably identified and organized, and the framework provides a solid foundation upon which future guidance can be developed. In fact, it is precisely because it is so good and so relevant that many have wanted it to be extended well beyond this foundation phase, asking for the frame to be filled with pieces of the puzzle needed to directly implement a cumulative assessment. Recognizing that the aim of this document is to simply establish the necessary first step (as clearly stated in a number of places), it is a compliment to its effectiveness that it has inspired expectations for so much more, which makes the desire for the next phase even stronger.

- a. *Does the Framework document capture the relevant terminology?*

Yes, the document captures relevant terminology, and inclusion of a glossary is commendable. It might be helpful to revisit this glossary to provide a more internally consistent set of practical definitions for terms that directly focus on cumulative risk. Also, the definitions of certain terms are confusing (such as stressor and vulnerability), and per various field inputs I consider it important to integrate sociocultural and economic risks with health and ecological risks in an “integrated multiples” cumulative risk assessment framework. (See related notes under Specific Comments.)

- b. *Does the Framework document provide an adequate assessment structure?*

Yes, the general assessment structure is quite good and effectively incorporates constructive elements and principles of previous work. While a wide range of cumulative risk assessment scenarios exists, several core concepts will be common to many applications, and the framework provides a good overview of those concepts. The framework is also well organized according to the three basic parts – planning, scoping, and problem formulation; analysis; and interpretation – which provide a clear backbone for the report. Further, an outstanding effort has been made to accommodate a variety of technical backgrounds by walking readers through basic components of the assessment process, illustrating key points, explaining terms, and providing a general “roadmap figure” to indicate where each section fits. (The communication of this information could be even further improved if certain figures were refined for greater readability and consistency.)

In addition, active solicitation of broad stakeholder input is crucial to a balanced and widely responsive community-based assessment. In many ways “public involvement” has changed over the past 10-15 years, as many community members have stepped away from active engagement in the environmental assessment and decision-making process. Without an effort to solicit full input, the expectations and desires of a sometimes very large silent majority can go unreported, causing the objectives, conduct, and outcome of an assessment to be skewed toward a small but vocal subset of an affected or interested population group. Another point for stakeholder involvement: as effectively expressed by a Native American storyteller at a State and Tribal

Forum on Risk-Based Decision Making (sponsored by DOE in 1995), consensus means every voice that wants to be heard is heard. It does *not* mean that decisions will be held captive until unanimous approval is reached. This framework does an excellent job of identifying the importance of stakeholders to the assessment process.

c. Does the Framework document outline the relevant methods for cumulative risk?

Yes, the document indeed identifies a number of methods, outlining some more than others, and also highlights a variety of very nice examples in text boxes. It would be helpful if the direct relevance to cumulative risk (i.e., beyond risk assessment in general) could be emphasized. This could be achieved via a summary table, where targeted methods or adaptations of standard methods are distinguished per their unique applicability or features relevant to cumulative assessments. It would also be helpful if general rules of thumb could be captured in “thumbprint” text boxes. (For example, this could include screening secondary effects that are >5 to 10 times higher than the critical effect, or where an interaction is indicated, by applying a default interaction magnitude of 5 as modified by relative exposure levels of other chemicals – as well as general rules of thumb related to contaminant fate and transport and distinction from “background” levels).

Further, it would be helpful if the framework further stressed the importance of jointly identifying sources/stressors and pathways/exposure routes, subgroups potentially at risk or increased risk, effects, and the potential for interactions early in the planning, scoping, and problem formulation phase, as interconnections will affect the selection process. Also very important to the timely and efficient completion of cumulative risk assessments is the use of phased analyses that begin with screening approaches. This topic could benefit from more treatment.

For example, in screening to focus the cumulative assessment for health risks, contaminants can be grouped according to their opportunity for interaction both in terms of environmental fate and exposure potential, and in terms of toxicological interactions once taken in by a receptor. It is important to emphasize the use of realistic exposure scenarios for predictive estimates versus high-end hypothetical scenarios. Current and projected environmental co-location of stressors can be evaluated by testing predictive models with hind-casting or history-matching calculations, modeling forward from past measurements to determine if predictions match existing data. Concentration-toxicity screens and comparisons to benchmarks can also be used to narrow the set of stressors to a reasonable core number for the initial phase of the assessment.

For the toxicity component, different combinations of mode/mechanism of action, target system/organ, and effect endpoint can be considered in determining where adverse effects may be increased by multiple stressors and exposures (e.g., all the same, different modes and same targets and effects, and different modes and different targets) to focus the assessment on those stressors most likely to increase adverse effects. And secondary effects can be considered in addition to critical effects, also accounting for severity, reversibility, and screening thresholds, as well as compensatory responses.

Further, methods exist to estimate sociocultural and economic risks, which can dominate certain cumulative assessments (including place-based assessments such as the Baltimore project and

assessment for federal cleanup sites, such as the Department of Energy Hanford site in Washington). Because these can be important assessment issues, the framework should be structured to accommodate them as a major components of a comprehensive cumulative risk assessment. For sociocultural and economic risks, the nature, severity, and duration of changes in public behavior and activities resulting from different types of events can be assessed based on historic data and somewhat similar circumstances, with special attention to methods for assessing values of nonmarket goods. Economic sectors (such as farms or fisheries) most likely to incur impacts based on historic concerns and data relevant to the assessment being conducted should be targeted for the screening assessment, recognizing that impacts can readily extend from the local to the regional scale. Capacity-building within local community groups can result in better information being provided for the sociocultural assessment. Finally, by including sociocultural and economic risk components, the framework can lay the groundwork for self-reporting (e.g., by groups that are often underserved), which can ultimately lead to better decisions and greater net protection.

- 2. Does the Framework document include any scientific or technical inaccuracies in its presentation of terminology, assessment structure, and methods? With respect to methods, does the Framework adequately convey the state of the science with respect to currently available cumulative risk assessment methods/approaches and areas in need of further research and development?*

The authors have done an outstanding job of providing sound, accurate information, and it is a technically strong report. (A few misinterpretations might result from somewhat unclear descriptions or slightly uncommon uses of certain terms, such as the discussions of vulnerability or stressors, but these will naturally be reduced as the process continues to move forward.)

With regard to the second question, I did not understand that this document was to convey the state of the science for relevant methods. To do so would in my opinion require a more extensive description of existing methods and approaches beyond what is presented here (which relies considerably on incorporation by reference and deferment to forthcoming guidance for full descriptions). A genuine state-of-the-science presentation would include explanations sufficient to readily allow implementation, indications of current “conditions of application” and limitations, and future outlooks. If it is desired to fully convey the state of the science for these methods and approaches then a companion compendium could be prepared. However, if this question is merely asking whether the document imparts a general feel for current methods and related research and development needs, then I would say yes. In many places the discussion of the current knowledge gaps and research needs is excellent (in others, such as biomarkers of exposure and effect, a slightly clearer discussion could even further strengthen the presentation).

- 3. Does the Framework adequately characterize the importance of uncertainty analysis in cumulative risk assessment? What additional discussions of uncertainty should be included in the Framework (in what sections of the document)?*

Different types of uncertainty have been nicely described, and the importance of this topic has been emphasized. It may help to also include an overview characterization of the unique aspects of uncertainty analysis for cumulative risk assessments. It is also important to emphasize that many uncertainties will likely remain unknown, and that especially for cumulative risk assessments it is essential to identify which uncertainties *that we can do something about* can significantly affect the results (considering sensitivity analyses) so efforts can be focused on those. It is useful to involved parties to explain that chasing all uncertainties or waiting until all are understood will likely translate to doing nothing (no decisions) for a long time. It is also important to note that the full set of nested uncertainties should be considered in evaluating dominant contributors to the overall system (including those propagated through individual analyses that are then combined) so true drivers can be identified. It is also important to distinguish between predictive and protective estimates, for example with regard to incorporating uncertainty factors, so these can be limited as appropriate where realistic predictions for practical decisions are the objective. It may also be helpful to identify as a research need the development of methods to communicate the results and uncertainties of these assessments to decision makers and other stakeholders (e.g., Steven Hanna's work at Harvard, George Mason, and soon back at Harvard), given that the aim of this framework is to guide assessments to their ultimate objective: better environmental decisions. Maxine Dakins (University of Idaho at Idaho Falls) has nicely captured in lay language the bottom line of environmental uncertainty and tools that exist to address it, including neural networks (with pattern recognition and feed-forward and feedback loops), system dynamic modeling (with non-linear simulations and feedback loops), and Bayesian decision networks (with iterative incorporation of experience and judgment). Dr. Dakins captures the dilemma in a quote from psychologist Erich Fromm: "The quest for certainty blocks the search for meaning." It is important that cumulative risk assessments focus on the decisions that need to be made, and that we identify those parts of the process where we can reasonably get better information that will matter for the decision. (Reference: presentation at the American Nuclear Society Spectrum 2002 meeting, Reno, Nevada, August 8, 2002.)

4. *What are the adequacy and accuracy of the Framework's presentation in each of the following areas? (These topics have been identified by the Risk Assessment Forum technical panel as technically difficult areas that will pose challenges to cumulative risk assessment.)*

a. *Vulnerability*

As applied to cumulative risk assessment, it is useful to think of four components of vulnerability: the susceptibility or sensitivity of the human or ecological receptors; the differential exposures of the receptors; the differential preparedness of the receptor to withstand insult from exposure; and the differential ability to recover from effects. The issue for cumulative risk assessment is how to consider these aspects of vulnerability and their potential impacts on risk. This is highlighted in the framework as an issue in need of further research and development. Comment on the discussion of vulnerability on the draft Framework. Has the state of the science been captured in the discussion? How can the discussion of this issue be improved?

The four components as written seem to confuse rather than clarify the vulnerability issue. Three seem to reflect characteristics of the receptor (including individual sensitivity/susceptibility), while one relates to the nature of the environmental setting and is important in identifying relevant population subgroup(s). Overlaps seem to exist among the definitions, and the distinction between individual and population also seems to be muddled in related discussions.

I would prefer a more traditional split into two categories: one dealing with the receptor and the other with the source-stressor-exposure setting. For the receptor, sensitivity or susceptibility relates to inherent characteristics including past exposures (body burden), as well as age at exposure and associated potential for differential effects. As a complement to this “internal” piece, characteristics of the “external” exposure setting will help guide the determination of what individual or group is most likely to incur exposures and associated effects. Both should be used to define the center of the bullseye for a cumulative assessment or to guide screening criteria. That is, the question about what makes a group vulnerable per existing stressors can also be turned around, to identify contributing stressors working backwards from observed effects. An early evaluation of potential target receptors can be useful in identifying sensitive subpopulations that can in turn help focus the determination of stressors warranting consideration.

b. Cumulative Risk Assessment Involving Chemical and Non-Chemical Stressors

Viewing cumulative risk assessment as an evaluation of the accumulation of stressors presents many challenges. These may be seen when attempting to combine, in some meaningful way, the risks from multiple chemicals that may act as synergistic, antagonistic, or additive doses leading to a single effect. The situation is exacerbated when non-chemical stressors (e.g., radiation, biological agents, and psychological stress) are considered. Comment on the Framework’s discussion concerning the combining of disparate environmental stressors. In commenting, consider the state of the science with respect to understanding the effects of different stressors acting together (e.g., chemical exposure and viral infection). What can be added to the framework to adequately convey the state of the science in this area?

The framework indicates that this research area remains open for development, and I agree. Some data and approaches are becoming available through innovative science and technology research and development projects, including in the areas of genomics, proteomics, and metabolomics. It might be helpful to tabulate progress that has been made and key gaps to be addressed (e.g., within the three-element organizational structure of this document, or per the four steps of the NRC paradigm). An example of what could be included in a summary text box of information needs/ongoing research at the end of the section relating to mixed exposures alone follow (summarized from the NIOSH National Occupational Research Agenda, external review draft July 2002).

- A more realistic representation of mixed exposures to improve basic input assumptions for the risk assessment models, and more effective approaches for distinguishing between risks

from occupational and ambient exposures and for determining which mixtures drive risk concerns.

- Improved mathematical models to better predict health risks from multiple stressors, especially formulas for extrapolating from in vitro to in vivo conditions; across exposure routes, durations, and sequences; and across mixture components and dose levels.
- Approaches for improving how variability is reflected in risk assessments, to replace the use of single default parameter estimates in predictive models, and for reducing uncertainties that significantly affect the risk outputs, for example by resulting in unrealistic bounding assumptions that limit the practical utility of results with regard to guiding interventions.
- More effective approaches for translating response information from emerging research, including molecular- and cellular-level studies (such as genomics and proteomics), into risk estimates meaningful to the whole organism, also considering compensatory responses, effect severity and reversibility, and recovery to evaluate net or effective health risk.
- Better methods for identifying deviations from dose and response additivity (such as where the severity of an effect exceeds that predicted from simple dose addition), and for extrapolating from existing data on specific chemicals or mixtures to develop general rules of thumb and default factors that can be applied to estimate risks from exposures to untested combinations.
- Improved approaches for incorporating multiple mixture toxicities into risk models where component characteristics vary, building on current methods that consider, for example, indicator chemicals, comparative potency, and combined pairwise interactions, and better methods for testing the validity of these approaches for estimating occupational risks.

c. Cumulative Risk Assessment Involving Different “Types” of Risk

Conveying combined risks from multiple chemical and non-chemical stressors, in a meaningful way, is the ultimate challenge for cumulative risk assessment. Experience in this area is extremely limited. Indices, common metrics (e.g., Disability Adjusted Life Years, DALYs) and graphical (e.g., GIS) approaches have been explored but much methods development work remains to be completed. Cumulative risk assessment can be a valuable part of the decision-making process, but only if results are conveyed in a meaningful way. Comment on the Framework’s discussion concerning the combining of separate measures of risk. Do the example approaches discussed capture the state of the science in this area? In particular, consider the role of valuation (i.e., the assignment of societal values to disparate health outcomes) implicit in some of the approaches. Suggest changes or additions that may improve this discussion.

I strongly agree that results must be presented in a meaningful way in order to be directly useful for decisions. However, this discussion seems to describe approaches without giving a clear explanation of why and when they should be applied, and without sufficient cautions regarding

lumping distinctly different risk estimates into a potentially meaningless number. It is important to retain all key risk results and consider how the discriminating information can be presented together, but as combined information captured in matrices or other multi-dimensional forms rather than as a single metric. For me, the downsides of a single-metric approach outweigh any imagined benefit from having one number.

Visualization tools including geographic information systems (GIS) are among useful methods for assessing cumulative risks, and they can also be effective in communicating results. Other methods include trend analyses, matrices, and indices, which can include weight-of-evidence or lines-of-evidence considerations as well as relative ranking approaches.

Specific Comments

Page xviii, line 26

Including the absence of a necessity in the definition of a stressor seems a bit odd. Absence of something such as an adequate habitat could certainly be considered *stressful*, but would seem not to represent a *stressor* as traditionally defined but rather a condition more appropriately identified as a risk modifier or susceptibility factor. (This comment also applies elsewhere, e.g., from page 2 footnote 2 to the glossary.) For example, a fire could result in the loss of a habitat, with the habitat being the “*stressee*” (and that condition can subsequently affect organisms aiming to live there) while the fire is the causal stressor. Perhaps it would be useful to consider a direct-indirect distinction here.

Page xviii, line 35

The definition of cumulative risk assessment as covering qualitative to quantitative representations of combined risks to health or the environment from multiple agents or stressors is very good, for it also captures economic and sociocultural risks per the definition of “environment” (the human environment) under the grandfather of our environmental regulations, the National Environmental Policy Act (NEPA). (Also see glossary comments regarding agent-stressor use, and additional related comments.)

Page xix, lines 12-14

The three phases of the framework are clearly identified and nicely described. It might be helpful at this first discussion of the planning, scoping, and problem formulation phases to note that the conceptual model would also establish initial population groups to be evaluated (including potentially susceptible subgroups, as may be affected by the stressors and effects of interest).

Page xix, lines 23-27

Given that risk characterization provides the bridge/overlap with risk management and this description invokes an evaluation to determine whether original objectives and goals were met (with risk managers having been identified as members of that team), it might be useful to emphasize here that the framework is intended to guide assessments toward useful decisions, i.e., it is outcome-oriented and not a general format for circular (or repetitive) evaluation, as this otherwise represents a potential tar pit if clear definitions of scope and timelines are not

developed at the outset. (Iteration is inevitable and appropriate, but up-front clarification of what is to be assessed and how the information will be used can be critical to limiting unrealistic expectations.)

Page 1, Figure 1-1

Figures are used in this document very effectively. One note: inclusion of “chemical” in the center circle here may seem redundant as it is included in the definitions of both agent and stressor. (Also, the differences between those two have not been clearly described, to explain why both are being used. Would agent be considered a subset of stressor?) (Same comment applies to Figure 1-2 on page 2). Note that language reflecting stressors as the umbrella category within which chemicals and other “agents” reside is nicely captured on page 7, lines 15-16: “... an assessment which covers a number of chemicals or other stressors ...”

Page 2, footnote 1 (and elsewhere)

‘... for traditional, chemical-focused assessments we say we conduct a “risk assessments for a certain chemical. In contrast, the essence of a cumulative risk assessment is that the assessment is conducted “for a certain population.’ Some might not see the same distinction between these two types of assessments as indicated here, as the population or population segment is also the basis for source-specific or chemical-specific assessments. That is, for those assessments we have generally conducted traditional risk calculations for *individuals* representing a population group (e.g., beginning with the maximally exposed and evolving to the reasonably maximally exposed individual and more central tendency estimates) that have simply considered chemicals one at a time rather than in combination with their associated potential interactions. This is what I see as the contrasting distinction – *interaction considerations and combined contributions to risk* from multiple stressors, sources, and routes. Also, neither are cumulative assessments limited to population- or place-based analyses (despite the suggestion that this term does not apply to those conducted for chemical classes, such as organophosphate pesticides). And for both traditional and cumulative assessments, the *individual* is still the basis of the non-cancer estimate for this threshold-related value (summing hazard quotients to an index for the traditional case, calculating an interaction-based hazard index for mixtures), and while the cancer risk estimate is based on population statistics it is still commonly reported as the risk for an *individual* (or set of individual receptors) representing whatever subgroup(s) have been selected for the given risk assessment situation. Perhaps it would be an option to describe Figure 1-2 as illustrating a “place-based cumulative assessment” that looks at how multiple stressors can act together on a group in a given area, with an indication that cumulative assessments are *often* of this type?

Page 4, lines 11-23

Inclusion of NEPA in this very nice historic progression is excellent, especially because that Act represents our first formal invocation of cumulative assessment from more than 30 years ago, but the description is misleading by explicitly leaving out impacts to human health. (Per CEQ’s implementing regulations at 40 CFR 1508.8: “Effects and impacts as used in these regulations are synonymous. Effects includes ecological (such as the effects on natural resources and on the components, structures, and functioning of affected ecosystems), aesthetic, historic, cultural, economic, social, or health, whether direct, indirect, or cumulative.”) Given that human health is

a key concern for many cumulative assessments and this framework emphasizes chemical risks to human health (e.g., see page 5, line 8), it would seem appropriate to add something to (e.g., at line 18) like "..., and impacts to human health as well economic and social resources." (This comment also applies to the text box on page 97.)

Page 6, lines 8-14

This is a nice summary of the context for this framework. It might be helpful to add a text box here that captures what this framework does and doesn't do, to further strike home its scope.

Page 7, line 12

Including in the definition of an agent or stressor "... the absence of a necessity such as habitat ..." is confusing to me (e.g., see related note for page xviii).

Page 8, line 33

The terminology here seems a bit non-standard? I have understood certain risk factors identified for breast cancer such as age at first childbirth to be not stressors themselves but rather modifiers. Taking another example, malnutrition that results in increased susceptibility to disease reflects a lifestyle-related risk factor (e.g., associated with poor diet per multiple contributors) that can affect one's subsequent response to a biological stressor, but here again malnutrition reflects the condition of the system (compromised or otherwise) when it is subsequently put to the test of a given stressor, rather than the stressor itself. Similarly, an increased likelihood of cancer death due to limited access to health care (such as is reflected in higher rates of cervical cancer mortality in certain areas of the southeastern United States) does not make access to health care a stressor. Rather it is a condition (here, societal rather than biological) that affects the ultimate outcome of a stressor, but it relates to the management and not the probability of the disease. The language being used in my opinion confuses the issue considerably; the fix would be straightforward (e.g., distinguishing between actual stressors and stress or risk factors or related descriptive indicators of stress or stress levels).

Page 9, lines 26-32

Columbia River Basin studies at the Hanford Site have also applied the "bottom up" approach, considering multiple stressors present and predicting effects that extend from human health and ecological risks to economic and sociocultural impacts (see, for example, <http://www.bhi-erc.com/projects/vadose/sac/sacdocs.htm>, Appendix F, May 2001).

Page 9, line 36 (and elsewhere in the document)

Consider moving callouts to those reports or articles not prepared by EPA or national peer groups (such as NAS/NRC) to a "related scientific literature" text box at the end of each section. Otherwise, as currently written citations are imbalanced (seemingly due to individual reviewer self-reporting in some cases), and they may or may not carry the full weight of extensive, broadly accepted peer review as met by standard Agency references and similarly extensively reviewed reports.

Page 9, text box

Again, in my view the anchor of cumulative risk assessment needn't (shouldn't) be populations,

because calculations are still being made for single individuals (or a very small subset of receptors) taken to represent populations/ subgroups, and estimates of the potential for systemic effects (hazard indices) are individual- not population-based. (For example, see the first bullet under “risk descriptors” in the box on page 54.) Further, many cumulative risk assessments are more chemical-based than place-based (e.g., assessments for specific categories or mixtures, such as dioxins/furans or jet fuel). An option would be to identify the combined effect of multiple sources-stressors-exposures as the heart of a cumulative risk assessment. Also, as a note “different sequences” could be inserted in front of “multiple durations, ...”(line 20) and “multiple effects or impacts” (line 22.5) could be followed by “with associated severities and durations” (the latter to incorporate the time scale).

Page 10, lines 6-8

I don’t consider the definitions of cumulative risk in NEPA and FQPA to be quite adequately reflected, as the latter seems to have been somewhat excluded and the former has been considerably limited (e.g., see page 4 note). The 1997 CEQ handbook identifies the importance of conducting cumulative assessments per natural ecological boundaries or sociocultural boundaries, not political or administrative boundaries, while this report at times seems to endorse the generic geographic definition (e.g., page 9, lines 20-24; page 18, line 7) that tends to be based on the latter. It may help to clarify that the specific population to be studied is not for example an urban area as demarcated on a county map, but rather the reasonable potential for a given group or groups to be affected by a given set of sources/stressors. Further, it may be useful to note that not all impacts are adverse, and that the range from beneficial to adverse (including the magnitude and significance of effects) must be considered in determining the net effect, consistent with NEPA.

Page 10, lines 29-31

The use of “i.e.” here seems too restrictive, so as to undo the earlier excellent identification of qualitative analyses as an important feature of cumulative risk assessment (page 7, line 20). For me, it would be more helpful to indicate that each phase includes elements of both the analytic and deliberative processes, with certain phases typically emphasizing one over the other, as dependent on the given assessment (e.g., this could be inserted in line 31 ahead of “Much ...”, and less prescriptive words could be used in the following text, such as “*For example*, much of what is discussed ... is *typically* deliberative”

Page 11, lines 12-13

Given that this sentence references the text box where economic and social objectives are highlighted, consider extending the description of the CBEP approach to: “... encompasses ecological and human health assessments as well as economic and social considerations.”

Page 11, lines 25-31

It might also help to ask “when should cumulative risk not be done?” and this may be a good place to note the utility of screening analyses to focus the assessment on those specific resources, population groups, stressors, sources, and exposures for which significant adverse effects are relevant.

Page 12, line 25

Consider adding something like: “Nevertheless, because this framework is outcome-oriented, it is important for the specific decisions to be made to be identified up front so the overall assessment process will focus on the information needed to address them.”

Page 13, Figure 1-3; Page 14, Figure 2-1; and others

Consider changing the double arrows to make the primary point (and limit confusion regarding do-loop analyses).

Page 15, lines 22-24

Economists and engineers also assess risks (in fact the need for, components of, and results of an economic risk assessment may be better understood by many in the lay community than parallel information for human or ecological health risk assessment). Further, it is important to include an assessment of economic and safety risks (among others) in a cumulative assessment for it to genuinely be cumulative. This is also more consistent with NEPA and the 1997 CEQ handbook (and referred to per the SAB excerpt on page 12, lines 19-21). A possible reword could be: “... along with other technical experts who assess risks and impacts, such as economists and engineers) ...

Page 21, lines 21-22

Not sure “jurisdiction” applies to academia; may want to consider “purview” or some more general term, and add industry (a key source of support for hypothesis-driven research that is crucial to progress in cumulative risk assessment).

Page 22, lines 40-42

Consider adding the importance of the conceptual model in identifying key data gaps, to guide the collection of additional data (as possible for a given assessment) depending on resources, timing, and relative importance of those data in providing information necessary for the decision at hand.

Page 23, lines 25-27

A conceptual model needn't include both a written description and visual representation of actual or predicted relationships, and it seems a framework that aims to accommodate a full cumulative assessment should present a conceptual model that includes economic and sociocultural components as well as ecological and human health components (as reflected in the accompanying Figure 2-2, which calls out environmental justice communities, and also nicely referred to on page 26, lines 3-4).

Section 2

This section is very well organized, with good text boxes illustrating key points made in the text and effective emphasis on the importance of incorporating lessons learned from past assessments (both cumulative and traditional). It may be helpful to note the usefulness of value of information methods (such as those developed at Harvard) for focusing data collection.

Page 31, lines 25-33

Given that cumulative risk assessment methods are still being developed, it may be more realistic to indicate that the plan will indicate the expected method(s) for generating risk estimates or measures, and that this method or set of methods will likely be refined along with the exposure, hazard, and dose-response information as more is learned during the assessment process.

Pages 32-44, Section 3.2

This section describes general issues more than the methods available to address them (referring to Appendix B for relevant resources, for example). It would be helpful to include here, if possible, a summary table of key methods with unique features (or adaptations) relevant to cumulative risk assessments compared with traditional assessments.

Page 33, subsection on time-related aspects

It is not clear how a cumulative assessment differs from the traditional assessment in this regard, as both should use toxicological data relevant to the exposures being assessed.

Pages 34-36, subsection on vulnerability

Similar to the previous comment, it is not clear how a cumulative assessment differs from a traditional assessment as both should consider highly exposed or highly susceptible groups. Further, the categories identified for vulnerability seem odd (as also noted in the charge questions).

Page 36, subsection on subpopulations with special exposures

This subsection seems similar to the preceding one; consider combining and streamlining.

Section 3

This section contains good information; it may help to review and streamline the organization and content, to emphasize those elements truly unique to cumulative risk assessment (rather than implying uniqueness for issues also common to traditional assessments).

Page 46, lines 5-7

Per earlier notes, I strongly support inclusion of the economic risk context, as this is certainly part of the assessment process and of considerable interest to the affected and interested communities (for example, as highlighted by the Baltimore example and others).

Pages 47-48, Section 3.3.2

The discussion of biomarkers and biomonitoring could be refined and updated. The discussion of biomonitoring is limited (suggest expanding). Not all biomarkers are inherently cumulative risk measures, although some are available to address cumulative issues. For example, cumulative exposure to radiation can be assessed by measuring the frequency of balanced reciprocal translocations in human chromosomes using fluorescence in-situ hybridization (FISH) to “paint” specific chromosomes with fluorescent chromosome probes that bind to test chromosomes along base pair sequences. Chromosomes with translocations can then be readily detected and scored by optical scanning. Because evidence indicates that these translocations are extremely stable over time, their relative abundance is proportional to the cumulative dose

over the lifespan of the organism. (See, for example, Lucas, J.N., 1997, *Chromosome translocations: a biomarker for retrospective biodosimetry*, Environmental Health Perspectives, 105 [Supplement 6]:1433-1436, and Ulsh, B., W. Whicker, et al., 2000, *Chromosome translocations in turtles: A biomarker in a sentinel animal for ecological dosimetry*, Radiation Research, 153:752-759.)

Pages 48-51, Section 3.3.3

The discussion of a single risk metric is cause for some concern, as more can be lost than gained by collapsing useful risk estimates into a single lumped number, which typically reflects subjective judgments with which not everyone will agree. For this reason, it may be appropriate to include more discussion about the pitfalls of pursuing a single metric, and to provide a summary table capturing key benefits and limitations..

Pages 51, Section 3.3.4

This section on qualitative approaches is important and deserves emphasis.

Pages 64-66, Glossary

It may seem that an inordinate amount of time was spent nitpicking this section, but it is only because I consider a clear set of definitions vital to the success of an overarching framework – especially given historic problems with inconsistent terminology that have made “accumulating” risk estimates across different types, approaches, and studies very difficult. I have commented on what is here rather than what is not, but several additional terms are warranted, including those unique to cumulative risks (such as mixture [various types], interaction and no interaction, inhibition, and potentiation, as well as traditional terms such as synergism and antagonism that are often misconstrued). By these comments, I only hope to illustrate how one might give this glossary a good scrub before the document is finalized so it can serve as the cornerstone of a consistent, broadly useful framework. In the interest of keeping this section brief, an option would be to refer to a separate, fuller cumulative risk glossary from which selected terms are excerpted for this report – with the main criterion for selection being direct relevance to cumulative risk assessment.

Page 64, line 7: Agent

Inclusion of “mineralogical” seems a bit odd – I interpret this as chemical components of mineral material (such as asbestos) and so do not understand the distinction between this and the “chemical entity” already listed in this definition. (Recognizing that radionuclides are simply radioactive chemicals, I appreciate that in this case these have commonly been referred to separately.) Would “physical” have been an option instead? This would also allow inclusion of such entities as heat and noise, which have in certain cases been shown to enhance effects beyond those predicted from simple additivity when combined with chemical agents. The distinction between agent and stressor is not clear to me (one may cause a deleterious effect, the other can induce an adverse response ...) if both terms are to be retained it may help to indicate if they are interchangeable or explain why not if not.

Page 64, lines 21-23: Conceptual model

I appreciate the need for brevity, but this definition seems to have lost something in the

compression. Conceptual models can be used to identify relationships among stressor sources, releases, receptors, associated exposure or impact pathways, and effects. Also, they can extend from human health and ecological risks to sociocultural and economic effects. As a minor note, conceptual models can be either written or visual (needn't be both).

Page 64, lines 30-37: Dose additivity

The extent of this definition is a bit inconsistent with others. Consider perhaps putting the dioxin part in a text box within the document where this topic is discussed. Minor editorial note: the first sentence seems incomplete and could be joined to the second by a comma after “every other chemical.”

Page 64, lines 42-43: Endpoint

It might be useful to also include “physical” manifestations, and to add “for health effects” at the end of the current sentence (whether human or ecological). As written, this definition does not lend itself to extrapolation to other types of endpoints, so it may be useful to add text that extends its relevance to other risk types (such as sector revenue loss, or net regional impact such as job loss, for economic effect assessment endpoints).

Page 65, lines 1-4: LOAEL

For consistency among related terms, should this also have “some effects may be produced ...” as included for NOAEL (within lines 11-16)?

Page 65, lines 6-9: Model

“Model” is an umbrella term not limited to mathematical models – i.e., it covers a wide range of qualitative to quantitative, conceptual to calculational models. Suggest either renaming this “mathematical model” or changing the definition. (Minor note, the second sentence sounds a bit buzzy and could be ended after “computer programming.”) An option would also be to fold “conceptual model” under here as a subset with various types briefly described, rather than having separate entries?

Page 65, line 18: Ototoxic stressor

Not sure why this term is included. It is not very commonly used, is not unique to cumulative risk, and is at a much lower level (more specific) than the others in this set. I'd recommend deleting it here (define it in the text where used, page 42 line 11), although it could certainly be retained in a fuller glossary from which these terms are excerpted. In that case it would make sense to also present more common, similar terms (such as neurotoxic and fetotoxic stressors) in that glossary.

Page 65, lines 20-23 and 25-27: RfC and RfD

The order of magnitude parenthetical phrase may elicit questions (as some consider it higher).

Page 65, lines 29-33: Response additivity

Consider revisiting this definition to make it a bit more friendly to a non-mathlete.

Page 65, lines 35-41: Risk

Consider also revisiting this definition. For example, many readers could be familiar with the National Oil and Hazardous Substances Pollution Contingency Plan (NCP) target incremental risk range of 10^{-4} to 10^{-6} , and this definition may not seem to offer much insight for that “practical implementation” context.

Page 65, lines 43-45: Stakeholder

Many have interpreted this term to apply primarily to external groups, beyond the formal project decision makers who are often responsible for implementing a compliance program. (I personally prefer its application to “all with a stake in the process” which of course includes the agency or other implementing party.) Because misconceptions regarding roles and authority have been an issue in some cases, you might consider changing “making decisions” to “providing input to decisions.”

Page 66, lines 1-2: Stressor

See earlier comments (e.g., page xviii and page 7).

Appendix A

This Appendix contains good information. Capturing key research needs at the end of each main chapter of the report might also be useful. Also, it may be helpful to re-structure this appendix into more organized categories (e.g., within the three phases that serve as the backbone of the framework), possibly with cross-references to related portions of the main text.

Appendix B

Similar to comment for Appendix A.

Appendix C

A discussion of background (or ambient) is important, and the authors are to be commended for including it. Baseline or background information that accounts for natural variability across the appropriate spatial and temporal scales and focuses on characteristics of the environmental setting that affect contaminant mobility and ultimate effects (including across human and ecological health, and sociocultural and economic risks) is essential for the context it provides for an integrated analysis and ultimate interpretation of risks (e.g., per exposures beyond ambient or baseline levels). Background is often taken to mean ambient. For example, arsenicals were widely used decades ago in vast agricultural areas, and arsenic remains in the soils across the midwestern United States. Thus, reference sites should be practically defined – more as a reasonable bases for comparison rather than as a rare, pristine location (although the latter also provides useful context for absolute risk estimates).

Appendices D and E

The inclusion of an example plan and overview of the toxicologic similarity issue is excellent. (But it’s interesting that an FQPA example is used and referred to as a cumulative risk

assessment, as portions of the main body of this document seemed to indicate that this was not appropriately considered a cumulative assessment?)

Very Minor Editorial Notes

Page xvi, List of Abbreviations and Acronyms

I think CEQ is Council *on* Environmental Quality, I've also seen OP as organophosphate pesticides (with both organophosphorous and organophosphate found on EPA websites), APCA may be ACPA (also on page 67, line 30), Material in MSDS may be singular, and I've also seen GIS as Geographic (no "al") Information Systems.

Page 2, footnote 1

Excerpt: "... for traditional, chemical-focused assessments we say we conduct a "risk assessment (*delete s*) for a certain chemical. (*Here and elsewhere end quotes seem to be missing, e.g., page 4, lines 33, 35; through page 64, lines 37 and 39, and beyond – software glitch?*)

Page 6, line 1

The referenced box is on the previous page (rather than "at right")?

Page 6, line 34

Tiny note: are vs. "ar e"

Page 8, line 14

Possibly insert "with" before "health"?

Page 18, line 35

Consider changing "brainstorming" to "discussions"? (Classic brainstorming involves quickly polling a group for input on a topic, then combining those responses that are common and deleting duplicates to assemble a final list. The typical process for soliciting community input is more measured and not completed within a single meeting.) (In line 43: is it "or" versus "of"?)

Page 18, text box

Consider including non-health examples (e.g., Chesapeake Bay for ecological risks, closure and realignment of neighboring bases for economic risks).

Page 19, line 8

Consider changing "risk" to "overall viability" (the first involves probability, the second simply reflects an umbrella "health" status).

Page 19, lines 33-34

The phrase "to choose from" seems funny here; possibly consider rewording, e.g.: "... some examples of interested or affected parties that could be involved in the deliberative ..."

Page 22, line 20

Pluralize “Lesson.” (An excellent point is made in this subsection.)

Glossary

Page 64, lines 30-37: Dose additivity

First sentence seems incomplete, could be joined to the second by a comma after “... chemical.”

**Review by
Pavel Muller – ToxProbe Inc.**

1. Background

Dr. Pavel Muller of ToxProbe Inc. conducts this peer review at the request of Mr. David Bottimore of Versar Inc. ToxProbe Inc. has reviewed the report titled *Framework for Cumulative Risk Assessment* prepared for USEPA by the USEPA's *Risk Assessment Forum* and dated April 23, 2002.

Versar Inc. has also provided Dr. Muller a copy of *The Risk Assessment Forum Draft Framework for Cumulative Risk Assessment* dated April 26, 2002. Response to the charge questions contained within constitutes the main component of the review. Some general comments not directly related to the charge questions are also presented.

2. General comments and recommendations

USEPA produced a thorough, well researched framework for cumulative risk assessment. The report is intended as a first step in the development of a guidance report which would serve the Agency and other organizations in conducting cumulative risk assessments. The Framework is strong on providing data, discussion of the data and references relevant to cumulative risk assessment, and providing definitions of the process. However, the Framework seems weaker in explicitly defining how it will be applied in the decision-making process and in recommending when it should be used in preference over simpler, faster and less costly alternatives. The actual assessment process is defined only in a rudimentary fashion and this makes the report harder to follow. Finally, there are other existing processes conceived as frameworks for cumulative risk assessment (ILSI, 1999) or which could serve as such frameworks (USEPA 1999, 2000b). Given the existence of these frameworks, I believe it would be preferable to build and expand particularly on the SAB framework. The SAB framework appears particularly well developed and it is recommended that it be used as a starting point for the USEPA's Framework.

My vision of the scope of a framework report is wider than that of the authors and this is where my main concerns are found. It appears that the authors focused on providing factual, technical framework only, and have decided not to provide a framework for performing, communicating and acting upon the results of the assessment, relegating these issues to the eventual Guidance document. I would have like to see a brief discussion of a complete, balanced framework, which include the following issues:

- Criteria for conducting cumulative risk assessment. Cumulative risk assessment brings about considerably higher level of complexity and is likely to require more time and resources than more limited traditional risk assessment. Resources committed to these cumulative risk assessments will not be available for other worthy projects. It is therefore important that the cumulative risk assessment is the appropriate tool for a given situation in terms of science and that the net increase in costs is justified by the additional benefits from conducting the assessment.
- The definition of specific roles of stakeholder groups including scientists/assessors and managers.

- It is important to give risk managers an opportunity to assure that the output of the assessment is in a form which gives risk managers optimal tool to conduct informed and effective risk management decisions. I am not comfortable that risk management step is not perceived to be an integral part of the envisioned process. In that sense I find the approach used by SAB (USEPA 2000b) clearly preferable.
- Although I agree that a multi-stakeholder participation is a positive and perhaps necessary feature of the cumulative risk assessment, I feel that a separate and independent technical risk assessment report should be prepared in addition to the overall report. For risk managers the separation is important. For example, if the technical report concludes that the risk from mobile sources is orders of magnitude below what is commonly seen as a level of concern and if the multi-stakeholder report identifies mobile sources as an important source of concern, the management solution may not be an attempt to further reduce the emissions, as this would in all likelihood not diminish public concerns about such emissions. Instead other solutions designed to deal with the causes of public concern would be preferable.

I feel strongly that the framework should contain a “table of contents” for the eventual guidance. By that I mean that the framework should indicate what key elements (such as ranking and prioritizing, a detailed flowchart describing the cumulative risk process etc.) are expected to eventually constitute the guidance on cumulative assessment. It is understood, that some elements will not be described in detail within the framework report, but the inclusion of statements identifying issues which need to be addressed in the eventual guidance would have several benefits:

- It would reassure readers and peer reviewers that the authors are aware of the issues and that these issues will be addressed.
- It would improve clarity of the report by adding brief presentation of issues that would be anticipated by at least some readers.
- It would help the eventual authors of the guidance report by providing a handy “checklist” of issues to address.

3. Charge questions

1.a) Does the Framework document capture the relevant terminology?

I am unaware of any major omission or inconsistency. Some terminology contained in the reports cited in the Framework is not specifically discussed in this document (e.g. terminology related to complex mixtures – see USEPA, 2000a). I do not see it necessary to include a terminology unless it is needed to understand the Framework.

It would be useful to add a new section 2 (perhaps called *Definitions of Cumulative Risk Assessment and its Key Features*). *Include in this new section elements from pages 1-4 and Section 3.*

1.b) Does the Framework document provide an adequate assessment structure?

In my view, the assessment structure is not adequate. The current Framework is strong on discussion of issues, which could be included in the cumulative risk assessment, as well as the knowledge base in support of such an assessment, but the process is outlined in a minimal manner. One can argue that the way it is presented has its benefit; it allows the greatest flexibility in terms of the problems the process can be applied to and it places minimal constraints on future guideline developments. However, I find the assessment structure rudimentary to the point of not being entirely clear how the gathered information will be used to provide meaningful support in the decision-making process. I recommend adoption of the SAB assessment structure, perhaps complemented with extension or elaborations from the USEPA assessment structure for cumulative risk assessment.

It is recommended to add another new section, which would explain in some detail the differences between the existing approaches dealing with Cumulative Risk Assessments (such as some of those listed on page 5), especially the SAB Framework, and explain why USEPA had to develop a new framework, rather than expand on the one previously published by SAB. To me, the two frameworks are very compatible and incorporate the use of similar data and methods for interpretation and both encourage similar form of stakeholder participation. The apparent differences in their application do not seem to be significant and I believe, are reconcilable. I strongly believe that the USEPA (and in this context, includes SAB) should create only one internally consistent framework. USEPA Risk Assessment Forum needs to present a far stronger and more defensible rationale for separate frameworks than the one presented in Section 1.5. After examining both frameworks, I personally consider the SAB framework better defined and more practical. However, the Framework contained in the USEPA document presented for review provides more detail on cumulative risk assessment; and it could be made to complement the SAB framework relatively easily.

I feel strongly, that the Framework should discuss how decision-making, implementation and performance will be integrated into cumulative risk assessment. If resources are to be committed to complex time- and labour-intensive processes, such as those discussed in this Framework, it should be done only after it was ascertained what information (and in what form it takes) is needed by the decision-makers to make better decisions. Finally, performance measures need to be set to assure (in part) that management activity does not continue needlessly if the performance measures are reached or if these measures turn out to be ineffective or inappropriate. Explicit linkages with the decision-making component of the process would help assure that the resources committed to the analysis will be effectively utilizable by the decision-makers.

The Framework states (page 12) that *cranking out numbers will not be the sole basis for a decision*. That is acceptable. However, the Framework should assure that even though the process as a whole is analytic-deliberative, the decision-maker still has an ability to determine what are scientific/technical conclusions and what are the conclusions based on the overall deliberative process. Unless such distinction is made, important information will be lost to the decision-maker. It is therefore proposed that the Framework recommends that one of the reports

prepared to describe the outcome of the cumulative risk assessment be a technical report. This is consistent with the 1983 National Research Council report *Risk Assessment in the Federal Government* (NRC, 1983), which makes the following statement.

“We recommend that regulatory agencies take steps to establish and maintain a clear conceptual distinction between assessment of risks and consideration of risk management alternatives; that is, the scientific findings and policy judgements embodied in risk assessments should be explicitly distinguished from political, economic and technical considerations that influence the design and choice of regulatory strategies.”

On page 63, paragraph 3, the Framework states 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*”. On the other hand, the Framework envisages stakeholder and decision-maker input throughout the assessment, so that their concerns can be taken into consideration. These concerns may include availability of resources, community values, etc. As a result, the final report is expected to contain some mix of technical analysis, other concerns and interpretations, which decision-makers have an opportunity to influence. It therefore appears that the report should contain most, if not all, of the elements a decision-maker needs to make a decision. I therefore do not understand why the results of the risk assessment cannot be the primary basis for decision-making.

1.c) Does the Framework document outline the relevant methods for cumulative risk?

The planning and scoping phase of the Framework is, in my view, the most developed part of the process. However, the cumulative risk assessment process, as envisioned in the Framework, has the potential of being extremely complex and time- and resource-intensive. Before undertaking this type of assessment, it is prudent to determine whether the extra benefits of conducting a cumulative risk assessment justify the extra effort involved in using such a process rather than a more traditional risk assessment process. I recommend that the Framework incorporate a formal feasibility study as the first step of the cumulative risk assessment process.

Section 3.2 of the Framework (Available Methods and Approaches) gives mostly examples of increased complexity with the use of cumulative risk assessment. These examples are described and discussed, but the focus is not on specific methodologies of addressing the complexity. It is suggested that this section be more appropriately named.

The actual methods are discussed in Section 3.3 (Areas of Complexity and Current Research). I find the section headings unhelpful in identifying the methods of this Framework. Furthermore, it is not explicit how these methods will fit into the assessment process; there is a reliance on the readers' insight to make a connection.

It is recommended that this section be thoroughly rewritten, providing headings, which reflect more appropriately the contents of subsections. The methods should be named, and compared. The context within which the methods would fit in the assessment process should be clearly

described. This issue is also discussed in Section 2 of this peer review.

2. Scientific or technical inaccuracies

None found.

3. Uncertainty assessment

Overall, Section 4.2 of the Framework categorizes and describes uncertainty, but it does not tie it to the cumulative risk assessment process. I would suggest the section be revised to include the following type of discussion.

- In what way the uncertainty assessment is different for cumulative risk assessment relative to other forms of risk assessments.
- How the uncertainty assessment will be used to refocus the ongoing cumulative risk assessment process or to determine whether the use of cumulative risk assessment process is appropriate.
- How the uncertainty assessment will be used to help interpret the cumulative risk assessment.
- Any other intended uses of uncertainty.

The differences between the three types of uncertainty (page 58) are not clear. Specifically, how is uncertainty of type 3 different from type 1 and 2 uncertainties?

I would incorporate Section 4.2.3 into Section 3.2.2.

4.a) Vulnerability

Discussion was easy to follow.

4.b,c) Cumulative risk assessment involving chemical and non-chemical stressors and different *Types* of risk

The Framework omitted the discussion of the **surrogate approach**, where the toxicity of a mixture or its fraction is expressed in terms of the concentration of a surrogate. The implied assumption is that the concentration of each component of a given mixture rises or falls with rising or falling concentration of the surrogate. The surrogate is assigned potency of the entire mixture (regardless of what the potency of the surrogate itself may be) and the risk is the product of the intake of the surrogate and its assigned potency. This approach has been used, for example, for the polycyclic aromatic hydrocarbon fraction of a mixture by World Health Organization (Air Guidelines for Europe) and in other guideline reports and assessments.

The key to assessment involving different stressors and different types of risk is to identify ways to express the information using a common metric. Various approaches, which allow for expression of diverse stressors using a single metric (in use and under development), are

discussed in Sections 3.2 and 3.3. I find these sections useful and informative; they provided a good summary with references to key reports in the area.

It is clear that some means of dealing with a wide range of risk data with different metric will be needed if the cumulative risk assessment is to be a tool accessible to a wider range of stakeholders. A section should be dedicated to the discussion of (1) why a single common metric or few metrics is desirable and how the metric(s) would be applied, (2) situations where risk information is normally presented in a single metric (e.g. oral carcinogens), (3) combination of different effects into a single metric currently in use (e.g. hazard index and other indexes), (4) other proposed metrics (see Section 3.3). Much of this information is available in Section 3 of the Framework, but needs to be isolated from other issues covered in the section. A better focus on the purpose and application would aid in understanding.

4. References

ILSI, 1999. *A Framework for Cumulative Risk Assessment*. International Life Sciences Institute, Washington, DC. ISBN 1-57881-055-8

NRC, 1983. *Risk Assessment in the Federal Government: Managing the Process*. Committee on the Institutional Means for Assessments of Risk to Public Health, Commission on Life Sciences, National Research Council. National Academy Press, Washington, DC. ISBN 0-309-03349-7

USEPA, 1999. *Integrated Environmental Decision-making in the Twenty-first Century: Peer Review Draft*, U.S. Environmental Protection Agency, Science Advisory Board Integrated Risk Project Steering Committee

USEPA, 2000a. *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures*. Risk Assessment Forum, Office of Research and Development, U.S. Environmental Protection Agency. Washington, DC. EPA/630/R-00/002

USEPA, 2000b. *Toward Integrated Environmental Decision-Making*. Science Advisory Board, U.S. Environmental Protection Agency. Washington, DC. EPA-SAB-EC-00-011

**Review by
Barry Ryan - Emory University**

Review of Framework for Cumulative Risk Assessment

Pre-Meeting Comments

P. Barry Ryan

May 27, 2002

Overall Impressions

As I read the Background and Charge questions for this review prior to reading the document itself, I began to formulate in my own mind what I believed would be an appropriate document fulfilling the intent I had discerned. Upon my reading of the document, I felt that my vision for the piece was not being realized even remotely. I encountered a document that was, I felt, quite pedagogical in nature and not really descriptive of what must be done in a cumulative risk assessment. And I was disappointed.

But as I continued to read the document, I found myself making mental notes regarding the use of the document and the references therein in a second level risk assessment class that I teach. Here is a good glossary of terms- there is an excellent reference list- over here is a good discussion of what must go into a general risk assessment and a higher-level assessment that includes non-chemical components influencing the risk.

And so I continued to read and my disappointment was assuaged to a large degree. The intent of the document is not to give a detailed accounting of the methods by which cumulative risk assessments are to be done but to supply, as the title would suggest, a framework upon which to develop thinking about doing these types of assessments. With this new mindset, I reevaluated my view of the document. While not perfect, I believe this document is an excellent product with this intent. The list of authors, contributors, and reviewers speaks to the perceived importance of this document within EPA. Further, the fact that at least three stakeholder meetings were held to discuss it further suggests its utility.

I do not, however, think that the document will be well-received by all. The “teachers” of risk assessment, and I fall into this category, I think will find it a better document than the “doers” of risk assessment. The former will find the pedagogical approach to their liking and will likely see such a document acting as a central piece in a teaching curriculum whether it be in the classroom setting as I might implement, or in the private chambers of EPA regulators and other risk assessors attempting to design cumulative risk assessments in the future. The later will be looking for the meat and details of such an implementation. I think that the concerns of the “doer” group will be partially allayed by the numerous text boxes throughout the document giving specific examples of the way things have been done and by the various appendixes that address some “doer” issues. I must congratulate EPA on these text boxes. Many describe projects that were done that had poor outcomes and are used to illustrate ways of thinking that were not appropriate or were incomplete. Of course there are success stories as well, but it is the bad outcomes that teach us where we had poor thinking in the past and how to avoid such in the future.

The document still has a number of flaws in my opinion. It is quite long and, at times, pedantic. There is a significant amount of material that is quite generic applying to simple risk assessments, what one might call aggregate risk assessments, and other types of studies that do not fit any of the definitions supplied of cumulative risk assessments. While it is certainly EPA's prerogative to include these more generic discussion in this document, it could be made more hard-hitting (and considerably shorter) by referencing, rather than repeating, this generic material and focusing on the specific components unique to the cumulative risk assessment process. However, an alternative point of view would be to include such in this presentation so that the relative neophyte would have all of this information at her or his fingertips in a single document. The more experienced risk assessor could then choose to skip over the material that was well known and focus on the newer components.

Perhaps the best "new" material, in my opinion, is the expansion of the cumulative risk assessment concept past the FQPA definition to include all factors- whether chemical, physical, or social- that affect risk and risk characterization. This, I believe, represent the single biggest "breakthrough" in this report.

Charge Questions

The following questions are provided to help guide the peer review and associated discussions during the peer review workshop. When considering these topics, keep in mind the purpose of a framework is to identify and "frame" key issues for a broad audience of readers. Therefore a balance must be struck between adequately characterizing the issues and providing a detailed, comprehensive technical discussion.

1. *Comment on whether the Framework adequately captures, described, and reasonably organizes the key issues for cumulative risks assessment so as to serve as an adequate foundation for the development of future guidance. In your comments, please address the following questions. In answering each question, provide a supporting discussion that highlights any areas of the Framework that may need to be clarified and relevant topics that may be missing from the current Framework document. Include references to any published literature that could help improve the completeness and clarity of the Framework.*

a. *Does the Framework document capture the relevant terminology?*

Not only does the Framework capture the relevant and essential terminology, it expands on certain terms. In particular among these is the expansion of the term "cumulative risk assessment" to go beyond the "common mechanism" definitions of the FQPA to a more generalized definition involving other factors such as physical environment and non-chemical exposures that may influence the outcome. The Glossary presented on pages 64-65 gives a good compendium of definitions, but could be expanded to include more terms and thus be even more useful.

b. *Does the Framework document provide an adequate assessment structure?*

The Introduction details the assessment structure with Figure 1-3 presenting such in graphical form. In later sections, e.g., Figure 2-1, a modified version of Figure 1-3 is used to announce and kick off each new section. I think that consolidating the design would be an appropriate strategy, i.e., developing a single form for this presentation whereby the new section could be highlighted. It is almost done at this point, but there is enough difference between the figures as to cause some confusion.

c. *Does the Framework document outline the relevant methods for cumulative risk?*

The document offers examples of cumulative risk assessments, including the expanded definition, and offers some details in Section 3. However, if the reader is looking for a cookbook method of performing a cumulative risk assessment, this is not the document. Again, the concept of a framework for performing cumulative risk assessments is given, but the step-by-step procedure for carrying it out is left to the risk assessor/risk manager to design.

2. *Does the Framework document include any scientific or technical inaccuracies in its presentation of terminology, assessment structure, and methods? Please identify any problem areas and propose revisions or other actions that will result in a scientifically sound and supportable discussion. With respect to methods, comment on whether the Framework adequately conveys the state of the science with respect to currently available cumulative risk assessment methods/approaches and the areas that are in need of further research and development.*

Over the last ten years, there has been a great deal of work, much of it bordering on overly-pedantic, describing the differences between exposure, dose, delivered dose, biologically-relevant doses, toxicologically-relevant doses, etc., that tended to bore the practitioner to tears. I would not advocate such a rehashing of these definitions, but I would prefer to see some discussion of the terminology of exposure assessment and dose-response characterization in this document, even if only in the Glossary.

The assessment structure, I believe, is adequate to convey the framework concept. More could be included, but I think that little insight would be gained by such inclusion.

The Methods component could be increased in detail. However, this is a decision to be made based on the intent of the document. To stay within the rubric of a framework, little or perhaps no additional material is needed. However, to appease the “doers” as discussed above, more detail could be provided regarding the execution of cumulative risk assessments. Again, a significant allaying of fears has been accomplished through the use of Text Boxes throughout the document. Inclusion of a couple more in the Methods section may make for a document better received by those looking for specific guidance on performing such assessments.

3. *Uncertainty analysis is an important part of risk assessment (and policy analysis in general). However, historically, dealing with uncertainty has been a shortcoming of many assessments. Cumulative risk assessments present new challenges for uncertainty analysis.*

Perhaps more important, assessing cumulative risks will involve the use of “soft” assumptions. These are assumptions which may have a high degree of uncertainty that is difficult (or not possible) to quantify. Comment on whether the Framework adequately characterizes the importance of uncertainty analysis in cumulative risk assessment. What additional discussions of uncertainty should be included in the Framework (and in what sections of the document)?

Uncertainty is discussed at length in Section 4. The discussion focuses not merely on the differences between variability and uncertainty and the effects of parameter uncertainty, but it also discusses other forms of uncertainty such as model misspecification uncertainty. Further, there has been discussion of the “soft” assumptions and their influence on the expected results. Little quantitative guidance has been supplied, but the fact that the topic was even discussed is a big step in the right direction.

4. *The following topics have been identified by the RAF technical panel as technically difficult areas that will pose challenges to cumulative risk assessment. Comment on the adequacy and accuracy of the Framework’s presentation in each of these areas.*

a. *Vulnerability*

As applied to cumulative risk assessment, it is useful to think of four components of vulnerability: the susceptibility or sensitivity of the human or ecological receptors; the differential exposures of the receptors; the differential preparedness of the receptor to withstand insult from exposure; and the differential ability to recover from effects. The issue for cumulative risk assessment is how to consider these aspects of vulnerability and their potential impacts on risk. This is highlighted in the framework as an issue in need of further research and development. Comment on the discussion of vulnerability on the draft Framework. Has the state of the science been captured in the discussion? How can the discussion of this issue be improved?

I do not claim expertise in the assessment of vulnerability in populations, but the discussion seemed relatively complete to me. The discussion, presented on pages 34ff covers several aspects and supplies a number of references, including EPA-developed reviews. I leave it to others to assess the state-of-the-science level of the presentation; to me it appears adequate.

b. *Cumulative Risk Assessment Involving Chemical and non-Chemical Stressors*

Viewing cumulative risk assessment as an evaluation of the accumulation of stressors presents many challenges. These may be seen when attempting to combine, in some meaningful way, the risks from multiple chemicals that may act as synergistic, antagonistic, or additive doses leading to a single effect. The situation is exacerbated when non-chemical stressors (e.g., radiation, biological agents, and psychological stress) are considered. Comment on the Framework’s discussion concerning the combining of disparate environmental stressors. In commenting, consider the state of the science with respect to understanding the effects of different stressors acting together (e.g., chemical exposure and viral infection). What can be added to the framework to adequately convey the state of the science in this area?

The framework states that little work has been completed in this area that would address the simultaneous measurement of various chemical and non-chemical stressors on human or other receptors. I am unaware of any such work beyond the most rudimentary discussed in the text or Text Boxes. Examples include measurement of temperature and pollutant exposure, measuring of two or a small number of chemical exposures at the same time, or epidemiological investigations of groups with different sensitivity and exposure. Other experts may be able to cite a small number of specific studies addressing such issues, but it is clear that no truly systematic investigation of these effects has been done. More work is certainly needed in this area.

c. *Cumulative Risk Assessment Involving Different "Types" of Risk*

Conveying combined risks from multiple chemical and non-chemical stressors, in a meaningful way, is the ultimate challenge for cumulative risk assessment. Experience in this area is extremely limited. Indices, common metrics (e.g. Disability Adjusted Life Years- DALYs) and graphical (e.g., GIS) approaches have been explored by much methods development work remains to be completed. Cumulative risk assessment can be a valuable part of the decision making process, but only of results are conveyed in a meaningful way. Comment on the Framework's discussion concerning the combining of separate measures of risk. Do the examples approaches discussed capture the state of the science in this area? In particular, consider the real of valuation (i.e. the assignment of societal values to disparate health outcomes) implicit in some of the approaches. Suggest changes or additions that may improve this discussion.

The framework presents a discussion of attempts to combine different measures of risk with wildly different metrics or, perhaps, no metric at all. The authors give several examples and thereby attune the reader to the difficulties. I think that this is an excellent introduction to guidance, but that real guidance cannot be forthcoming because it is not yet available. However, this is not my area of expertise and others more experienced in this area may offer more insight.

Specific Observations

I noted a relatively small number of typographical problems and spelling errors that would likely be picked up on a final edit. I will supply these at the review workshop. Some of the graphics, notably Figures 1-1, 1.2, 2-2, and 2-3 appear to be of low quality and should be replaced by high quality art work. Similarly, the lead figures for Sections 2, 3, and 4 should be reworked and replaced with high quality art work. As mentioned previously, the art work for these figures and Figure 1-3 should be reworked to be consistent. EPA should consider the use of color in some of these figures to aid in clarity.

**Review by
Jennifer Sass - Natural Resources Defense Council (NRDC)**

June 22, 2002

Comments on the Technical Peer Review Workshop on the EPA Risk Assessment Forum
Draft Framework for Cumulative Risk Assessment: June 4-5, 2002

Comments submitted to David Bottimore, Versar
Cc: Peter de Fur, Workshop Chair

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AREAS OF UNCERTAINTY ARE OFTEN AREAS OF VULNERABILITY

The identification of uncertainty, susceptibility, and vulnerability issues need to be introduced early in the CRA framework, and carried throughout. These concepts are not separate from each other, but, rather, are closely related. Uncertainty within the CRA will mainly be in those areas in which the least data is available. It is commonly accepted that the areas of least data are often the most vulnerable populations and geographic areas. For example, minority ethnic groups are under-represented in the government data on eating patterns. Therefore, an area of uncertainty in the organophosphorus CRA is the eating patterns, and associated food-pesticide exposures, among certain ethnic groups. Likewise, fetuses, infants, and young children are under-represented in the national eating pattern data; yet, they represent a population with eating patterns usually consisting of a very limited selection of foods, substantially different from the adult population. For example, apples, which have an unusually high level of the most toxic pesticides are also the most popular fruit and juice choice for children. Therefore, compared with adults, children are more highly exposed to toxic apple-pesticides, and more at risk of permanent damage from the neurotoxic pesticides. These examples are meant to demonstrate the widely recognized paucity of data on what are often the most vulnerable subpopulations.

Geographic areas that are most at risk are often similarly under-represented in the data, and therefore represent the areas of greatest uncertainty in an ecological CRA. The unique and highly vulnerable ecosystems of deserts, for example, are poorly understood. Yet, they may be just as exposed to many air pollutants as more robust and well-understood climate zones, with less ability for recovery and repair. Similarly, forests in the temperate climate of the West Coast may take a decade to recover from a destructive exposure, whereas forests in the harsher Northern climates of the Canadian Shield may take over 50 years to achieve the same regrowth. Recognizing the unique vulnerabilities of geographical regions should be part of the vulnerability analysis within a cumulative risk assessment. Where these vulnerabilities are poorly understood, the uncertainty must be estimated and included in the assessment.

IDENTIFICATION OF UNCERTAINTY

The identification of uncertainty early in the CRA process must include the identification of sensitive subpopulations, sensitive geographic areas, and the “voiceless” or marginalized populations who are under-represented in the data available. This should be done in the context of CRA. A specific discussion of how uncertainty will be integrated into the cumulative risk assessment process would be helpful. Examples of uncertainty unique to CRA, and how it is acknowledged (quantitative, qualitative, or both) and integrated into the CRA process would be very instructive. The Agency need not invent the wheel; where others have already completed such cumulative risk assessments, these examples would be instructive to both the naïve and experienced reader. Examples should be drawn from national and international initiatives, from aboriginal approaches, from community-input approaches, and from traditional EPA approaches. Both successful and unsuccessful examples would be instructive.

A PROTECTIVE APPROACH SHOULD BE BUILT INTO THE FRAMEWORK

Since it is recognized that the greatest uncertainty in the CRA will often be areas of greatest vulnerability, and since it is also recognized that a public health and environmentally protective approach necessarily embodies the principles of precaution and conservatism, this should be overtly stated within the framework. The framework should embody the principles of the CRA, like a skeleton upon which layers of muscle will be laid. This principle should be guided by precaution and protection, even while recognizing the uncertainty in the process. Just as the advisory panel was quick to recognize that uncertainty cannot be identified late in the CRA process, but must be noted throughout, so, too, must the framework approach to uncertainty be noted throughout. It is rightly stated in the framework that the Agency must act, even in the face of uncertainty, to protect the environment and the public health. This protective approach should be formed in conjunction with the identification of uncertainty, to better ensure that all uncertainty is identified and included, where appropriate. Without stating such an approach within the framework, the Agency risks making policy-decisions on what uncertainty to include, and what to exclude, which may not be consistent with a protective approach. Complete disclosure of all uncertainties is essential, early and throughout the process, and therefore must necessarily be built into the framework.

THE ANALYSIS SHOULD BE ABLE TO IDENTIFY RISK DRIVERS; qualitative, quantitative, attributable, avoidable, baseline

While the Agency is tasked with the difficult process of presenting the cumulative risk, or total load, to a person, community, or ecology, the Agency must also be able to work backwards, breaking down the cumulative risk assessment to its component parts. This may not be possible in great detail, but in general any cumulative risk assessment must be able to not only describe the cumulative toxic load, but also to identify the main risk drivers contributing to the toxic load. This includes identifying the “background” or baseline contribution, which may be very significant.

Additional exposures above background must also be identified with as much detail as possible, including an estimate of the magnitude of exposure each contributes. Likewise, the distinction between attributable risk and avoidable risk must be made, with risk drivers identified and quantified. Without this ability to move both forwards and backwards through the cumulative risk assessment, it will not be helpful in the risk mitigation phase.

Much information regarding exposure and risk may be qualitative in nature. The collection of qualitative information may be very valuable to the cumulative risk assessment, and should be encouraged. Qualitative issues and priorities may differ across communities and geographical regions, even where measurable endpoints may not. For example, ability to relocate, access to health care, ethnic make-up of the community, closeness of the community, perception of risk, perception of cause of risk, and other factors may influence the ability of any cumulative risk assessment to be successfully accepted by the affected population. Without understanding such qualitative contributors, the community and the risk assessor may be speaking at cross purposes. Thus, this information should be integrated, as appropriate, in the cumulative risk assessment. And, like the measurable contributors, these qualitative contributors should ideally be able to be aggregated and disaggregated, as needed, to identify the risk drivers.

ENVIRONMENTAL JUSTICE ISSUES

The recognition of environmental justice issues runs throughout these comments; a) in recognizing that vulnerable populations are often where the greatest uncertainty lies, b) in recognizing that qualitative issues and priorities will differ with socio-economic status, ethnicity, and community bonds, 3) and in the call for public health and environmentally protective language to be built into the very framework of all cumulative risk assessments. These issues cannot be given meaningful discourse without including environmental justice considerations. Similarly then, the language of environmental justice should also be built into the framework, so that each and every cumulative risk assessment which arises from this framework includes environmental justice considerations at all stages. By building this language into the framework, each cumulative risk assessment is contextualized within the community and ecosystem it is meant to serve. This will contribute to the successful acceptance and implementation of the cumulative risk assessment by the local community, and give the assessment its best chance of success.

**Review by
Paul Schlosser – CIIT Centers for Health Research**

Review of EPA/630/P-02/001A: "Framework for Cumulative Risk Assessment" (external review draft, dated April 23, 2002)

Prepared by Paul M. Schlosser, CIIT Centers for Health Research

General comments

As government regulations now mandate cumulative risk assessments for pesticides acting by common mechanisms and there is a generally heightened concern that regulation of exposure to individual stressors may not adequately protect against cumulative effects, it is appropriate for the EPA to provide guidance on how one should go about assessing risks from multiple stressors or agents. Because the number of potential stressor combinations that might be considered is enormous and the methods for predicting and quantifying combined risks are still at the beginning of development, it is appropriate that this guidance be in the form of a framework or overall structure that is not proscriptive. The draft document achieves this goal quite well, with important emphasis on the extent to which methods development is needed.

While the framework seems to lay out very ambitious goals for risk assessments, these are likely necessary if cumulative risk is to be properly characterized and the results are to meet the needs and expectations of concerned parties.

A general area where the document could most use further discussion is in the combination of different responses into a total measure of "risk", or at least providing a level of comparison (section 3.3.3, pp. 48-52). It is suggested that the assessment may or may not use a common metric to 'sum up' all effects. But the underlying key issue is that the assessment should provide managers a way of weighing and comparing different responses, since one would wish to address the most important first and in some cases there may be risk-risk trade-offs. Such a weighting is necessary for responses to be combined into a single metric, but the discussion of those is focused more on a discussion of different types of such metrics rather than the fact that it provides such a weighting. Even if a single metric is not used, the input of stakeholders and experts could be used to at least rank different responses in level of importance or concern, and it would be a shame not to take advantage of their involvement to gather this information.

Charge Questions

1. I found the document to be well-organized overall, and except for the issue of endpoint "weighing" mentioned above, am not aware of any key points that have been missed. The issues are described and addressed at appropriate length, with good references to supporting materials. Specifically:

- a) The relevant terminology is appropriately defined and used.
- b) The structure defined appears to be comprehensive and broad enough to be

applicable to the wide range of assessments anticipated, and yet specific enough in listing the steps involved and what should be achieved to provide meaningful guidance.

c) As the framework correctly points out, methods for predicting and quantifying the combined effects of multiple stressors are still in the early stages of development. The document describes and references a number of methods described in the literature for dealing with combinations of stressors, but some other work that might be mentioned is that of Krishnan and colleagues on predicting pharmacokinetic interactions of chemicals (Haddad *et al.*, 1999; Haddad *et al.*, 2000; Haddad *et al.*, 2001).

2. There appear to be no significant inaccuracies in the document's description of current methods, the structure, or terminology. Some detailed corrections are noted in the "Specific Observations" below. As is noted throughout the document, this is an area where considerable research and development are still needed, and hence a detailed specification of methodology would be inappropriate.

3. The document does a good job of explaining the importance of uncertainty analysis and what types of uncertainty one might wish to understand. Uncertainty analysis is a very large area of research, which the document cannot address in great detail. However I believe some comments should be made about the magnitude of effort potentially required to fully characterize all sources of uncertainty, particularly where biologically based modeling is used.

An example is the fairly recent risk assessment for formaldehyde developed by CIIT and collaborators (CIIT, 1999). In the biologically based RA, computational fluid dynamics (CFD) models are used as inputs to pharmacokinetic models of formaldehyde and DNA-protein-crosslink (DPX) dosimetry, which had adjustable parameters fit to data. The output of the PK/DPX model was then used as input to multi-stage clonal-growth model, which again had adjustable parameters fit to data. To characterize the effects of uncertainty in the CFD model on the final output would require re-estimation of the PK/DPX parameters (and their upper and lower bounds) for the upper and lower bounds of the CFD model. The resultant ranges of PK/DPX predictions would then need to be used to estimate the ranges in clonal growth parameters. The clonal-growth predictions would then need to be calculated as a function of all of that underlying uncertainty. The effort required to do this would be quite substantial – on the order of months or perhaps a year, given that the computational effort for fitting the clonal growth model, which involved Monte-Carlo simulations. While this is doable, the personnel resources required were simply not available.

In short, quantitative uncertainty analysis involves testing multiple realizations of the risk assessment calculation, and when that calculation itself is computationally complex, the resources required can become prohibitive. Thus, as for the entire RA process, the resources available may proscribe what is achievable in the uncertainty analyses.

I firmly support the idea that all underlying assumptions and uncertainties should be listed, though. In the case of using quantitative models, the parameter uncertainties should be provided and some sensitivity analysis performed to identify those which are most significant to the calculations.

4. RAF technical panel issues

a. Vulnerability

I have considerable concerns with the division of vulnerability into the four components as described. *Differential exposure* is clearly defined. But given that dose-response and/or exposure assessments are basic components of any risk assessment, I am not sure of the value of including this as a special definition. Pointing out that past exposures may be pertinent is useful, but if those exposures make an individual more prone to future insult, that is a component of susceptibility.

I am having a very hard time distinguishing *susceptibility* from *differential preparedness* to withstand the insult. I don't see the distinction.

Differential preparedness to recover is not a factor if in fact it is the acute endpoint that occurs: the fact that I might recover from hearing loss doesn't matter if the risk assessment is to avoid acute hearing loss in the first place. On the other hand, if it is the chronic endpoint that is of concern, then differential ability to recover is another component of susceptibility. Thus, depending on the nature of the endpoint, this is either irrelevant or not distinct from susceptibility.

In summary, I believe that vulnerability is really a combination of two components: differential exposure and differential susceptibility. Differential exposure is handled by properly accounting for the dose-response relationship(s) and individual or population exposure assessment. Susceptibility in turn has two components: preparedness to withstand and (when a chronic endpoint is evaluated) ability to recover. The document can then note that both of these may be impacted by prior exposures.

I agree completely, though, that by accounting for multiple factors, cumulative risk assessments should be uniquely suited to addressing issues of vulnerability.

b. Chemical & Non-Chemical Stressors

I do not see that determining cumulative risks for chemical and non-chemical stressors is inherently more problematic or difficult than working with multiple chemicals that act by different mechanisms or modes of action. My awareness of disease probability models coming from the field of medicine is that these combine risk factors that are diverse in nature as easily as they combine similar factors. When trying to base the risk on a mechanistic understanding or model, the real challenge is in combining the effects of different stressors which act by different mechanisms, whether those stressors are all chemical or not. The long-term approach that will best enable predictions of cumulative response from differing agents is the development of biological systems models such as Entelos' PhysioLab technology, such that the impacts of multiple stressors can be simulated.

c. Different "Types" of Risk

Combining risks of different types of responses into a single metric is clearly a key issue. Any such combination must implicitly make use of a valuation which converts the likelihood or degree of each separate response to a single metric, be that QALYs, DALYs, or dollars. For site- and region-specific RAs with a clearly defined and manageable number of stakeholders, it is most appropriate that those stakeholders define the relative valuation for each response considered to achieve a metric to be used in management decisions. In fact, even if this is not explicitly done, any risk management decision cannot avoid implicitly weighting or valuing multiple responses.

But where a relatively small number of responses are being considered, it may often be possible to not combine them. In particular, if the objective is to assure that each response remains below some 'maximum impact' level which is response-specific, then the achievement of that objective can be pursued without a combined metric.

Specific Observations

Figures: The figures are quite grainy and the text in them is very hard to read (eg, Fig. 2-2 and 2-3).

P. 7, lines 12-17: It should be noted that description of interactions may simply be to say that the different stressors act independently (as per toxicological independence defined on p. 38), and hence there is no interaction.

P. 9, lines 40-41: Why is it preferable that the endpoints be independent? And what is meant by "independent"? In an aquatic system, water turbidity will effect the health of some fish, so these are not independent, but I do not see why that dependence should create a bias against using both turbidity and fish health as endpoints.

Section 2 – Planning, Scoping, and Problem Formulation Phase

What aspects of this section, if any, are unique to cumulative risk assessment? It may be that none are unique – it seems fairly general to me – and that is OK. But then

this should be acknowledged. Alternately it might be worth adding material on what one should do in a cumulative RA that differs from that for a single-agent ... such as identifying what stressors are to be considered.

One point that probably can't be over-emphasized: while it is possible to assure that all stakeholders have been heard and their opinions given due consideration and weight, that doesn't mean that everyone will get what they want.

P. 17, line 23: The 2nd half of this paragraph, starting with "For example...", seems totally disconnected from the first. I was confused by it.

P. 41, last para. (goes onto p. 42): While it may often be the case that the response assessment depends on the timing of multiple exposures, and hence cannot be performed independently of the exposure assessment, I do not believe the converse will typically be true. In other words, I expect that it will usually be possible to conduct the exposure assessment first, rather than together with the response assessment, although the response assessment will have to wait for those results.

3.3.2 – Biomarkers and Biomonitoring (pp. 47-)

Many biomarkers are not cumulative in the sense defined here because they are chemical- or stressor- specific. For example hemoglobin adducts formed from benzene oxide are such a biomarker. Thus the statement on p. 48, line 9, is simply incorrect – that may be true of biomarkers of effect but not biomarkers in general. A better term might be "aggregate". However it should also be recognized that biomarkers do not necessarily reflect the entire history of exposure. As red blood cells turn over in the body, hemoglobin adducts will be lost: so the current level of adducts will have little dependence on benzene exposures that occurred 6 months ago. Thus biomarkers are only cumulative over a particular time frame.

Risk Characterization

It's important to document how stakeholder input has influenced the process, and also where suggestions were not included and why. This documentation provides the assurance that individuals have at least been heard and supports their participation.

Appendix C – Background Exposures

For the purpose of identifying management options, in particular how well exposures can be reduced and the most effective means, identifying background levels vs. those from specific sources is critical.

P. 50, line 35, and p. 51, lines 27-29: While the meaning of common metrics may be less clear than specific individual responses, it is not necessarily obvious why this should make them less suitable for absolute risk-management decisions. Please provide some explanation.

Post-Meeting Addendum

To follow up on my comments during the meeting, I mentioned software tools that are now being developed to describe integrated physiological systems which have the potential to allow for mechanistic modeling of the effects of multiple agents on a given

system. While it is not my intent to promote commercial products, the fact is that several of these have been privately developed and are currently only available on that basis. Nevertheless, it is worthwhile to be aware of them for the future of cumulative risk assessment.

Particular resources are: Physiome.org (<http://physiome.org/>), a collaborative effort to link a number of models; the Physiome project at the University of Auckland (<http://www.bioeng.auckland.ac.nz/physiome/physiome.php>); PhysiLab by Entelos, Inc. (www.entelos.com) (I believe they have models for asthma, cardiovascular disease, and kidney disease); and the Immune System Modeling & Simulation tools at Princeton University (<http://www.cs.princeton.edu/immsim/>). This is not a comprehensive list of such modeling efforts. Further, these are mostly if not completely still in development and likely in need of modification to suite a toxicological analysis. But I believe these will become increasingly important to biomedical research in the future and could be powerful tools for cumulative risk assessment. So I think they should at least be mentioned in the framework document.

References:

CIIT (1999). Formaldehyde: Hazard characterization and dose-response assessment for carcinogenicity by the route of inhalation (Revised edition): Chemical Industry Institute of Toxicology, Research Triangle Park, NC

Haddad, S., Beliveau, M., Tardif, R. and Krishnan, K. (2001). A PBPK modeling-based approach to account for interactions in the health risk assessment of chemical mixtures. *Toxicol. Sci.* 63, 125-131.

Haddad, S., Charest-Tardif, G. and Krishnan, K. (2000). Physiologically based modeling of the maximal effect of metabolic interactions on the kinetics of components of complex chemical mixtures. *J. Toxicol. Environ. Health, Part A.* 61, 209-223.

Haddad, S., Tardif, R., Charest-Tardif, G. and Krishnan, K. (1999). Physiological modeling of the toxicokinetic interactions in a quaternary mixture of aromatic hydrocarbons. *Toxicol. Appl. Pharmacol.* 161, 249-257.

**Review by
Curtis Travis - Quest Technologies**

Scientific Peer Review for Framework for Cumulative Risk Assessment

By

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5/21/02

In general, I found the document to be well written, easy to understand, and to provide a comprehensive framework for evaluation of cumulative risks to humans from exposure to multiple stressors. The key elements of the proposed cumulative risk assessment framework are traditional and follow accepted risk assessment practice. The document discusses most of the major issues associated with the issue of cumulative risk. A strong point of the document is that it ties the proposed framework to other risk assessments (like pesticides or quality of life) currently being done in various parts of EPA. I think the document could be improved somewhat by giving more attention to steps in the process that are unique and critical to cumulative risk assessment. In general however, I believe that the current document represents a complete and comprehensive framework for analysis of cumulative risks resulting from exposure to multiple stressors.

I first answer the questions posed to the reviewers.

1. *Does the Framework adequately capture, describe, and reasonable organize the key issues of cumulative risk assessment so as to serve as an adequate foundation for the development of future guidance?*

In general the document does an adequate job of describing the key issues of cumulative risk assessment. However, more attention needs to be given to steps in the process that are unique and critical to cumulative risk assessment. The document needs to stress the following points:

- A cumulative risk assessment must identify a unique well, defined assessment endpoint. A general impact like the “health of a community” or “overall human health impact” is not well defined. Assessment endpoints that cannot be linked with measurable attributes are not appropriate for a cumulative risk assessment.
- A cumulative risk assessment must identify a common effect endpoint for all stressors. The combined impact of several stressors can only be evaluated when they have a common effect endpoint.
- It should be pointed out that assessment endpoints that cannot be measured directly but can be represented by measures that are easily monitored and modeled still provide a good foundation for the risk assessment.
- The document should separate stressors into those that directly cause the effect (direct stressors) and those that modify the magnitude of the effect (modifying stressors).

- Direct stressors can be separated into three classes: toxicologic independence (separate modes of action), toxicologic similarity (common modes of action), and toxicologic interaction (interacting modes of action).
 - Modifying stressors can act upstream of the mode of action of direct stressors, downstream of the mode of action, or both.
 - It may sometimes be desirable to have multiple assessment endpoints. However, they cannot be combined into single indicator of impact except through definition of some index of relative importance. This index definition process is a risk management step, not a risk assessment step.
 - The document should note that the Cumulative Risk Assessment Framework follows the NRC Risk Assessment Paradigm in all respects except that the toxicity component and the exposure component must be evaluated together rather than separately.
2. ***Does the Framework document include any scientific or technical inaccuracies in its presentation for terminology, assessment structure, and methods?***

No, I did not find any scientific or technical inaccuracies in the document. However, I do not think the document gives sufficient attention to the problem of defining assessment endpoints and determining the relationship between stressors and assessment endpoints. I realize that detailed prescriptions cannot be given, but a general framework is within the scope of this document.

3. ***Does the Framework adequately characterize the importance of uncertainty analysis in cumulative risk assessment?***

The document discusses the importance of uncertainty in the overall framework of the risk analysis process. However, I believe the discussion of uncertainty could be improved. The document correctly distinguishes between uncertainty and variability and discusses uncertainty in combining cancer risks estimates from exposure to multiple chemicals. However, these are not the main types of uncertainty that arise in cumulative risk assessment. There was no discussion of uncertainty in determining the combined impact of stressors nor how one must assess such uncertainty.

I would like to see more discussion of the unique uncertainties that may arise in cumulative risk assessment. What are the major categories of uncertainties that will arise in cumulative risk assessment? Possible answers to this question are:

- Direct stressor uncertainties (these can be assessed in traditional ways)
- Specific modifying stress uncertainties (those that directly affect the mode of action of direct stressors). These uncertainties can be assessed in traditional ways since they deal with mode of action.
- General modifying stress uncertainties (those that do not affect the mode of action, but increase general vulnerability). Maybe these could be handled through an uncertainty factor, like a factor of 10.

Are there any uncertainties that are unique to cumulative risk assessment? The answer is obviously yes. What can the document say about these? Currently, the document adds little insight into the issue of uncertainty in cumulative risk assessment.

4. ***Comment on the adequacy and accuracy of the Framework's presentation in each of the following areas:***

a. Vulnerability

I like the fact that the issue of vulnerability is given a separate section in the document and that four components of vulnerability are identified. This approach needs to be taken with other important issues in the document. However, a more through discussion of vulnerability needs to be added to the document. The definition given of vulnerability is not clear. The document lists four components to vulnerability: The susceptibility of the human or ecological receptors, the differential exposures of the receptors, the differential preparedness of the receptor to withstand the insult from exposure, and the differential ability to recover from the effects. It is not clear how susceptibility differs from preparedness to withstand the insult or from ability to recover from the insult. It would seem that these are two aspects of vulnerability.

The document needs to point out that vulnerability is an issue that needs to be considered while identifying stressors.

Why is vulnerability a special issue for cumulative risk assessment? How do different stressors affect different aspects of vulnerability and then combine to affect overall vulnerability?

As pointed out in the EPA guidance for Ecological Risk assessment: **Sensitivity** refers to how readily a receptor is affected by a particular stressor. Sensitivity is directly related to the mode of action of the stressor. For example, individual physiology and metabolic pathways influence chemical sensitivity. Sensitivity is influenced by individual and community life-history characteristics. Sensitivity may be related to the life stage of a receptor when exposed to a stressor. Frequently, the young are more sensitive to stressors than adults. Finally, sensitivity may be increased by the presence of other stressors or natural disturbances. For example, the presence of insect pests and disease may make plants more sensitive to damage from ozone.

There is not much discussion of these issues in the document.

b. Cumulative Risk Assessment Involving Chemical and non-Chemical Stressors

I'm not sure as to the purpose of this question. In some sense, the entire document is about this issue. I could not find a section in the report that specifically addressed this point, but I would say it is adequately addressed throughout the document.

c. Cumulative Risk Assessment Involving Different Types of Risk

I believe this issue is adequately addressed.

Assessment Framework

A major portion of the guidelines is devoted to describing the interaction among risk assessors, risk managers, and interested parties at the beginning (planning and problem formulation) and end (risk characterization) of the risk assessment process. The Guidelines emphasize that the interface between risk assessors, risk managers, and interested parties is critical for ensuring that the results of the assessment can be used to support a management decision. Most of this is standard guidance that would apply to any type of risk assessment, and I'm not sure of the value of repeating it yet once again, other than in general terms.

This document does an adequate job of describing the key issues of cumulative risk assessment, but more attention needs to be given to steps in the process that are unique and critical to cumulative risk assessment. The assessment framework presented in this document follows the standard risk assessment paradigm, with three main phases to a cumulative risk assessment: (1) planning, scoping and problem formulation, (2) analysis, and (3) interpretation. It is a little disappointing that the document discusses little that is unique to cumulative risk assessment. Most of the discussion on scoping is standard risk assessment guidance. It focuses on stakeholder participation (page 14-16), scope of assessment (page 16-22), conceptual model (page 22-30). Not much of this discussion is unique to cumulative risk assessment nor does it highlight issues in cumulative risk assessment that need special attention. For example, this section does not say that a key step in the scoping process for cumulative risk assessment is to identify well-defined assessment endpoints. This is a critical issue for cumulative risk assessment. Figures 2-2 and 2-3 do include assessment endpoints as part of the process, but the text does not mention them as important issues. (I discuss this issue more below).

With regard to identification of stressors, the text just says that it needs to be done. No extra guidance or discussion is given as to special issues that will arise when conducting a cumulative risk assessment. The major difference between a cumulative risk assessment and a regular risk assessment is the special attention that must be given to identification of stressors, assessment endpoints, and the relationship between them. This document needs to say more on the issue. Identification of assessment endpoints and stressors is a circular process. One can start with a list of possible stressors and identify possible effects. But then one has to identify those effects of primary concern and adjust the list of stressors to those that affect this endpoint.

How does one go about grouping stressors in a way that will facilitate cumulative risk assessment? The EPA pesticide cumulative risk assessment guidance identifies chemicals with a common mechanism of toxicity as one possible grouping. This suggests at least two groups: stressors that directly cause the toxic effect (the assessment endpoint) and stressors that modify the magnitude of the toxic effect. Current risk assessment methodologies suggest methods for assessing the affect of single toxic agents (there are basically two methods: those for carcinogens and those for non-carcinogens). Progress has been made for assessing the affect of multiple toxic

agents with a common mode of action (the EPA pesticide guidance and the TEQ methodology for dioxins are examples). How does one handle modifying stressors? One way might be to add another uncertainty factor to account for the presence of modifying stressors.

Approaches to Cumulative Risk Assessment

The document lists four approaches to cumulative risk assessment. Attempting to define the different approaches to cumulative risk assessment is an excellent idea, but this section is not clear and confuses the issue. It purports to present four approaches to cumulative risk assessment, but does not do so in a clear manner. After reading this section, I would like to ask the reader to tell me what are the four methods? I don't believe most readers could answer that question. I comment on each of these:

- Using single stressor information to provide information on multi stressor situations. This approach uses a single assessment endpoint, but attempts to assess to impact of multiple stressors on this endpoint by considering the impact of stressors independently. With the current state of knowledge regarding multiple impacts, this is the approach that will be used most of the time.

The document seems to apologize for this approach. It says it can be used for hazard identification. It says to go further in terms of quantitative risk assessment requires consideration of the potential for joint toxicity. It says transport and environmental transformation of a chemical can be influenced by presence of other chemicals. It says exposure to one stressor may influence the uptake of a second stressor.

It is fine to point out the weaknesses of this approach, but the point of this section of the report is to list four approaches to cumulative risk assessment. This is one approach and the most likely to be used! The document should say something positive about the approach and why it is a sound approach. The document seems to say, this is an approach but it is not sound (A statement I do not believe). If this approach is not sound, what is the document suggesting be done? This is the only approach currently available.

- Using information of multiple stressor interactions. This approach uses a single assessment endpoint, but combines all information on stressor interaction to arrive at an assessment of harm or risk. This is a true cumulative risk assessment. This is what one is always attempting to accomplish. The other three approaches are approximations to this situation.
- Using decision indices. The document notes that one approach to addressing the complexity of cumulative risk assessment is to combine the various measures of harm into an index like the smog index or the Hazard Ranking System used in Superfund. This is a valid exercise. However, each of the individual components of the index must be well-defined and approached in some concrete way. Thus, this method is not so much an approach to cumulative risk assessment, as a way of presenting an array of complex information. You could say it is an approach, if you define the approach as characterizing harm to a system by using multiple measures of stress. Thus, rather than using decision indices, this approach is really using multiple assessment endpoints. The decision indices are just a way of summarizing the result of using multiple assessment endpoints.

- Using a probabilistic approach. The document does not define what it means by a probabilistic approach, other than the intuitive notion that it must have something to do with probabilities. What is a probabilistic approach to cumulative risk assessment? What would be its main components? I'm actually not sure this is really an approach to cumulative risk assessment as opposed to a method for presenting risk estimates (its hard to tell since this approach was not defined in the document.)

I believe there is another approach to cumulative risk assessment that is not mentioned in the document. That is a combination of analytic and safety factor. This approach would quantitatively estimate the risk from the direct stressors and then add a safety factor to account for the additional impact from modifying stressors. This approach might be the most currently viable and deserves some discussion in the document.

Definition of Assessment Endpoint

A major deficiency in the present document is its lack of discussion of assessment endpoints. A definition of assessment endpoint needs to be added to the document. The major points that need to be made are:

- Cumulative risk assessments can only be performed on discrete well-defined endpoints. A general impact like the "health of a community" or "overall human health impact" is not well defined
- Assessment endpoints that cannot be linked with measurable attributes are not appropriate for a risk assessment
- The combined impact of several stressors can only be considered when they have a common effect endpoint. If stressors have different effect endpoints (and there is a desire to include these stressors), then more than one assessment endpoint must be identified.

It is possible to use a general assessment endpoint like "health of a community" in a cumulative risk assessment if one defines "health of a community" in terms of a collection of well-defined assessment endpoints. For example, in the "Quality-of-life Assessments (Appendix F)", a set of "quality-of-life" criteria (assessment endpoints) is used to describe various aspects of quality of life. Each of these criteria measures some aspect of overall quality of life. However, each of these measures needs to be well defined, which is not the case in the "quality-of-life" example given in Appendix F. For example, one of the criteria given is "economic well-being" and another is "fairness". These endpoints are not well defined and will need further refinement to obtain concrete, measurable definitions before they can be assessed.

Stressors Stressors can be separated into the groups: those that directly cause an effect (direct stressors) and those that modify the magnitude of the effect (modifier stressors). These groups can be further divided.

Direct stressors can be separated into three classes depending on their modes of action: toxicologic independence (separate modes of action to produce the same effect), toxicologic similarity (common mode of action to produce the same effect), and toxicologic interaction (interacting modes of action to produce a common effect). (Remember that the combined impact

of multiple stressors can only be assessed if they impact they have a common effect endpoint. This is a key observation that is missing from the document.) Methodologies for the first two have been or are in the process of being worked out. It is the third category that currently presents difficulty.

The example in the text on page 38 of toxicologic independence is somewhat misleading. The example given is joint but low exposure to heat (causing minor elevated heart rate) and toluene (causing minor hearing loss). A common health effect endpoint has not been selected so this is not a cumulative risk assessment in the sense of evaluating the cumulative impact of two stressors on a common, well-defined endpoint. It is the impact of two separate stressors on two separate endpoints. (I think this type of assessment should be considered to be a component of the class of “aggregate assessments”.)

The document points out (page 38) that in the case of toxicologic independence, “response addition” can be applied for each adverse effect that the stressors have in common. The text goes on to say, “When all the single stressor risks are low, the joint risk of a common effect under response addition can be approximated by the simple sum of the single stressor risks.” This is in the section on toxicologic independence. In fact, this is a rule that holds for all stressors regardless of mode of action. This point needs to be made clear in the document.

Modifying stressors can act upstream of the mode of action of direct stressors, downstream of the mode of action, or both. Unfortunately, exactly where they act is often not known. Even more difficult to deal with is the fact that nothing may be known about the mode of action of most modifying stressors.

Additivity of Effect

The document discusses additivity of effect, but the discussion is disjointed. The document should make clear:

- **Additivity for Toxicologic Independence** For stressors toxicologic independent stressors (separate independent modes of action to produce the same effect), the cumulative effect is the simple sum of the single stressor risks. The effect of modifying stressors on the toxicologic independent class is to modify the magnitude of impact of each direct stressor. Once the impact of modifier stressors on each direct stressor independently is known, the cumulative effect is the sum of the single modified stressor risks. Thus, in theory the methodology for performing a cumulative risk assessment on stressors with independent modes of action is known. This point should be made in the document.
- **Additivity for Toxicologic Similarity** For stressors in the toxicologic similarity class (common mode of action to produce the same effect), the cumulative effect is found by dose addition (the relative potency approach).

Modifying stressors in the case of toxicologic similarity can only act in one of three ways: they can act upstream of the common mode of action, downstream of the common mode of action, or both.

- If the modifying stressors act upstream of the common mode of action, they can change the relative potencies of the direct stressors; that is, increase or decrease the potency (as measured in dose equivalents) of the direct stressors themselves or relative to each other. In this case, the dose-response relationship between dose (as measured in dose equivalent) and effect is not changed. What may be changed in the effective dose of each direct stressor.
- If the modifying stressors act downstream of the common mode of action, they can change the dose-response relationship, but not the potency (as measured in dose equivalents) of the direct stressors. Thus, in this case the modifying stressors leave unchanged the relative ratio of the dose equivalents, but change the overall magnitude of effect of the reference stressor.
- **Additivity for Toxicologic Interaction** For stressors in the toxicologic interaction class (interacting modes of action to produce a common effect), Additivity occurs, as the document points out, when single stressor risks are low. This is rarely the case in risk assessment.

A Single Metric of Impact

The document spends considerable time discussing the possibility of developing a single metric for multiple types of hazard. The implication is that this process is somehow part of cumulative risk assessment. It is not! A cumulative risk assessment can only be performed on discrete well-defined endpoints.

The document needs to be clear that there is a difference between the following two processes:

1. Combining discrete impacts into an assessment of overall health
2. Defining overall health in terms of discrete impacts.

The document now intermixes these two concepts. For example, the following statements are made:

- “Ideally a cumulative risk assessment would provide ...an integration of these projections into a qualitative characterization of overall potential impact to human health.” Page 49.
- “Some cumulative risk assessments may employ some sort of single, common metric to describe overall risk.” Page 49.
- Some cumulative risk assessments “require synthesizing a risk estimate (or risk indication) by “adding up” risks for different parts of the risk picture.” Page 49.
- “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.” Page 54.

All of these statements utilize the first bullet concept that it is possible to “Combine discrete impacts into an assessment of overall health.” I do not believe that this is possible. All of the examples given in the document of developing a single index use the second bullet concept of defining overall health in term of discrete impacts.” For example, on page 51, the document says, “Recently, EPA has been working on several index-based approaches to dealing with cumulative risk issues.... This index uses a vulnerability index, and gauges the overall well-being of a locale

and various subpopulations.” This is a proper use of an index to measure well-being since EPA has defined “well-being” to be that which the index measures. (It may or may not be true that this index actually provides a good measure of well-being).

Combining Impacts

The document needs to be clear that there is a difference between the following two processes:

- Combining the impacts of multiple stressors to arrive at a combined impact of the stressors on a single, well-defined assessment endpoint (calculating impact of multiple stressors on single endpoint and combining them)
- Combining multiple impacts on a system to arrive at an assessment of overall system impact (calculating impact of stressors on multiple endpoints and combining them)

The document now intermixes these two concepts. For example, In Appendix A, page 84, the document says, “Another key concept in the definition of cumulative risk assessment is that it represents the combined risk from multiple stressors. This implies that, in some cases, it may be necessary to combine disparate measures of risk (i.e., different types of effects) to simplify the expression of cumulative risks.”

The document is clear that an assessment of the effect of combined exposures (from different environmental pathways) to a single compound is not to be considered a cumulative risk assessment. It is also clear that multiple effects or impacts may be considered (page 9). The document says that a cumulative risk assessment would ideally “provide projections regarding the potential for a particular complex exposure to cause particular effects to different physiological systems, and also provide an integration of these projections into a qualitative characterization of overall potential impact to human health.” This statement leads to two problems:

1. It implies that “overall impact on human health” is a proper assessment endpoint for cumulative impact assessment
2. It raises the issue of how does one assess “overall impact on human health” which is not addressed in this document. Simply combining individual impacts into a single index may not accomplish this. It may be better to leave the impacts separate.

Specific Comments

Page 2, footnote 2. The text says, “A stressor is a physical, chemical, biological, or other entity that can cause an adverse response in a human or other organism or ecosystem.” It may be that a stressor does not cause harm directly, but only makes a human, organism, or ecosystem more susceptible to harm by other stressors. An example would be poor nutrition causing a decrease in immune function making one more susceptible to infection.

Page 6, Definitions. A definition of assessment endpoint needs to be added. The point needs to be made that a cumulative risk assessment needs a well-defined endpoint. Overall impact on human health is not such an endpoint. A collection of assessment endpoints might be used to

measure various components of “overall human health”. An example is “Quality-of-life Assessments (Appendix F)” Here a set of “quality-of-life” criteria (assessment endpoints) is used to describe various aspects of quality of life, but no assessment is made of overall quality of life. Even in this example, the set of “quality-of-life” criteria are not well-defined assessment endpoints. For example, one is economic well-being and one is fairness. These endpoints need measurable definitions or they cannot be assessed.

Confusion over this issue permeates the document and needs to be straightened out in the definition section.

Page 8, Line 33. The document is clearer with regard to the definition of stressors when discussing the risk of breast cancer in women. The document states, “The “stressors” in the example of the breast cancer model are certain factors known to be correlated with that form of cancer, such as the woman’s age at first childbirth, age at menarche, having a previous biopsy with atypical hyperplasia, and others.”

Page 9, Table. The table says that cumulative risk is a population-based process. What does this mean? How is it different from a regular risk assessment? In any risk assessment, one must identify a population being assessed, whether it is a farm family or and an industrial worker. How is cumulative risk assessment different?

Page 11. Line 14. The text says, “Cumulative risk assessment, being a population-based or place-based analytic-deliberative process, ...” The text has not really defined what a population-based or place-based process is.

Page 37, line 12. The text says, “component based mixture assessments are rarely evaluated using the strict NRC paradigm, because the exposure and toxicity information must be compatible, requiring some iteration to obtain toxicity information that is relevant to the actual exposure estimates.” This is a good point that needs to be made more prominent in the text. You cannot separate the toxicity assessment phase and the exposure assessment phase of a cumulative risk assessment.

Page 38, line 40. The text says, “When all the single stressor risks are low, the joint risk of a common effect under response addition can be approximated by the simple sum of the single stressor risks. For example, if reproductive toxicity is the general effect common to the multiple chemicals, the cumulative risk of reproductive effects (at low single chemical risk levels) is approximately the sum of the single chemical reproductive risks.” This appears in the section on toxicologic independence. Does this only hold for toxicologic independence or for all toxicity?

Page 41, line 29. This section talks about traditionally, the exposure and dose-response steps of a risk assessment are separated. It proposes that in a cumulative risk assessment this may not be appropriate. It is not clear why this is not appropriate. Nor is it clear how one would combine the steps. What point are you trying to make? That different exposure situations require different dose response functions? That there is uncertainty in the dose response function, so you need a range of dose response functions?

Page 41, line 45. The text says, "If the dose response data do not represent the same conditions as the exposure being assessed, ..." Here it seems like you are saying that this is something unique to cumulative risk assessment. The same problem arises in regular risk assessment. One often has a dose-response for ingestion, but needs one for inhalation. There are methods for making the adjustment. However, I do not see how this is related to the issue of separating or combining the exposure and dose-response steps in a risk assessment. The document needs to be more explicit about what issue it is trying to make.

Page 42, line 5. The text says, "toxicologic interactions have been shown to change using the same doses but with a reversal of the sequence of exposure (i.e., chemical B then A instead of A then B), so that the exposure and dose-response steps must be compatible and performed together." What does the text mean by "must be performed together"? It is apparent that one must use the correct dose-response function for the situation, but it still looks like the operations (exposure and dose-response) are performed in sequence, not together. I am not even sure what it would mean to perform exposure and dose-response "all together". Again, the text needs to be more explicit about what point it is trying to make.

Page 43, line 5. The text says, "The issues for these cases are now presented along with their main research implications, starting with the simplest case where only chemical interactions are considered." I do not see where these cases are presented. There are only two paragraphs following this sentence.

Page 43, line 8. This section is a good addition.

Page 43, line 20. This paragraph is a little confusing, but still contains good information. It would help if the paragraph gave some indication of what should be done about the concepts of synergism and antagonism for cumulative exposure. Are they to be abandoned completely when one has multiple chemical exposures or is there a way to define these concepts that makes sense? It would seem that using the "dose additive" approach to defining no-interaction is the way to go? If a mixture of chemicals causes a greater effect than the sum of the effects produced by each chemical alone, the situation is called synergistic. What is wrong with this definition in the case of cumulative exposure? The document needs to be clearer about this issue.

Page 44, line 16. The text says, "The main disadvantage of a simple index is that the uncertainties in its calculation are largely hidden." I'm not sure this is the main disadvantage. Why is this any different than any other risk assessment number? When one presents an estimate of cancer as 1.2×10^{-4} , the uncertainties in this calculation are also largely hidden! What is the difference?

Page 44, box. It would seem that a Hazard Index like that presented in the box would defeat the purpose of a cumulative risk assessment. This Hazard Index is based on the assumption of additivity of effects, while the purpose of a cumulative risk assessment is to understand the possible impact (additive, non-additive) of multiple exposures.

Page 44, line 25. The text states, “One alternative for addressing multiple effects is to recast these qualitative judgments in terms of severity categories or levels of concern” It then states, “The result is not a risk of a particular toxic effect, but rather a risk of exceeding a certain minimum toxic severity level, or level of minimal concern.” This is just the weakness in the Hazard Index that you were trying to avoid.

Page 45, line 14. The text needs to provide a little detail on the approach taken by Bogen. If you are citing it as an example, you need to tell why it was good. What did he do that added to the field of cumulative risk assessment?

Page 45, line 21. This paragraph is not clear. The document states, “Any approach to cumulative risk assessment needs to carefully define the set of relevant endpoints.” The document has said earlier that a specific endpoint must be defined. But why does it have to be carefully defined? What are the problems that may arise from non-careful endpoint definition? The document states, “the risk of inducing a given endpoint may differ among different people in a population at risk for some endpoints.” This is true of any risk assessment. Why does this fact introduce that need for careful definition of endpoint? And even with a careful definition, one will always still have this problem. What is the point that the document is trying to make here?

Page 45, line 27. The text says, “Defining the latter risks in terms of individual risk *per se* will thus complicate calculating cumulative risk if a probabilistic approach to cumulative risk assessment is used.” It is not clear why this is true. Even in a probabilistic risk assessment, risk is defined on an individual basis. The probabilistic risk assessment gives the probability distribution of individual risk. Again, the document needs to be clear on the point it is making.

Page 45, line 31. The text says, “In contrast, the probabilistic approach to cumulative risk assessment may be facilitated by defining the risk of a given endpoint in terms of **population risk**, i.e., in terms of the predicted number of cases of that endpoint.” It is not clear how using population risk instead of individual risk makes probabilistic risk assessment easier. To obtain population risk, one still has to determine how individuals will respond and then take account of the number of individuals involved. It seems like population risk and individual risk are just two different measures of impact. The risk assessment process to arrive at an estimate of impact is basically the same for both.

Page 45, line 33. The text says, “Alternatively (or additionally), similar simplification can be achieved for all heterogeneous endpoints by defining the risk of that endpoint only with respect to those persons in the population at risk who are reasonably maximally exposed (e.g., individuals adjacent to a proposed source).” It is true that a risk assessment may want to focus on maximally exposed individuals, but I don’t see what this has to do with making probabilistic risk assessments better. I think this sentence belongs above in the section defining population-based risk assessment, no in the section on probabilistic risk assessment.

Page 48, Section 3.3.3. In this section the document discusses the issue of developing a single index of risk when there are multiple impact endpoints. The document is not sufficiently clear that creation of a single index of risk is more of a risk management decision than a risk

assessment decision. Unless the index of risk is a well-defined assessment endpoint (than can theoretically be measured), it is just a risk management tool to aid in decision making and risk communication. If a cumulative assessment is to use an index of risk, it should state during the scoping phase that the assessment end point will be a defined function (the index of risk) of multiple assessment endpoints. This is obviously a risk management decision. Page 49, line 1. The text says, "Ideally, this evaluation would provide projections regarding the potential for a particular complex exposure to cause particular effects to different physiological systems, and also provide an integration of these projections into a qualitative characterization of overall potential impact to human health." This implies that "overall impact on human health" is a well-defined endpoint for cumulative risk assessment. It is not and this needs to be made clear in the document.

Page 49, line 9. This assessment had well defined "observed adverse conditions" and preformed a cumulative assessment for the impacts on these conditions. It did not attempt to combine individual impacts into an index of overall impact.

Page 49, line 33. The document says some cumulative risk assessments "require synthesizing a risk estimate (or risk indication) by "adding up" risks for different parts of the risk picture." I believe this sentence is misleading. Cumulative risk assessment does not require this. Cumulative risk assessment can only be performed on discrete well-defined endpoints. One may want to present these in matrix form, but combining them into an assessment of overall impact is not scientifically possible (unless that overall impact is defined by some single measurable quantity).

Page 54, line 11. The text says, "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." Again this implies that it is possible (and the proper function of a cumulative risk assessment) to combine endpoints into a single measure of impact.

Page 54, section 4.1. This section is more about risk assessment in general than about cumulative risk assessment.

Page 61, line 12. The document says, "The Framework report 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." This statement is not true. The document has discussed that lack of a methodology is a problem, but it has not done much to discussing how to improve current methods.

Page 62, section 4.4. This section is more about risk assessment in general than about cumulative risk assessment

Appendix G

Draft Framework for Cumulative Risk Assessment

EXTERNAL REVIEW DRAFT

EPA/630/P-02/001A
April 23, 2002

Framework for Cumulative Risk Assessment

Risk Assessment Forum
U.S. Environmental Protection Agency
Washington, DC 20460

DISCLAIMER

This document is in the process of being reviewed in accordance with U.S. Environmental Protection Agency's peer and administrative review policy. It has had extensive peer involvement in development (including other Federal, State, and public involvement), but it has not yet completed the formal peer review process or administrative review process, so it should not be quoted or cited. The mention of commercial products is for illustration only and in no way implies EPA endorsement of these products.

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Acknowledgments

1
2
3 This U.S. Environmental Protection Agency (EPA) report has been developed under the
4 auspices of EPA’s Risk Assessment Forum, a standing committee of EPA scientists charged with
5 developing risk assessment guidance for Agency-wide use. An interoffice technical panel
6 chaired by Michael Callahan (Region 6) was commissioned to write this report. Other members
7 of the panel are Edward S. Bender (Office of Science Policy), George L. Bollweg (Region 5),
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17 project as well as participated as a member of the panel. The resulting document included peer
18 involvement and peer review by scientists from EPA, other federal agencies, state agencies,
19 academia, public interest groups, and the private sector.
20

Foreword

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 develop methods to assist consideration of cumulative risks are some of the cases filed with EPA under Title VI of the *1964 Civil Rights Act*.

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

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

William P. Wood, Ph.D.
Executive Director
Risk Assessment Forum

Preface

1
2
3 In the past several years, cumulative risk assessment, aggregate exposure assessment, and
4 research on chemical mixtures has taken on increased importance. This is underscored by reports
5 such as the National Research Council’s 1993 report *Pesticides in the Diets of Infants and*
6 *Children*, (NRC, 1993) the 1994 NRC report *Science and Judgment in Risk Assessment*, (NRC,
7 1994), the 1995 National Academy of Public Administration report *Setting Priorities, Getting*
8 *Results* (NAPA, 1995), the 1997 report by the Presidential/Congressional Commission on Risk
9 Assessment and Risk Management titled *Risk Assessment and Risk Management in Regulatory*
10 *Decision-Making* (PCCRARM, 1997), and the EPA Science Advisory Board report *Toward*
11 *Integrated Environmental Decision-Making* (USEPA, 2000a). There also have been several
12 recent pieces of legislation that mandate the consideration of cumulative risk and variability
13 factors in the risk characterization process. Specifically, the *Food Quality Protection Act of 1996*
14 (FQPA) [PL 104-170, August 3, 1996] directs EPA in its assessments of pesticide safety to
15 focus, in part, on the cumulative effects of pesticides that have a common mechanism of toxicity,
16 considering aggregate dietary and non-occupational pathways of exposure.
17

18 Assessment of cumulative risk through complex exposures is one of the high priorities of
19 the Agency, especially in light of FQPA mandates, and is germane and of great interest to all
20 program and regional offices. This area of research is also directly applicable to children’s risk
21 issues. This Framework is meant to lay out broad areas where analysis might be conducted if
22 needed. It does not suggest that cumulative risk assessment is a tool that should be used with
23 every issue, nor does it suggest that when cumulative risk assessment is applied, that all areas of
24 analysis outlined or discussed here must or even should be conducted in every assessment. The
25 scope of the assessment will define the areas to be analyzed. In some areas discussed in this
26 Framework, the methodology for doing the risk analysis may not yet exist.
27

28 According to the expert panel report *Safeguarding the Future: Credible Science, Credible*
29 *Decisions* (USEPA 1992a), a key role of science at EPA is to reduce uncertainties in
30 environmental decision-making. The report points out that while many EPA programs have
31 historically focused on chemical-specific impacts, methods to assess or control the effects of
32 chemical mixtures and general stressors on human health and ecosystems remained to be
33 developed. In *Pesticides in the Diets of Infants and Children*, (NRC, 1993) the NRC
34 recommended that all exposures to pesticides – dietary and nondietary – need to be considered
35 when evaluating the potential risks to infants and children. Estimates of total dietary exposure
36 should be refined to consider intake of multiple pesticides with a common toxic effect. Further,
37 the report identifies important differences in susceptibility with age. NRC in *Science and*
38 *Judgment in Risk Assessment* (NRC, 1994) states that health risk assessments should generally
39 consider all possible routes by which people at risk might be exposed, and recommends this
40 approach universally in the assessment of hazardous air pollutants regulated by EPA under the
41 *Clean Air Act Amendments of 1990* [P.L. 101-549, November 15, 1990]. Regarding variability,
42 the NRC *Science and Judgment* report recommended that EPA assess risks to infants and

1 children whenever it appears that their risks might be greater than those of adults. Public
2 criticisms cited in this report include statements made by some experts that EPA does not appear
3 to recognize the possibility of synergistic interactions when multiple chemical exposures occur,
4 nor does it consider extreme variability among individuals in their responses to toxic substances.
5 A related issue is the problem of how risks associated with multiple chemicals are to be
6 combined. Finally, the FQPA [P.L.104-170, August 3, 1996], requires research on the influence
7 of complex exposures on non-cancer human health effects of pesticides and other toxic
8 substances.
9

10 The issue of cumulative risk is also an important issue with the general public. In public
11 meetings of Superfund stakeholders, held in late 1996 in San Francisco and Washington, DC,
12 and in early 1998 in Atlanta, the issue of cumulative risk was raised several times in each session
13 (USEPA 1996a, USEPA 1998a).
14

15 Cumulative risk assessments will identify the need for many different kinds of data –
16 some of them are not the data commonly used now for risk assessment – and often, cumulative
17 risk assessment will demand large quantities of such data. Until data bases and data generation
18 research can provide such data, for the near term, identification of critical data and research
19 needs may be the primary result of many cumulative risk assessment endeavors.
20

21 As of August 1, 2001, there were 19,533 pesticide products on the market (USEPA,
22 2001a), and 79,120 existing chemicals on the TSCA inventory (USEPA, 2001b). Each year, an
23 additional number of chemicals are added. Assessing the cumulative effect of these chemicals
24 will be a great challenge to the Agency and may become the primary issue in the risk assessment
25 field in the next ten years.
26
27

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List of Abbreviations and Acronyms

| | | |
|----|-------|---|
| 1 | | |
| 2 | | |
| 3 | ACGIH | - American Conference of Government Industrial Hygienists |
| 4 | AFS | - AIRS Facility Subsystem |
| 5 | AIChE | - American Institute of Chemical Engineers |
| 6 | AIHA | - American Industrial Hygiene Association |
| 7 | AIRS | - Aerometric Information Retrieval System |
| 8 | AMTIC | - Ambient Monitoring Technology Information Center |
| 9 | APCA | - American Crop Protection Association |
| 10 | APEX | - Air Pollution EXposure model |
| 11 | ARE | - Acute Reference Exposure |
| 12 | ATSDR | - Agency for Toxic Substances and Disease Registry |
| 13 | CARES | - Cumulative and Aggregate Risk Evaluation System |
| 14 | CBEP | - Community-Based Environmental Protection |
| 15 | CEQ | - Council for Environmental Quality |
| 16 | CFR | - Code of Federal Regulations |
| 17 | CHIEF | - Clearinghouse for Inventories and Emissions Factors |
| 18 | COHb | - Carboxyhemoglobin |
| 19 | CRIA | - Cumulative Risk Index Analysis |
| 20 | DALY | - Disability-Adjusted Life Year |
| 21 | DOT | - United States Department of Transportation |
| 22 | EPA | - United States Environmental Protection Agency |
| 23 | FIFRA | - Federal Insecticide, Fungicide, and Rodenticide Act |
| 24 | FQPA | - Food Quality Protection Act |
| 25 | GAO | - United States General Accounting Office |
| 26 | GIS | - Geographical Information System |
| 27 | HAP | - Hazardous Air Pollutant |
| 28 | HEC | - Human Equivalent Concentration |
| 29 | HRS | - Hazard Ranking System |
| 30 | HUD | - United States Department of Housing and Urban Development |
| 31 | IED | - Integrated Environmental Decision-making |
| 32 | ILSI | - International Life Sciences Institute |
| 33 | LADD | - Lifetime Average Daily Dose |
| 34 | LDP | - Locational Data Policy |
| 35 | LLE | - Loss of Life Expectancy |
| 36 | LOAEL | - Lowest Observed Adverse Effect Level |
| 37 | MOE | - Margin of Exposure |
| 38 | MSDS | - Materials Safety Data Sheet |
| 39 | NAAQS | - National Ambient Air Quality Standards |
| 40 | NAPA | - National Academy of Public Administration |
| 41 | NATA | - National Air Toxics Assessment |
| 42 | NEPA | - National Environmental Policy Act |

List of Abbreviations and Acronyms (Continued)

| | | |
|----|-----------|--|
| 1 | | |
| 2 | | |
| 3 | NHEXAS | - National Human Exposure Assessment Survey |
| 4 | NIOSH | - National Institute for Occupational Safety and Health |
| 5 | NOAEL | - No Observed Adverse Effect Level |
| 6 | NRC | - National Research Council |
| 7 | OAR | - Office of Air and Radiation (EPA) |
| 8 | OECA | - Office of Enforcement and Compliance Assurance (EPA) |
| 9 | OP | - Organophosphorous |
| 10 | OPP | - Office of Pesticide Programs (EPA) |
| 11 | OPPTS | - Office of Prevention, Pesticides, and Toxic Substances (EPA) |
| 12 | ORD | - Office of Research and Development (EPA) |
| 13 | OSWER | - Office of Solid Waste and Emergency Response (EPA) |
| 14 | P.L. | - Public Law |
| 15 | PAH | - Polycyclic Aromatic Hydrocarbon |
| 16 | PCB | - Polychlorinated Biphenyl |
| 17 | PCS | - Permit Compliance System |
| 18 | PM-10 | - Particulate Matter with diameter of 10 micrometers or less |
| 19 | pNEM | - Probabilistic NAAQS Exposure Model |
| 20 | QALY | - Quality-Adjusted Life Year |
| 21 | RfC | - Reference Concentration |
| 22 | RfD | - Reference Dose |
| 23 | SAB | - Science Advisory Board |
| 24 | SAP | - Scientific Advisory Panel |
| 25 | SAR | - Structure-Activity Relationship |
| 26 | SCRAM | - Support Center for Regulatory Air Models |
| 27 | SHEDS | - Stochastic Human Exposure and Dose Simulation model |
| 28 | SPC | - Science Policy Council |
| 29 | TEAM | - Total Exposure Assessment Methodology |
| 30 | TEMRAP | - The European Multi-Hazard Risk Assessment Project |
| 31 | TIA | - Transient Ischemic Attack |
| 32 | TRI | - Toxic(s) Release Inventory |
| 33 | TRIM.Expo | - Total Risk Integrated Methodology, Exposure Module |
| 34 | U.S.C. | - United States Code |
| 35 | UF | - Uncertainty Factor |
| 36 | USEPA | - United States Environmental Protection Agency |
| 37 | | |
| 38 | | |

Executive Summary

1
2
3 This report, “Framework for Cumulative Risk Assessment,” is the first step in a long-
4 term effort to develop cumulative risk assessment guidelines. Its primary purpose is to offer a
5 simple, flexible structure for conducting and evaluating cumulative risk assessment within EPA.
6 Although this Framework report will serve as a foundation for development of future guidelines,
7 it is neither a procedural guide nor a regulatory requirement within EPA and is expected to
8 evolve with experience. This Framework report is intended to foster consistent approaches to
9 cumulative risk assessment within EPA, identify key issues, and define terms used in these
10 assessments.

11
12 This Framework is meant to lay out broad areas where analysis might be conducted if
13 needed. It does not suggest that cumulative risk assessment is a tool that should be used with
14 every issue, nor does it suggest that when cumulative risk assessment is applied, that all areas of
15 analysis outlined or discussed here must or even should be conducted in every assessment. The
16 scope of the assessment will define the areas to be analyzed. In some areas discussed in this
17 Framework, the methodology for doing the risk analysis may not yet exist. Appendix A includes
18 a summary of areas where research is needed.

19
20 In this report, “cumulative risk” means “the combined risks from aggregate exposures to
21 multiple agents or stressors.” There are several key points which come from this definition of
22 cumulative risk. First, cumulative risk involves multiple agents or stressors, which means that
23 assessments involving a single chemical or stressor are not “cumulative risk assessments” under
24 this definition. Second, there is no limitation that the “agents or stressors” be only chemicals.
25 “Agents or stressors” may be chemicals, but they may also be biological agents, or physical
26 agents, or even the absence of a necessity such as habitat. Third, this definition requires that the
27 risks from multiple agents or stressors be combined. This does not necessarily mean “added,”
28 but it means that some analysis needs to be conducted as to how the risks from the various agents
29 or stressors interact. It also means that an assessment which covers a number of chemicals or
30 other stressors, but which merely lists each chemical with a corresponding risk without
31 consideration of the other chemicals present, is not an assessment of cumulative risk under this
32 definition.

33
34 Likewise, “cumulative risk assessment” in this Framework report means “an analysis,
35 characterization, and possible quantification of the combined risks to health or the environment
36 from multiple agents or stressors.” One key aspect of this definition is that a cumulative risk
37 assessment need not necessarily be quantitative, so long as it meets the other requirements.

38
39 The framework itself is conceptually similar to the approach used in both human health
40 and ecological assessments, but it is distinctive in several areas. First, its focus on the combined
41 effects of more than one agent or stressor makes it different from many assessments conducted
42 today (which, if multiple stressors are evaluated, are usually evaluated individually and presented

1 as if the others were not present). Second, by the fact that multiple stressors are affecting the
2 same population, there is increased focus on the specific populations potentially affected, rather
3 than a focus on hypothetical receptors. Third, consideration of cumulative risk may generate
4 interest in a wider variety of non-chemical stressors than traditional risk assessments.
5

6 The framework describes three main phases to a cumulative risk assessment: (1)
7 planning, scoping and problem formulation, (2) analysis, and (3) interpretation. In the planning,
8 scoping and problem formulation phase, a team of risk managers, risk assessors, and other
9 stakeholders establishes the goals, breadth, depth, and focus of the assessment. The end products
10 of this phase are a conceptual model and an analysis plan. The conceptual model establishes the
11 stressors to be evaluated, the health or environmental effects to be evaluated, and the
12 relationships among various stressor exposures and potential effects. The analysis plan lays out
13 the data needed, the approach to be taken, and the types of results expected during the analysis
14 phase.
15

16 The analysis phase includes developing profiles of exposure, considering interactions (if
17 any) among stressors, and predicting risks to the population or populations assessed. It is in this
18 phase that difficult technical issues are addressed and hopefully resolved, for example, issues
19 relating to toxicity of mixtures, vulnerability of populations, or the interactions among stressors
20 which may be chemical or non-chemical. The end product of this phase is an analysis of the risks
21 associated with the multiple stressors to which the study population or populations are exposed.
22

23 The third phase, interpretation, includes what is usually termed the “risk characterization”
24 discussion in risk assessment, where the risk estimates are put into perspective in terms of their
25 significance, the reliability of the estimates, and the overall confidence in the assessment. It is
26 also in this phase that an evaluation is made of whether the assessment met the objectives and
27 goals set forth in phase one.
28

29 The discussion of cumulative risk in this Framework report takes a broad view of the
30 topic, including many aspects of an assessment that might conceivably be conducted in the
31 future, even though techniques may not currently exist to examine every question. It also
32 includes aspects of cumulative risk which may be outside of EPA’s current legislative mandates,
33 and where expertise outside of the Agency would be needed to address certain questions if they
34 should arise. These aspects of cumulative risk are discussed here for the sake of technical
35 completeness and not as a recommendation that EPA perform all possible aspects of a
36 cumulative risk assessment in all EPA risk assessments – even all EPA cumulative risk
37 assessments.
38

39 EPA is currently engaged in activities which fall under various aspects of the cumulative
40 risk assessment umbrella. Some of these activities are listed as illustrations in the box on the next
41 page. The broad interpretation of cumulative risk in this Framework report allows these activities
42 to be put into perspective relative to one another, and can illustrate how they fit together under

Some Example Cumulative Risk Assessment Activities within EPA in late 2001

- The **Superfund Program** has updated its guidance on risk assessment to include planning and scoping for cumulative risk assessment and problem formulation for ecological risk assessments. The plan for the **Office of Solid Waste's** Surface Impoundment Study includes both a conceptual model and an analytical plan, per the agency guidance on planning and scoping for cumulative risk.
- The **Office of Water** is planning a watershed scale risk assessment involving multiple stressors in ecological risk. This approach was developed through a collaboration with external scientists and is now being field evaluated.
- Several **Regional Offices** are evaluating cumulative hazards, exposures, and effects of toxic contaminants in urban environments. In Chicago (**Region 5**), citizens are concerned about the contribution of environmental stressors toward endpoints such as asthma and blood lead levels. In Baltimore (**Region 3**), a regional/OPPTS/community partnership tried to address the long term environmental and economic concerns in three neighborhoods that are adjacent to industrial facilities and tank farms. **Region 6** (Dallas) is developing a geographic information system approach for planning and scoping cumulative risks.
- The Food Quality Protection Act (FQPA) of 1996 requires the EPA to consider the cumulative effects to human health that can result from exposure to pesticides and other substances that have a common mechanism of toxicity. The **Office of Pesticides Programs (OPP)** has developed guidance for conducting cumulative risk assessments for pesticides, and has prepared a preliminary cumulative risk assessment for Organophosphorous pesticides.
- The **Office of Air and Radiation's** air toxics program has a cumulative risk focus. Under the Integrated Urban Air Toxics Strategy (IUATS), OAR will be considering cumulative risks presented by exposures to air emissions of hazardous air pollutants from sources in the aggregate. Assessments will be performed both at the national scale - release of a national scale assessment for base year 1996 is planned for later this year - and at the urban or neighborhood scale. In partnership with ORD/NERL, the Office of Air Quality, Planning & Standards is developing the Total Risk Integrated Methodology (TRIM), a modular, modeling system for use in single or multi-media, single or multi-pathway, human health and ecological risk assessments of hazardous and criteria air pollutants at the neighborhood or city scale. The Agency's guidance for planning and scoping of cumulative risk was used to develop a conceptual model and analysis plan for the national scale air toxics risk assessment.
- The **National Center for Environmental Assessment (ORD)** has completed ecological risk assessment guidelines which support the cumulative risk assessment guidance. Five watershed case studies are being assessed to demonstrate the guidelines approach. Each of these cases deals with cumulative impacts of stressors (chemical, biological, and in some cases physical). In addition, NCEA has done a draft reassessment of dioxin and related compounds.
- The **Risk Assessment Forum** has convened a technical panel to develop guidance for conducting cumulative risk assessments, of which this Framework is a first step.

1 the framework. Individual Program Offices and Regions may have to make decisions affecting
2 the scope, types of stressors, or methods used for their programs' cumulative risk assessments,
3 based on legislative mandates or other criteria. Nothing in this Framework report should be
4 interpreted to mandate that cumulative risk assessment must be conducted, or must be conducted
5 a certain way, for any specific case. Likewise, this Framework report is not an attempt to lay out
6 protocols to address all the risks or considerations that are needed to adequately inform
7 community decisions. Rather, this Framework report is an information document, focused on
8 describing various aspects of cumulative risk, *whether or not the methods or data currently exist*

1 *to adequately analyze or evaluate those aspects of the assessment.* Because of the limitations of
2 current science, cumulative risk assessments in the near future will not be able to adequately
3 answer all questions posed by stakeholders or interested parties. This does not mean, however,
4 that they can't answer *some* of the questions asked; in fact, cumulative risk assessment may be
5 the best tool available to address certain questions dealing with multiple stressor impacts.

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 “sources” of pollution. In addition, criteria and standards were established as goals for cleanup of the various environmental media. By the 1980s, this “command and control” strategy was well established in environmental laws and regulations, but was reaching the point of diminishing returns from a cost-benefit viewpoint.

The development of risk assessment methodology during the 1970s and early 1980s closely followed the Agency’s strategy for control of pollution, since risk assessments were being used as one of the factors in EPA’s decision-making for regulations. The focus on sources led naturally to analysis of what types of pollutants were in effluents, air emissions, and waste sites.

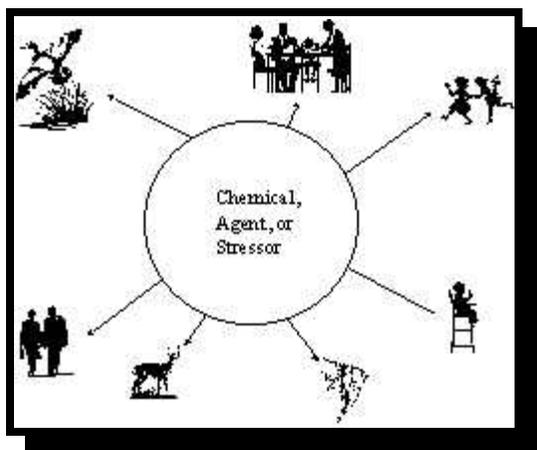


Figure 1-1. Chemical (or stressor) focused assessment starts with a source and evaluates how the chemical gets to various populations or ecological targets. Individual assessments may choose to pursue some or all pathways, media, or population segments.

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.

The risk assessment methodology of the 1970s and early 1980s, for this reason, tended towards single chemical assessments (see Figure 1-1). The 1983 National Research Council report *Risk*

1 *Assessment in the Federal Government* (NRC, 1983) was largely focused on the single chemical
2 risk assessment approach when it spoke of the four parts of a risk assessment: hazard
3 identification, dose-response assessment, exposure assessment, and risk characterization. EPA’s
4 *1986 Risk Assessment Guidelines* (USEPA 1986a), with the exception of the mixtures guidelines
5 (USEPA, 1986b), were also largely focused on single chemical assessment.
6

7 Research conducted or sponsored by EPA in
8 the early 1980s, however, was taking the first steps
9 toward investigating a different type of risk
10 assessment methodology, one that focused on the
11 persons exposed, investigating the chemicals or
12 stressors to which they were exposed, and
13 consequent risks (Figure 1-2). This is in contrast to a
14 focus on either a chemical, to investigate its
15 environmental fate, exposed populations, and risks
16 (Figure 1-1), or focus on a source to investigate its
17 environmental releases, exposed populations, and
18 risks. The goals of the population-focused approach¹
19 were much more useful to decision-makers who
20 were dealing with public health or ecological health
21 questions, rather than controlling sources of
22 pollution.
23

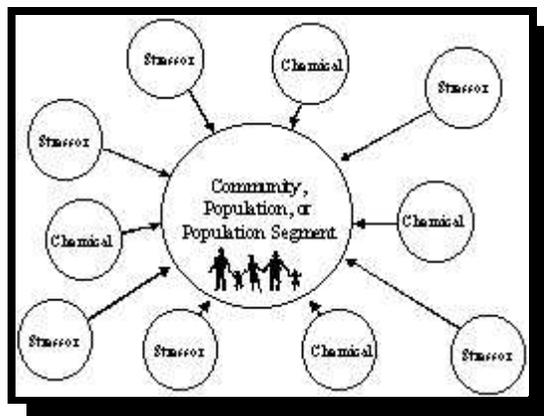


Figure 1-2. Population-based assessments start with the receptors, and determine what chemicals, stressors, or other risk factors are affecting them.

24 The challenges posed by the population-
25 based assessment can be daunting, even if only a few of the stressors affecting a population are
26 evaluated together (i.e., cumulatively). Taken to the extreme, Figure 1-2 represents a concept of
27 “total risk” for the population or population segment being evaluated, with each chemical,
28 biological, radiological, or other stressor² adding some fraction of the total risk. Looking at the
29 problem from an individual stressor viewpoint, to do this type of assessment would require not

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

² A stressor is a physical, chemical, biological, or other entity that can cause an adverse response in a human or other organism or ecosystem. A stressor can be exposure to a chemical, biological, or physical agent (e.g., radon), or it may be the lack of, or destruction of, some necessity such as a habitat. A socioeconomic stressor, for example, might be the lack of needed health care, which could lead to adverse effects. Harmful events, such as automobile crashes, could also be termed stressors. Obviously, calculating risks from different types of stressors can use widely different methods, including probabilistic estimates of disease via dose-response relationships, looking up rates in statistical tables of historical events, and other methods.

1 only evaluating each individual stressor, but also developing a way to add up all the risks among
2 stressors across a population of individuals with different exposures and susceptibilities. In the
3 early 1980s, the state of the science was unready for virtually any part of the methods for doing
4 this type of assessment.
5

6 But progress was being made toward developing a population-based methodology.
7 Starting in the late 1970s, a group of EPA researchers and contractors began developing what
8 would become the Total Exposure Assessment Methodology (TEAM) study (USEPA 1987).
9 TEAM measured the concentrations of a number of chemicals simultaneously at the point of
10 exposure. This led to a larger study, the National Human Exposure Assessment Survey
11 (NHEXAS) in the 1990s (Sexton, et. al. 1995). Both TEAM and NHEXAS were population-
12 based exposure assessment approaches which developed analytical tools and methodologies to do
13 this type of exposure assessment.
14

15 Also in the early 1980s, some progress was being made toward the question of how to
16 cumulatively consider the risks from different chemicals or stressors. The 1986 *Risk Assessment*
17 *Guidelines* (USEPA, 1986a) included a guideline on chemical mixtures (USEPA, 1986b), which
18 discussed how the risks from multiple chemicals could be evaluated as a whole. The work on this
19 guidance has continued most recently with the *Supplementary Guidance for Conducting Health*
20 *Risk Assessment of Chemical Mixtures* (USEPA, 2000e) which expands and supplements the
21 1986 beginnings.
22

23 About the same time the Agency made some progress on single chemical and chemical
24 mixture risk assessment with the 1986 *Guidelines*, some different kinds of risk assessment
25 problems began to catch the Agency’s attention. In 1986, eleven Chicago-area community
26 groups joined together to file a petition under Section 21 of the *Toxic Substances Control Act*
27 asking for a community assessment in Southeast Chicago. A series of community-based actions
28 which started in 1982 and grew throughout the 1980s focused on disparities of risk among
29 various population subgroups, calling specific attention to cumulative effects of pollution on
30 minority subgroups (GAO, 1983; United Church of Christ, 1987). This series of community-
31 based actions, chronicled in the 1990 book *Dumping in Dixie: Race, Class and Environmental*
32 *Quality* (Bullard, 1990) eventually became known as the Environmental Justice movement. The
33 issues raised by the Environmental Justice movement were the basis of a 1994 Presidential
34 Executive Order [Executive Order 12898, February 11, 1994] which told Agencies, among other
35 things, that “Environmental human health analyses, whenever practicable and appropriate, shall
36 identify multiple and cumulative exposures.” In the 1990s, Environmental Justice cases,
37 including the cases which have been filed under Title VI of the *1964 Civil Rights Act*, [P.L. 88-
38 352, July 2, 1964] have further emphasized the need for a cumulative human health risk
39 assessment methodology.
40

41 Even before Executive Order 12898 was issued, it was apparent that population-focused

1 assessments (like Figure 1-2) were going to be needed, in addition to the chemical- or stressor-
2 focused assessments (like Figure 1-1), if EPA was going to be able to answer the questions and
3 issues being raised by the public. Community spokespersons and other “stakeholders,” as well as
4 scientific panels, were increasingly coming to the Agency with problems that demanded a multi-
5 stressor approach (e.g., NRC 1994). Ecological problems, especially, were demanding a “place-
6 based” context (such as the Chesapeake Bay watershed) in which the various populations within
7 the area were looked at from a “total system” viewpoint. This place-based focus was a part of the
8 1992 *Framework for Ecological Risk Assessment* (USEPA 1992b) and the 1998 *Guidelines for*
9 *Ecological Risk Assessment* (USEPA 1998b).

10
11 Although clearly addressing more than cumulative human health or ecological risk
12 assessment, the *National Environmental Policy Act* of 1969 (NEPA) [P.L. 91-190, 42 U.S.C.
13 4321-4347, January 1, 1970, as amended by P.L. 94-52, July 3, 1975, P.L. 94-83, August 9,
14 1975, and P.L. 97-258, §4(b), Sept. 13, 1982], which was passed at about the same time EPA
15 was established, requires assessments on the cumulative impacts of federal or federally-funded
16 projects (such as roads, dams, power lines, military projects, and infrastructure development) on
17 natural ecosystems, endangered species, habitats, and opportunities for public enjoyment and
18 natural resource use. A primary concern for NEPA is “cumulative effects analysis,” defined as
19 “the incremental impact of the action when added to other past, present, and reasonably
20 foreseeable future actions . . . Cumulative impacts result from individually minor but
21 collectively significant actions taking place over a period of time” (CEQ, 1997). Much of the
22 NEPA cumulative effects analysis is qualitative, but risk assessments and cause-and-effect
23 relationships are key parts of the analysis process for controversial projects.

24
25 In 1997, the Agency issued a policy memo, *Guidance on Cumulative Risk Assessment,*
26 *Part 1: Planning and Scoping* (USEPA, 1997a), which took the first formal step towards
27 developing guidance and guidelines for cumulative risk assessment.

28
29 By the first decade of the twenty-first century, cumulative risk assessment applications
30 have become relatively common. These applications are not only for assessments of chemicals
31 which operate by the same mode of action, as is mandated for the USEPA Pesticides Program,
32 but also community based, population-based, assessments which may include more varied
33 stressors than just chemicals alone. Much like the “place-based” ecological assessments, which
34 may cover a wide variety of physical, chemical, and biological stressors, some communities have
35 added human health and perhaps “quality of life” to the endpoints of interest in their place-based
36 assessments. It is the demand for more sophisticated human health risk assessments that has
37 driven the need for research into cumulative risk assessment, population-focused assessments,
38 aggregate exposure assessment, and risk from chemical mixtures.

1.1. Purpose and Scope of the Framework Report

An understanding of the finite purpose and scope of this Framework report is important. EPA and other organizations need detailed, comprehensive guidance on methods for evaluating cumulative risk. Before such detailed Agency-level guidance is developed on a relatively new field of risk assessment, it has been the recent policy of the Agency to first develop a simple framework as a foundation for later comprehensive guidance. This *Framework for Cumulative Risk Assessment* 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 report.

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 report provides wide latitude for planning and conducting cumulative risk assessments in many diverse situations, each based on common principles discussed in the Framework report. The process also will help foster a consistent EPA approach for conducting and evaluating cumulative risk assessments, for identifying key issues, and for providing operational definitions for terms used in cumulative risk assessments.

In the longer term, the Framework report offers the basic principles around which to organize a more definitive set of Cumulative Risk Assessment Guidance. With this in mind, this report does not provide substantive guidance on certain issues that are integral to the risk

EPA’s Risk Assessment Guidelines

Chemical Mixtures (USEPA 1986b)
Mutagenicity Risk Assessment (USEPA 1986c)
Carcinogen Risk Assessment (USEPA 1986d)
Developmental Toxicity Risk Assessment (USEPA 1991a)
Exposure Assessment (USEPA 1992c)
Reproductive Toxicity Risk Assessment (USEPA 1996b)
Proposed Carcinogen Risk Assessment (USEPA 1996c, 1999a, 1999b)
Ecological Risk Assessment (USEPA 1998b)
Neurotoxicity Risk Assessment (USEPA 1998c)

Selected Policy and Guidance Documents

Risk Assessment Guidance for Superfund (USEPA 1989a)
Locational Data Policy (USEPA 1991b)
Framework for Ecological Risk Assessment (USEPA 1992b)
Application of Refined Dispersion Models (USEPA 1993a)
Policy /Guidance for Risk Characterization (USEPA 1995ab)
Benchmark Dose (1995c, 2000b)
Cumulative Risk Planning and Scoping (USEPA 1997a)
Guiding Principles for Monte Carlo Analysis (USEPA 1997b)
Acute Inhalation Exposure (USEPA 1998d)
Chemical Emergency Risk Management (USEPA 1998e)
Draft Comparative Risk Framework (USEPA 1998f)
Aggregate Exposure and Risk (USEPA 1999g)
Community Involvement in Superfund RA (USEPA 1999c)
Guidance for Offsite Consequence Analysis (USEPA 1999d)
Guideline on Air Quality Models (USEPA 1999e)
Framework for Community Based Env. Prot. (USEPA 1999f)
Handbook for Risk Characterization (USEPA 2000c)
Handbook for Peer Review (USEPA 2000d)
Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures (USEPA 2000e)
Cumulative Risk Assessment of Pesticide . . . Common Mechanism of Toxicity (USEPA, 2002a)

1 assessment process (see box at right and Appendix B for a listing of useful resources). These
2 include specific analytical methods, techniques for analyzing and interpreting data, and guidance
3 on issues influencing policy. Rather, on the basis of EPA experience and recommendations of
4 peer reviewers, EPA has reserved discussion of these important aspects of cumulative risk
5 assessment for future Guidance, which will be based on the risk assessment process described in
6 this Framework report.
7

8 This Framework report is meant to lay out broad areas where analysis might be conducted
9 if needed. It does not suggest that cumulative risk assessment is a tool that should be used with
10 every issue, nor does it suggest that when cumulative risk assessment is applied, that all areas of
11 analysis outlined or discussed here must or even should be conducted in every assessment. The
12 scope of the assessment should be defined in the planning and scoping stage (see section 2.1),
13 and may include or exclude stressors or pathways as relevant to the particular context or
14 application. In some areas discussed in this Framework report, the methodology for doing the
15 risk analysis currently may not exist.
16
17

18 **1.2. Intended Audience**

19
20 This Framework report is primarily intended for EPA risk assessors, EPA risk managers,
21 and other persons who either perform work under EPA contract or sponsorship or are subject to
22 EPA regulations concerning risk assessments. The terminology and concepts described here also
23 may be of assistance to other Federal, State, and local agencies as well as to members of the
24 general public, including stakeholders, who are interested in cumulative risk assessment issues.
25 The style and language used in this Framework report are chosen to be understood by as wide a
26 variety of interested parties as possible, from the policy maker to the risk assessment scientist to
27 the concerned non-scientist member of the general public. It is hoped that this Framework report
28 will be the first step in developing a broad scientific consensus about cumulative risk assessment,
29 and that further guidelines and guidance will build upon this foundation.
30
31

32 **1.3. Key Definitions in Cumulative Risk Assessment³**

33
34 In this Framework report, “cumulative risk” and “cumulative risk assessment” are defined
35 as follows, assuming a defined population:
36

³ 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.

1 **Cumulative Risk:** The combined risks from aggregate exposures⁴ to multiple agents or
2 stressors.

3
4 **Cumulative risk assessment:** An analysis, characterization, and possible quantification
5 of the combined risks to health or the environment from multiple agents or stressors.
6

7 There are several key points which come from this definition of cumulative risk. First,
8 cumulative risk involves multiple agents or stressors, which means that assessments involving a
9 single chemical or stressor are not “cumulative risks” under this definition. Second, there is no
10 limitation that the “agents or stressors” be only chemicals. “Agents or stressors” may be
11 chemicals, of course, but they may also be biological agents, or physical agents, or even the
12 absence of a necessity such as habitat. Third, this definition requires that the risks from multiple
13 agents or stressors be combined. This does not necessarily mean “added,” but it means that some
14 analysis needs to be conducted as to if, and how, the effects or risks from the various agents or
15 stressors interact. It also means that an assessment which covers a number of chemicals or other
16 stressors, but which merely lists each chemical with a corresponding risk without consideration
17 of the other chemicals present, is not an assessment of cumulative risk under this definition.
18

19 The definition of cumulative risk assessment follows from the definition of cumulative
20 risk, but again, there is a key point: cumulative risk assessments can be qualitative as well as
21 quantitative.
22

23 Some examples of types of cumulative risk assessments, and some examples of
24 assessments we would not describe as “cumulative risk assessments,” are listed below. Each of
25 these presupposes a defined individual or population⁵:
26

27 **1. Single agent or stressor assessments.** Risks can be added or accumulated over time
28 for a single agent or stressor across sources, environmental pathways, or exposure routes. This
29 is consistent with “aggregate risk” in the FQPA terminology in the box on the next page.
30 Although this might conceivably be termed a cumulative risk assessment by some scientists, for
31 clarity in this Framework report, such single-stressor assessments will be termed “aggregate risk
32 assessments,” rather than “cumulative risk assessments.” Examples of this type of assessment
33 might be a multi-source assessment of benzene risk in a community, or an assessment of
34 individual risk to a specific pesticide from all uses combined. This type of assessment is not

⁴ See the text box on the following page for a definition of aggregate exposure.

⁵ 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 included in or excluded from the population.

1 discussed in this *Framework* except to be
2 referred to occasionally for clarity and
3 contrast to cumulative risk assessments.

4 2. Multiple stressor assessments.

5 Exposures can be accumulated over time,
6 pathways, sources, or routes for a number of
7 agents or stressors. These stressors may cause
8 the same effects (e.g., a number of
9 carcinogenic chemicals or a number of
10 threats to habitat loss), or a variety of effects.
11 A risk assessment for multiple stressors may
12 evaluate the risks of the stressors associated
13 health effects or ecological impacts, one
14 effect or impact at a time, or it may evaluate
15 the combined risk from some or all the
16 effects or impacts together. In either case, we
17 will call these assessments cumulative risk
18 assessments.
19

20
21 A multiple stressor cumulative risk assessment is distinct from a series of aggregate risk
22 assessments as it includes consideration of any combined impact of the stressors including the
23 potential for interactions among stressors (e.g., synergism or antagonism). One example of a
24 multiple stressor, single effect cumulative risk assessment would be the combined risk to an
25 individual or population from a series of pesticides all acting by the same mode of action and
26 causing the same effect.

27
28 Another example would be a dioxin assessment, where toxic equivalency factors (TEFs)
29 are used to combine the toxicities of dozens of different congeners of chlorinated dibenzo-p-
30 dioxins and dibenzofurans, resulting in a single estimate of risk for a specific effect from the
31 combination of congeners.

32
33 Another example is a physician’s use of a model, derived empirically from
34 epidemiological studies, to estimate the probability of a woman’s developing breast cancer over
35 the next ten years. The “stressors” in the example of the breast cancer model are certain factors
36 known to be correlated with that form of cancer, such as the woman’s age at first childbirth, age
37 at menarche, having a previous biopsy with atypical hyperplasia, and others. This example shows
38 that stressors may not necessarily be chemical stressors, nor do they all even need to be the same
39 types of stressors.

40
41 Another type of cumulative risk assessment that will be discussed in this report is the
42 multiple stressor, multiple effects assessment. Again, stressors need not be limited to chemicals,

FQPA’s Terminology Interpretations

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

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

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

1 nor do they even have to be the same
2 types of stressors to be included in this
3 type of assessment. Nor do the effects
4 have to be similar. For example,
5 chemical, biological, radiological, other
6 physical, and even psychological stressors
7 can cause a variety of human health or
8 ecological health effects. Assessing the
9 risk for these situations is considerably
10 more complex methodologically and
11 computationally than the examples of
12 aggregate risk assessments or single-
13 effect cumulative risk assessments given
14 in the above paragraphs.

15
16 As complex as this may sound,
17 there are several examples of this type of
18 assessment. Although these analytical
19 approaches may start with the stressors
20 and predict the risk of effects, more
21 generally these types of assessments start
22 with a defined geographical area or
23 defined population and try to determine
24 what stressors are important.

25
26 For example, cumulative
27 ecological risk assessments such as those
28 that have been conducted in the Columbia
29 River Basin and the Chesapeake Bay
30 focus on a number of observed adverse
31 conditions, then attempt to determine, among all of the possible stressors, which particular
32 combination is responsible for the observed adverse conditions (Barnthouse, et al., 2000).
33

34 The National Research Council, in its 1994 book *Science and Judgment in Risk*
35 *Assessment* (NRC, 1994, appendix I), lays out the general mathematics for a quantitative
36 approach to multiple stressor, multiple effect assessments. Recently, Bogen (2001) used this
37 approach to quantify combined risk of cancer and noncancer endpoints induced by the chemical
38 trichloroethylene (TCE), including quantitative characterization of associated interindividual
39 variability and associated uncertainty (including uncertainty regarding mechanism of
40 carcinogenic action). Technical hurdles involved in implementing this approach become those of
41 defining the set of relevant (preferably independent) endpoints and of quantifying the likelihood
42 of inducing each adverse health or ecotoxic response considered unacceptable as a function of the

Cumulative Risk Assessment Features

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

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

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

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

1 endpoints.

2
3 Another example of a type of multiple stressor, multiple effect assessment would be a
4 cumulative community health risk assessment.

5
6 We believe that the definition of cumulative risk used in this Framework report is
7 consistent with the sense of most definitions of “cumulative” such as are included in NEPA or
8 FQPA. A summary of the features and options of a cumulative risk assessment, by the definition
9 used in this report, is given in the box on the previous page.

10 11 12 **1.4. The Cumulative Risk Assessment as a Tool for a Variety of Users and Purposes**

13
14 As discussed in the Introduction, the results of the assessment should reflect the purpose
15 for doing the assessment. Information from cumulative risk assessments can also serve a variety
16 of other purposes, however. Insights gained may also be used to partly meet regulatory
17 mandates, to help identify targets for enforcement actions, or be considered when shaping policy
18 and regulation. Assessments may also conceivably be used in the long term planning with regard
19 to siting new sources of potential pollution in specific areas. Assessments also may be used for
20 general educational purposes not directly related to an immediate decision on a course of action.
21 Assessment results can also help guide priorities for voluntary or regulatory action, or to
22 mobilize community efforts to address concerns. They can be done retrospectively (to determine
23 past or current risks), prospectively (to assess the risks of, say, proposed facilities), or even
24 creatively (to design a development plan for a community). As helpful as results may be in any of
25 these other uses, however, some consideration must be given to the *appropriateness* of using the
26 assessment for these purposes, given the objectives and scope of the assessment.

27
28 Risk assessment, including cumulative risk assessment, is conceptually an analytic-
29 deliberative process (NRC, 1996). It includes both analytic (i.e., rigorous, replicable methods,
30 evaluated under the agreed protocols of an expert community) and deliberative (i.e., stakeholder-
31 value-and-judgment based) parts. Much of what is discussed in Chapter 2, the Planning and
32 Problem Formulation Phase, is deliberative in nature, which means it depends on input from
33 experts other than those who know how to do risk assessments. These include persons who are
34 knowledgeable about a community and its values. Although much of Chapter 3, the Analysis
35 Phase, is given over to the analytic process where risk assessment experts apply science to a
36 problem, the deliberative aspect returns in Chapter 4, the Interpretation Phase, especially where
37 risks of different types are being evaluated and combined.

38
39 Cumulative risk assessment, because of this analytic-deliberative process, can be applied to a
40 variety of different problems where analysis of the overall impacts of multiple sources, stressors,
41 pathways, or routes is necessary. It can be used as a regulatory analysis tool, such as in reviewing
42 the overall impact of several different pesticides that all act by the same mode of action (ILSI,

1 1999), or in NEPA analyses (CEQ, 1997).
2 It can be used to analyze the overall
3 impacts of permit decisions or the results
4 of compliance with permits in a given
5 community.
6

7 Cumulative risk assessment can
8 also be used in a community-based
9 assessment approach, such as is outlined
10 in EPA’s *Framework for Community-
11 Based Environmental Protection*

12 (USEPA, 1999f). The CBEP approach
13 (see box) encompasses both ecological and human health assessments. Cumulative risk
14 assessment, being a population-based or place-based analytic-deliberative process, is ideal for
15 CBEP-type applications.
16

17 Cumulative risk assessment is also applied in ecological assessments. The definition of
18 cumulative ecological risk assessment, as given in the EPA’s 1998 *Guidelines for Ecological
19 Risk Assessment* is: A process that involves consideration of the aggregate ecological risk to the
20 target entity caused by the accumulation of risk from multiple stressors (USEPA, 1998b). A
21 recent Society of Environmental Toxicology and Chemistry publication (Foran and Ferenc, 1999)
22 discusses multiple stressors in ecological risk assessment, and gives a good overview of the topic
23 of cumulative ecological risk assessment.
24

25 When should a cumulative risk assessment be done? Recognizing that the scope and
26 nature of a cumulative risk assessment may range from a very limited qualitative assessment of a
27 local situation, to a comprehensive assessment of the cumulative risk patterns for a large
28 community, to a national assessment conducted within one of EPA’s programs, the simple
29 answer is that one should be conducted whenever the combined impact of multiple stressors
30 needs to be considered. Only experience with these assessments over a period of time will
31 provide the wisdom needed to develop practical guidelines on this question.
32
33

34 **1.5. The Broader Decision-Making Context for Cumulative Risk Assessment**

35

36 Cumulative risk assessments may be used to form hypotheses that could be tested, but it
37 is more likely that these assessments will be used as decision-making tools. Decisions can be at
38 a wide variety of levels, from a neighborhood group evaluating ways to improve or safeguard
39 their health and environment, to a Federal official weighing options for action at a much broader
40 geographical level. Although the decision-making method is beyond the scope of this Framework
41 report, such decisions usually involve more than the basic science and analysis that make up the
42 “scientific” part of risk assessment. Robert T. Clemen, in his book *Making Hard Decisions* notes

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, 1999f

1 that in one type of decision-making approach (called decision analysis):
2

3 Managers and policy makers frequently complain that analytical procedures from
4 management science and operations research ignore subjective judgments. Such
5 procedures often purport to generate “optimal” actions on the basis of purely objective
6 inputs. But the decision-analysis approach allows the inclusion of subjective judgments.
7 In fact, decision analysis *requires* personal judgments: they are important ingredients for
8 making good decisions. (Clemen, 1996, page 5)
9

10 Regardless of the type of decision being made or the decision-making approach, a
11 cumulative risk assessment’s analytic part is not the decision-making vehicle in itself. That is,
12 “cranking out the numbers” will not be the sole basis for a decision. Although in some cases, the
13 estimated risks can weigh heavily in the decision, understanding the risk estimate is but one
14 factor in a broader decision-making process including risk management components such as
15 technical feasibility, economic costs and benefits, political realities, and other factors. The U.S.
16 EPA’s Science Advisory Board (SAB) in their August, 2000, publication *Toward Integrated*
17 *Environmental Decision-Making* (USEPA, 2000a), constructed a framework for what it termed
18 Integrated Environmental Decision-making (IED). The SAB noted that “The IED Framework
19 recognizes that risks often are experienced simultaneously and are cumulative. . .”. It speaks of
20 risk assessments in a very broad way, including human health effects, ecological effects, and
21 quality-of-life effects. The first phase and part of the second phase of the IED, “Problem
22 Formulation” and “Analysis and Decision-making” essentially correspond to the three phases we
23 discuss in this *Framework for Cumulative Risk Assessment*. Decision-making, and the SAB’s
24 third phase, “Implementation and Performance Evaluation,” are beyond the scope of this
25 Framework report.
26

27 The SAB’s report (USEPA, 2000a) gives a good insight into the broader context for
28 cumulative risk assessment, and some of the aspects of the analytic-deliberative parts of the
29 assessment. The analytical-deliberative process will be discussed more in Chapters 2 through 4,
30 as these phases of the cumulative risk assessment process are examined.
31

32 The 1996 book *Understanding Risk* (NRC, 1996) also provided much information on the
33 analytic-deliberative aspects of a risk assessment, and devoted a great deal of discussion to risk
34 characterization. Needless to say, it is very important to apply cumulative risk assessment in the
35 context of the decision or decisions to be made. This is most efficiently done by early and
36 continued attention to the “risk characterization” step in the risk assessment process (NRC, 1996;
37 USEPA, 2000c). The box in section 4.1 summarizes some of the points made in *Understanding*
38 *Risk*.
39

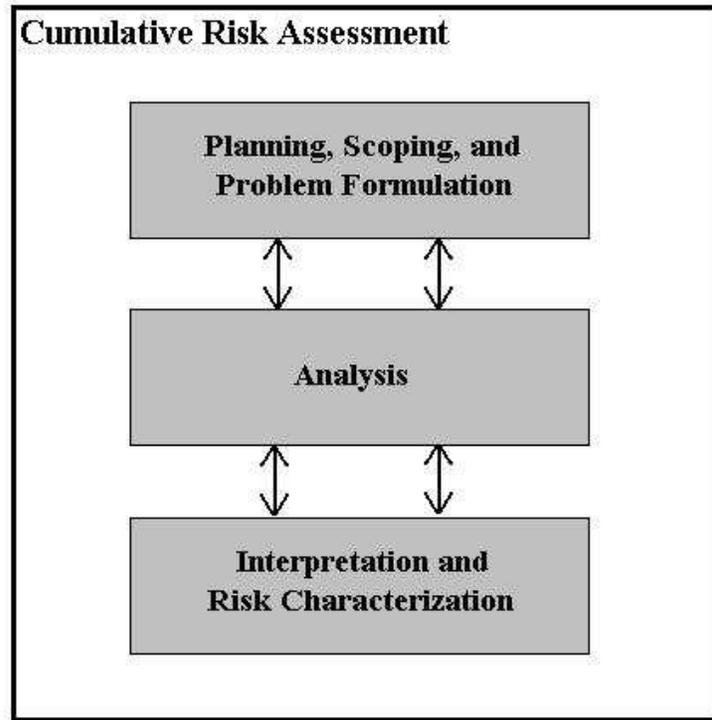


Figure 1-3. Framework for Cumulative Risk Assessment

1
2
3 **1.6. Organization of this report**
4

5 Figure 1-3 shows the basic structure of this Framework for Cumulative Risk Assessment.
6 Each of the three general process steps are described in detail in later chapters. The Framework is
7 organized to follow the outline in Figure 1-3, namely (a) a planning, scoping, and problem
8 formulation phase (Chapter 2), (b) an analysis phase (Chapter 3), and (c) an interpretation phase,
9 where the risk characterization is completed (Chapter 4). Chapter 5 is a glossary of terms,
10 followed by References in Chapter 6. Additional information on selected resources and
11 cumulative risk related topics are provided in the appendices.
12
13

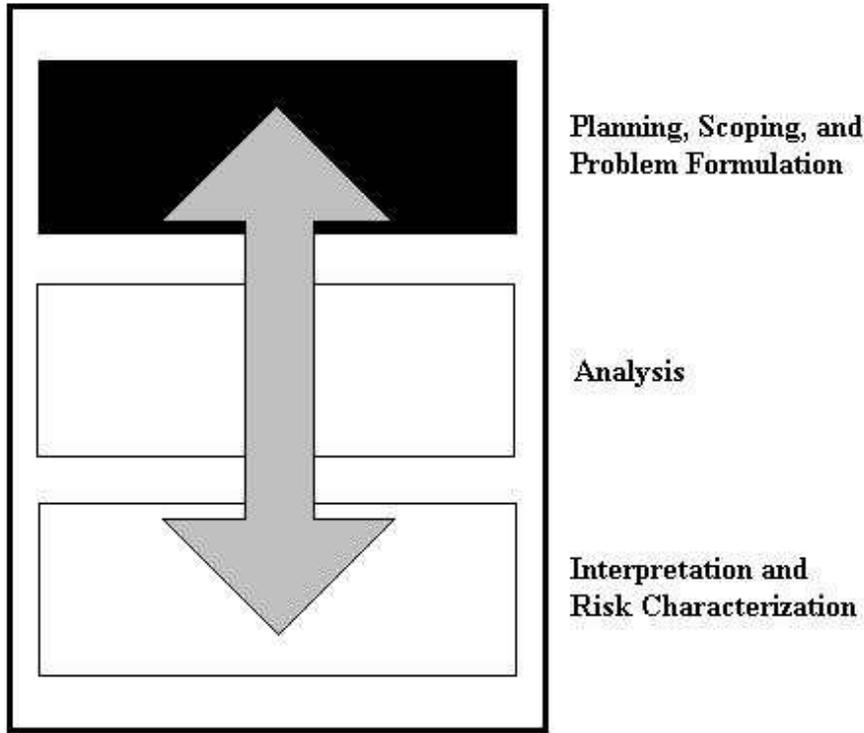
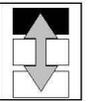
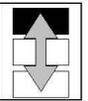


Figure 2-1. The Planning, Scoping, and Problem Formulation Phase.

2. THE PLANNING, SCOPING, AND PROBLEM FORMULATION PHASE

The first step in any risk assessment process is to define the problem to be assessed. This step has been called “problem formulation” 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



1 Scoping as a separate activity before problem formulation begins (USEPA, 1997a). Whether it is
2 considered a separate phase or not, it takes place at the very start of the process of doing a
3 cumulative risk assessment. For convenience, this section incorporates both Planning and
4 Scoping and Problem Formulation into a single phase.
5
6

7 **2.1. Planning and Scoping**

8

9 Risk assessments are conducted within some context, that is, they are usually conducted
10 because of a regulatory requirement, a community need, a health crisis, or some other “driving
11 force.” This context generates individuals or groups with interest in having the assessment done,
12 and there are several summary articles or books available about the challenges of successful
13 participation by these interested parties (e.g., Chess and Purcell, 1999; Frewer, 1999; Thomas,
14 1995). They may be public officials, risk experts, community leaders, or any number of others.
15 Planning and scoping begins with a dialogue among these interested parties.
16

17 Among these interested parties, there will be a person or a group of people charged with
18 making decisions about how a risk may be mitigated, avoided, or reduced. For the sake of
19 simplicity, we will call this person or group the “decision maker,” or “risk manager⁶,” and for
20 ease of discussion, will discuss the risk manager as if it were a single person.
21

22 During planning and scoping, risk experts (including those involved in assessing risk
23 such as ecologists, toxicologists, chemists, along with other technical experts such as economists
24 and engineers) and decision makers work together as a team, informed by stakeholder input, to
25 develop the rationale and scope for the risk assessment and characterization.
26

27 As part of the initial discussions concerning the need for a risk assessment, other
28 “interested and affected parties” besides the risk manager and risk assessor may help define
29 purpose, scope, and approach. This “risk assessment planning team” seeks agreement through
30 extensive dialogue and discussion on what analytical and deliberative steps need to be taken, and
31 by whom, by when, and why (USEPA, 2000a). The SAB’s report *Toward Integrated*
32 *Environmental Decision-Making* explains some of the roles of the various participants on the risk
33 assessment planning team during the Planning and Problem Formulation phase:
34

35 “Scientists play an important role in [this phase] by collecting, analyzing, and presenting
36 data in such a way that all parties can appreciate the type and magnitude of the problem(s)
37 under discussion. This activity will generally involve all four parts of risk assessment,
38 including assessment of exposures experienced by special populations and/or ecological
39 resources. Planning, scoping, and screening -- including selection of endpoints of

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



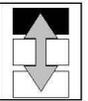
1 concern -- also requires explicit input of societal values and stakeholder participation.
2 For instance, while some of the ecological endpoints may be chosen because of their role
3 in a valued ecosystem, there may also be ecological endpoints chosen because of their
4 direct significance to society. Examples of the latter include both economically important
5 species and ‘charismatic’ species. Similarly, in integrated decision-making, judgments
6 may have to be made about diverse health endpoints, such as cancer risks in the general
7 population and the risk of reproductive/developmental risks in children. While scientists
8 can help characterize such risks, they are not uniquely qualified to set priorities among
9 them and broader deliberation is essential. Finally, decision-makers also play an
10 important role during problem formulation; in addition to bringing the scientific and other
11 resources of the Agency to bear on the problem, they also should help to identify the
12 range of potential decisions and viable management options, while examining economic,
13 political, or other constraints on those options. Decision-makers also serve as managers
14 of the overall process.” (USEPA, 2000a)
15

16 Another role of the risk assessment planning team is documentation. The activities of the
17 following sections are important, and should be documented by the team for several reasons.
18 Written records can be referred to by assessors and people at public meetings. They can also help
19 prepare for responding to comments, and begin establishing a peer-review record for any later
20 decisions or plans that need to be peer reviewed (USEPA, 2000d). The risk assessment planning
21 team should consider whether or not the overall project is to be peer reviewed, and if so, what
22 type of peer review will be conducted. The team should plan and execute the peer review at the
23 appropriate time. A peer review by an independent review group will not only help establish the
24 validity of the science, but can also provide neutral comments on some of the interpretations of
25 the assessment.
26

27 In some cases, it may be useful for the stakeholders to appoint a “point person” to serve
28 as point of contact for communications. This is not to imply that stakeholders must speak with a
29 single voice (which is not likely in any case), but that they have at least one person to help
30 facilitate interactions and identify available technical resources and other sources of information.
31 The Agency or stakeholders may also consider a public web site for the project. A variety of
32 resources can be posted, including cumulative risk tools and databases, project-related news, list
33 of experts, glossary, reports, related links, etc. An online discussion forum could also be
34 included on the web site as a more interactive way of exchanging information with stakeholders.
35

36 Finally, while including stakeholders in the risk assessment process, a regulatory agency
37 like EPA needs to balance stakeholder participation with the Agency’s need to retain the ability
38 to carry out its responsibility to protect public health and the environment. For this reason, EPA
39 will usually need to set some reasonable boundaries around the process to ensure that progress is
40 being made in a timely and efficient fashion.
41

42 2.1.1. Defining the Purpose of the Assessment 43



1 As discussed in section 1.5 above, the risk assessment should be developed to inform the
 2 risk management decision by constructing an appropriate, decision-relevant risk characterization.
 3 After the risk assessment planning team is assembled, the dialogue between the decision maker
 4 and risk experts begins with a discussion on risk management objectives and information needed
 5 to manage risks in the particular situation. The manager and assessment planning team must
 6 discuss any regulatory or legal basis for the risk assessment, and what kind of information is
 7 needed to satisfy such requirements. If interested and affected parties are part of the risk
 8 assessment planning team, it is especially important that the entire team agree on the purpose of
 9 the assessment, since a differing sense of purpose among the team will lead to problems later.
 10 The purpose and risk management objectives guide the risk assessment strategy (see box for
 11 some possible management goals from which risk management objectives can be derived, e.g., in
 12 terms of key participants, data sources, selection of assessment endpoints, approach, and the
 13 schedule for developing the assessment).

14
 15 The previous discussion follows the
 16 typical situation where the risk manager is
 17 presented as an independent decision-maker,
 18 such as a senior official in a regulatory agency
 19 who is responsible for establishing permit
 20 conditions for a facility of some type. There
 21 are situations, however, where the risk
 22 manager may be one of the interested parties,
 23 such as a local citizens’ board. For example,
 24 the risk assessment may indicate that
 25 mitigation of risks may not be significantly
 26 affected by any permit decisions but will
 27 depend instead on local zoning decisions or on
 28 decisions which affect traffic patterns in a
 29 community. This is one of the reasons why, in
 30 the final step in the planning and problem
 31 formulation phase, the discussion of possible
 32 outcomes (discussed in section 2.3), is so
 33 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

34
 35 **2.1.2. Defining the Scope of Analysis and Products Needed**

36
 37 Scoping a cumulative risk assessment effort involves defining the elements that will or
 38 will not be included in the risk assessment⁷ (USEPA, 1997a). These include the stressors,
 39 sources, pathways, routes, and populations to be evaluated. As illustrated by the examples in the
 40 text box (next page), the scope of a cumulative risk assessment may be narrow or broad. Initially,

⁷ 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.



1 the risk assessment planning team needs to
 2 select the kind of risk information, exposure
 3 scenarios and assessment issues that need to
 4 be covered. These should be directly linked
 5 to the risk-related questions being asked
 6 when establishing the purpose. Limitations in
 7 scope can be geographical (such as political
 8 or ecological boundaries), environmental
 9 (such as assessing only certain media),
 10 demographic (such as assessing only risks to
 11 children or asthmatics), statutory, or by using
 12 other criteria such as data limitations. The
 13 issue of “background” exposures to stressors
 14 should be discussed and agreements reached
 15 (see Appendix C). An adequate assessment
 16 scope should make it clear what’s included
 17 and what’s excluded from the assessment.

18 Care must be taken to reconcile the
 19 limitations of scope with the list of questions to be answered in the statement of purpose. If, for
 20 example, data limitations preclude the addressing of certain of the questions outlined in the
 21 purpose, the list of questions to be addressed should be modified and the risk assessment
 22 planning team agree to the narrower scope of the assessment.

23
 24 Reasons for choosing the particular scope of the assessment, and how it will address the
 25 questions posed in the purpose statement, should be stated explicitly. Defining the scope of the
 26 assessment should include details on the limitations of resources, limitations of data, the impact
 27 of risk elements on the risk estimate (i.e., some pathways may be seen as having negligible
 28 impact on the risks related to the questions being addressed), and limitations of the methods
 29 available. In cases where an element of risk is likely to be important, but no valid data are
 30 available, the assessor must highlight this deficiency or use judgment or assumed values to
 31 approximate the missing data. Such judgments and approximations should be clearly
 32 documented, and explained to the manager in the risk characterization.

33
 34 Once the elements (sources, stressors, populations, etc.) have been identified through
 35 brainstorming with all participants, the participants should discuss the need for and availability of
 36 technical information and how such information may affect the overall uncertainty of the
 37 assessment. Using input from the risk assessor, the risk assessment planning team must
 38 determine what elements will and will not (or, can and cannot) be included in the risk
 39 assessment. Some of the stakeholder concerns may not be suitable for analysis by risk
 40 assessment, so other expertise and evaluation may be required to provide this additional analysis.
 41 Information gathered at this stage is preliminary and may be modified during the analysis phase.
 42 Identification of potential stressors, populations to be assessed, and potential effects are all part
 43 of the scoping process, and help define the method of approach.

Examples of Different Cumulative Risk Assessment Scopes

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



1
2 As examples of some of these scoping elements, stressors can include physical (including
3 radiological) stressors or chemical or biological agents that may cause an adverse effect. The
4 sources of the stressors can be human activities in sectors of society (e.g., manufacturing,
5 transportation, agriculture, land development), personal human activities (e.g., smoking, diet, and
6 other “lifestyle activities”) or natural phenomena (e.g., forest fires, floods). Stressors that are not
7 physical, chemical, or biological, such as economic or other quality-of-life stressors may also be
8 identified, but good techniques for including the effect these have on risk currently may not exist.
9

10 Possible population elements to be assessed usually focus on the entities that are at risk,
11 e.g., populations, communities, ecosystem functions, or vulnerable subpopulations such as
12 persons with certain diseases, or persons at vulnerable life stages, such as children. The more
13 specifically these can be defined, the more focused the analysis can be. This will be helpful in
14 interpreting the results of the assessment.
15

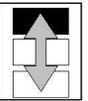
16 2.1.3. Agreeing on participants, roles and responsibilities
17

18 The risk assessment planning team will usually recommend others who should participate
19 in the assessment’s planning, scoping, and risk analysis phase. Depending on the schedule,
20 approach, and level of effort envisioned for the risk assessment, there may be no additional
21 participants, or there may be many. Assessments will usually require substantial technical
22 expertise in the analytic portions of the assessment. Some of the fields of science that may be
23 necessary or helpful include toxicology, epidemiology, ecology, risk assessment, exposure
24 assessment, fate and transport modeling (e.g., indoor and outdoor air, surface and drinking
25 water), computer science (including geographical information systems [GIS]), chemistry,
26 biology, various engineering fields (e.g., chemical, mechanical, industrial, civil), economics,
27 sociology, and others.
28

29 For the deliberative portions of the
30 assessment, there can be a number of
31 stakeholders and other interested parties that
32 should be considered for participation. The
33 box at the right lists some examples to choose
34 from among interested or affected parties for
35 the deliberative portions of the assessment.
36

37 For community-based assessments, in
38 particular, it is important that community
39 involvement be sought and encouraged. The
40 Presidential/Congressional Commission on
41 Risk Assessment and Risk Management
42 [hereafter, the “Commission”] (1997) suggests
43 the following questions to identify potential

| | |
|---|------------------------|
| Examples of Possible Interested or Affected Parties (Stakeholders) (adapted from USEPA 1999b) | |
| State governments | Affected industry |
| Tribal governments | Civic organizations |
| Local governments | Business owners |
| Community groups | Trade associations |
| Grassroots organizations | Labor unions |
| Environmental groups | Public health groups |
| Consumer rights groups | Academic institutions |
| Religious groups | Impacted citizens |
| Civil rights groups | Other federal agencies |



1 interested or affected parties (stakeholders):
2
3

- 4 • “Who might be affected by the risk management decision? (This includes not only
5 groups that already know or believe they are affected, but also groups that may be
6 affected but as yet do not know it.)
7
- 8 • “Who has information and expertise that might be helpful?
9
- 10 • “Who has been involved in similar risk situations before?
11
- 12 • “Who has expressed interest in being involved in similar decisions before?
13
- 14 • “Who might be reasonably angered
15 if not included?”
16

17 It has become increasingly recognized
18 as important that stakeholders be involved in
19 risk assessment (e.g., NRC 1996,
20 Presidential/Congressional Commission. . .
21 1997, USEPA 1996a, 1997a, 1998a, 1999c,
22 1999f, 2000a). The Commission suggested
23 guidelines for stakeholder involvement (see
24 box at right).
25

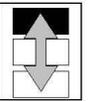
26 There are several issues concerning
27 the stakeholders’ capacity to participate that
28 should not be overlooked by the risk
29 assessment planning team. First, some
30 stakeholders may need training to be able to
31 participate in technical and risk management
32 discussions. Second, as noted in the box at
33 right, some stakeholders may require
34 incentives such as travel funds or lodging at
35 sites of meetings outside the area where they
36 live. The risk assessment planning team,
37 along with the potential source of funds for
38 such incentives, should decide to what extent,
39 if any, such incentives can be provided, based
40 on the scope, level of effort, and financial
41 constraints of the risk assessment project.
42

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

43 Roles and responsibilities for technical and non-technical participants (i.e., ground rules



1 for participants) should also be proposed by the planning team, depending upon the schedule,
2 approach, and level of effort that is envisioned for the risk assessment. There will be several key
3 points in the risk assessment process where stakeholder input will be critical. Some of these are
4 the agreements on purpose, scope, and approach. Each project should define and agree upon a list
5 of critical points for stakeholder input. The team may even decide to break stakeholders out into
6 several subgroups, with specific tasks such as (1) to understand the technical information and
7 report back to the larger group; (2) to elevate and clarify stakeholder issues as needed; or (3) to
8 provide information and facts to their peers and the analysts.

9
10 Sometimes citizens choose not to participate because they feel they will not influence the
11 outcome, the issue is too complex or technical, the effort is too great, or because the decision
12 process is unclear (USEPA, 2001c). Moreover, despite increased emphasis on stakeholder
13 participation, there are instances where it may not be appropriate for large scale stakeholder
14 involvement. EPA (as the decision maker) must determine whether, and to what degree,
15 stakeholder involvement in a cumulative risk decision will be useful and what objectives it may
16 accomplish. There is a continuum of objectives that may apply to individual cases, from
17 exchanging information on one end, through obtaining stakeholder recommendations, to
18 developing agreements for joint activities at the other end (USEPA, 1998g).

19
20 Much of the activities and data needed for cumulative risk assessment overlap the
21 jurisdiction of EPA, other public health agencies, and academia. The most successful future
22 cumulative risk assessments are likely to be those where cooperation among organizations
23 (Federal, State, private, environmental, academic, etc.) leads to use of the best data and tools for
24 the various parts of the assessment.

25 26 2.1.4. Agreeing on the Depth of the Assessment and the Analytical Approach

27
28 The analysis approach (discussed further in section 2.2.3 and chapter 3) may fall
29 anywhere on a continuum from relatively unsophisticated methods which rely heavily on default
30 (and often conservative) assumptions, and consequently have greater uncertainty, to increasingly
31 refined assessments in which data are substituted for assumptions and uncertainty is reduced.
32 Some of the factors that go into deciding on the approach include the level of uncertainty in the
33 risk estimates that is acceptable to the participants, the intended use and audience for the
34 assessment, the time and money resources available, and the amount, quality and accessibility of
35 data. In making the decision on approach, there will need to be an understanding of both the
36 level of effort necessary for conducting the assessment selected, with an insight to alternatives,
37 and the features and limitations of the selected approach, in comparison to other approaches.

38 39 2.1.5. Agreement on the Resources Available and Schedule

40
41 Schedule and resources are often interrelated. They may also affect whether the work is
42 performed in-house by the organization or team desiring the assessment, or by contractor or other
43 external source. The need to meet external deadlines or coordinate with schedules of other



1 organizations may become an overriding factor in defining what will be prepared. Assessments
 2 requiring short-term, low budget efforts, or preliminary screening assessments, may not have the
 3 scope, time or resources where extensive stakeholder involvement is necessary or beneficial. For
 4 assessments, especially those where there is extensive stakeholder involvement, a budget and
 5 time schedule should be developed and known by all participants.

6
 7 2.1.6. Review of Lessons Learned in
 8 Similar Studies

9
 10 Much time and effort can be saved by
 11 taking the advice of those who have been
 12 through this process – or similar processes –
 13 before. Risk assessment reports will often have
 14 a review chapter of “lessons learned” (or, “if I
 15 had to do this over again, this time I would . .
 16 .”). We have tried to include some of the
 17 discussion of recent Agency experiences as
 18 examples to illustrate parts of this Framework
 19 report. In addition, the reader is encouraged to
 20 find similar advice in other reports (e.g., *Lesson*
 21 *Learned on Planning and Scoping for*
 22 *Environmental Risk Assessments*, USEPA,
 23 2002b). EPA’s Office of Water has conducted
 24 several watershed studies over the past decade
 25 and has compiled a web page with lessons
 26 learned (USEPA, 2001d). One of the lists from
 27 that source is in the box at right, but there are
 28 many others. Even though the studies were not
 29 all cumulative risk studies, much of the wisdom
 30 gained is relevant.

31
 32 **2.2. Problem Formulation, Conceptual**
 33 **Model, and Analysis Plan**

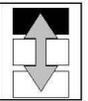
34
 35 One outcome of the problem
 36 formulation phase is a conceptual model that is
 37 intended to identify relevant stressors, sources,
 38 pathways, exposure routes, receptors, and
 39 effects, and to identify relationships among
 40 them. The conceptual model serves as a basis
 41 for the analysis plan, which is used to focus the
 42 analysis phase of the assessment. These three
 43 components are discussed in the sections

Reed Holderman's Lessons Learned

(California Coastal Conservancy, Santa Ynez Watershed)

1. Be sure that [the project] is needed, and if it is, build community support for it before proceeding.
2. Invite everyone into the process and ask political leaders to select the steering committee. Otherwise, people will ask, “Who appointed you?”
3. Don't be presumptuous. On the Santa Ynez River, we assumed everybody would appreciate a well thought out scope of work, budget, and schedule. Wrong. They said it only proved that the whole thing was a set-up. Next time, let [the whole planning team] figure it out!
4. When the majority of stakeholders tell you that they want to deal with their issue first, believe them. I remain convinced that our failure to sustain interest in the Santa Ynez River plan was primarily because we were not willing to assist the County in carrying out its proposed channel clearing activities in the Lompoc valley as a separate and distinct project.
5. Do whatever you can to break down barriers and perceptions people have of each other. Be creative. Family BBQs, softball games, and parties have done wonders to improve relationships among stakeholders and build trust.
6. Maintain constant communication among stakeholders throughout the process – and especially in the beginning – to pass information along, answer questions, or deal with rumors. Whether it's through regular meetings, newsletters, web sites, phone trees, or all four, good communication is a must.
7. And finally, line up your money and in-kind services in advance of starting your [assessment] project, or else two bad things will happen: (a) your stakeholders will buy into a process and scope of work only to find out they can't afford it; and (b) you will spend more time looking for cash than participating in the planning process. Either way, you lose.

[Source: Lessons Learned Web page (USEPA, 2001d)]



1 below.

2
3 The Science Advisory Board in their report *Toward Integrated Environmental Decision-*
4 *Making* (USEPA, 2000a) suggests a list of desired outputs from the Problem Formulation part of
5 an environmental decision-making exercise. Although this is not precisely the same as a risk
6 assessment, many of the points they list have applicability to risk assessment, also. The SAB
7 suggests these should not only be left to the visual presentation of the Conceptual Model
8 Diagram, but should also be explained in narrative form. Some of the SAB's recommended
9 outputs, included here as an example, are listed in the box below. Not all of these would
10 necessarily be applicable to a given risk assessment, depending on the scope.

Example: SAB's Desired Outputs for Problem Formulation

- The initial goals for the decision-making exercise, including environmental goals to be achieved
- Which environmental problems/stressors/systems will be included and which will not, and the reasons for these decisions
- The health, ecological, and quality-of-life effects of concern
- The spatial, temporal, and organizational dimensions 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)

11 12 2.2.1. Problem Formulation.

13
14 Problem formulation is a systematic planning step that identifies the major factors to be
15 considered in a particular assessment. It is linked to the regulatory and policy context of the
16 assessment. Problem formulation is an iterative process within which the risk assessor develops
17 preliminary hypotheses about why adverse effects might occur or have occurred. It provides the
18 foundation for the technical approach of the assessment. The outcome of the problem
19 formulation process is a conceptual model that describes the relationship between the stressors,
20 the population exposed, and the assessment endpoints that will be addressed in the risk
21 assessment.

22 23 2.2.2. Developing the Conceptual Model

24
25 A conceptual model includes both a written description and a visual representation of
26 actual or predicted relationships between humans (or populations, population segments) or
27 ecological entities and the chemicals or other stressors to which they may be exposed.

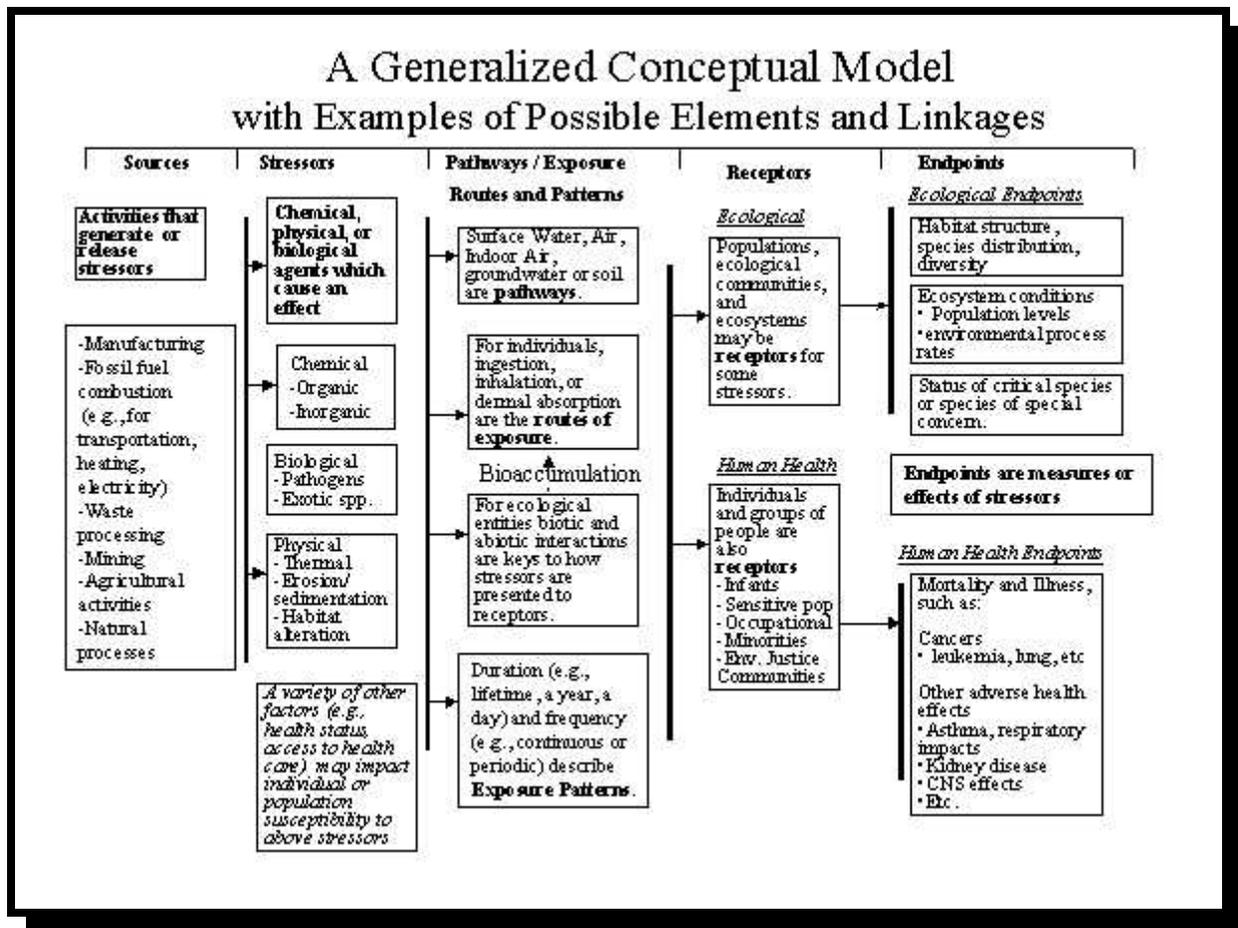


Figure 2-2. An example of a generic conceptual model (adapted from USEPA, 2002a).

1 Conceptual models represent many relationships, and may describe primary, secondary,
 2 or tertiary exposure pathways. The model is developed by the risk assessor and may include input
 3 from other experts (including stakeholders). The model narrative needs to distinguish – to the
 4 extent possible – between what is known or determined, and what is assumed. Also, it needs to
 5 include a discussion of uncertainties in the formulation of the assessment and state how the
 6 assessment is cumulative, i.e., for which sources, stressors/agents, pathways/exposure routes,
 7 receptors/populations, and endpoints. In some cases, conceptual models will be submitted for
 8 peer review. A general conceptual model is illustrated in Figure 2-2. The conceptual model
 9 includes factors and endpoints which may not be analyzed in the risk assessment, but may be
 10 evaluated in the overall decision-making process.

12 The conceptual model and the associated narrative show the basic rationale for the
 13 decisions made in pursuing a particular course of action in a cumulative risk assessment. It
 14 provides a record of decisions for future reference during risk analysis, characterization, and
 15 communication of the risk management decision. It is also valuable as a risk communication tool
 16 both internally within the Agency and externally in interactions with the public. The

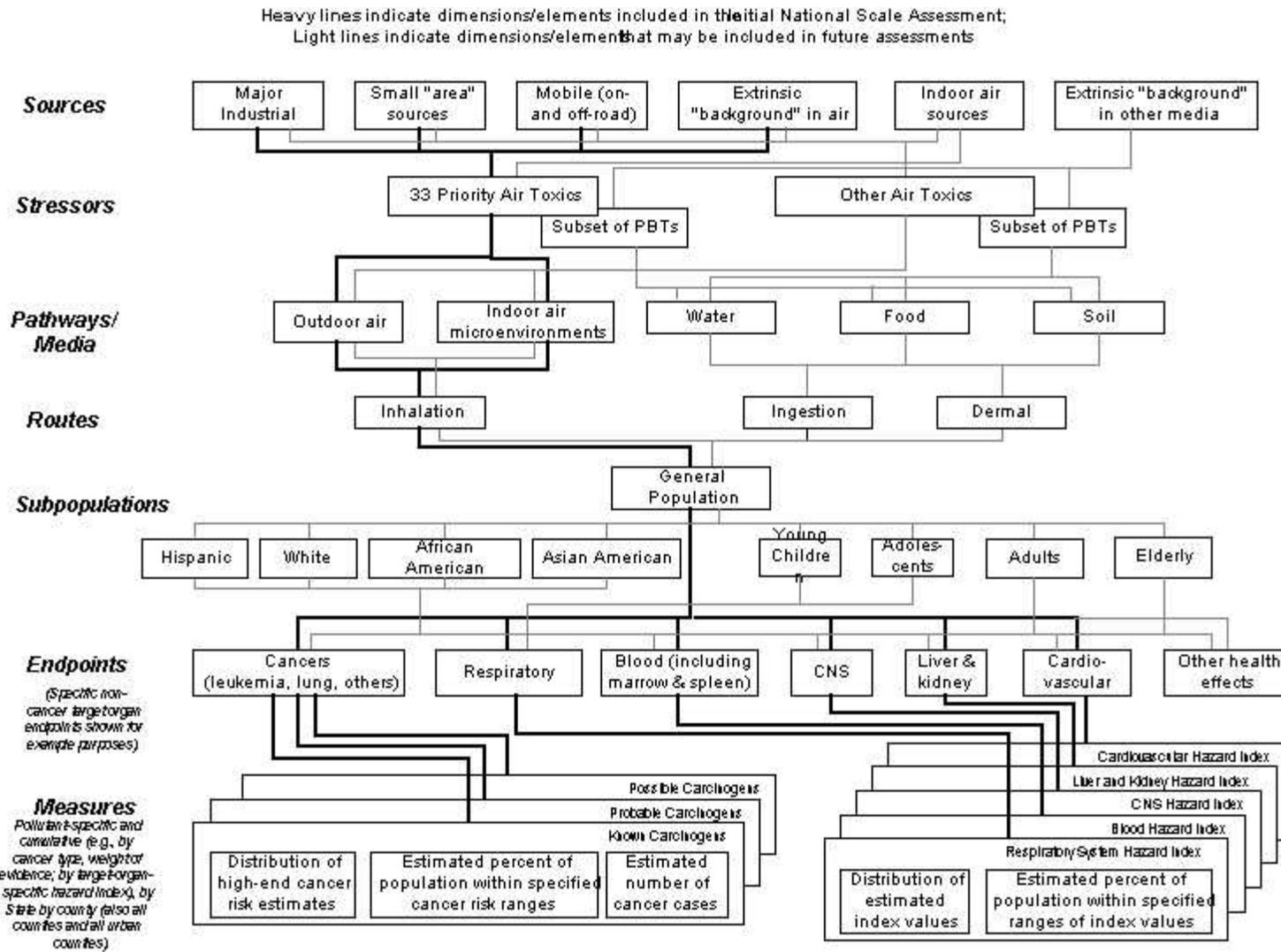
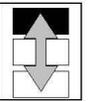


Figure 2-3. Specific conceptual model for a complex project, OAQPS' National Scale Air Toxics Assessment



1 conceptual model provides a scientific or technical work product that includes: (1) the scientific
2 rationale for the selection of the stressors, sources, receptors, exposed populations, exposure or
3 environmental pathways, endpoints or effects, (2) the scientific, technical, economic, or
4 sociologic basis for the construction of the conceptual model; and (3) the scientific implications
5 of additional data gathering. Figure 2-3 is an example of a conceptual model from the National
6 Air Toxics Assessment⁸.

7
8 It is not inconceivable, given the deliberative nature of the process of developing a
9 conceptual model, that more than one model will be considered as alternatives. If the team
10 decides to ultimately use more than one model, and to evaluate each as part of hypothesis testing,
11 a careful consideration of time and monetary resources needs to be made, as well as a very
12 careful consideration of how the results will be interpreted (see section 2.3).

13 14 2.2.3. Constructing the Analysis Plan

15
16 The analysis plan is the final stage of planning and scoping before the risk assessment.
17 The analysis plan is discussed in the Ecological Risk Assessment Guidelines (USEPA, 1998b),
18 Section 3.5. The analysis plan describes how hypotheses about the relationships among the
19 sources, stressors, exposure conditions, populations, and adverse effects, presented in the
20 conceptual model and narrative, will be considered during the risk analysis phase of the
21 assessment. The plan includes the rationale for which relationships (referred to as “risk
22 hypotheses” in the Guidelines for Ecological Risk Assessment) are addressed, methods, models,
23 and a discussion of data gaps and uncertainties. It also may include a comparison between the
24 level of confidence needed for the management decision with that expected from alternative
25 analyses in order to determine data needs and evaluate which analytical approach is best. In
26 some cases, a phased, or tiered, risk assessment approach can facilitate management decisions,
27 particularly in cases involving minimal data sets.

28
29 The analysis plan provides a synopsis of measures that will be used to evaluate risk
30 hypotheses (as shown in Appendix D) . The plan is strongest when it contains explicit
31 statements for how measures were selected, what adverse effect (or assessment endpoint) they
32 are intended to evaluate, and which analyses they support. Uncertainties associated with selected
33 measures and analyses and plans for addressing them should be included in the plan when
34 possible. The analysis plan can be a brief summary of what the key components of the risk
35 assessment are and how each component will be measured or calculated.

36
37 As in the conceptual model, the economic or societal importance, complexity, data and
38 resources available will determine the degree of sophistication and detail needed in the analysis
39 plan. Key data gaps should be identified. It should also include thoughts about how to fill the
40 information needs in the near-term using existing information, in the mid-term by conducting

⁸ NATA is the technical support component of EPA’s National Air Toxics Program [see 64FR38706-38740 (“National Air Toxics Program: Integrated Urban Strategy”) or USEPA, 2001e.



1 tests with currently available test methods to provide data on the agent(s) of interest, and over the
2 long-term to develop better, more realistic understandings of exposure and effects and more
3 realistic test methods to evaluate agents of concern. The plan should explain how measures were
4 selected, what they are intended to evaluate, and which analyses they support. Uncertainties
5 associated with selected measures and analyses, and plans for addressing them, should also be
6 explicitly stated.

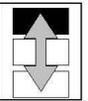
7
8 The analysis plan should include (where feasible) milestones for completion of the risk
9 assessment. The plan may be revisited and revised periodically. Such revisions may be
10 anticipated, if new information is acquired, to refine hypotheses of exposure and toxicity, to
11 modify the risk hypotheses addressed, or to compare public concerns with the projected risk
12 management options.

13 14 15 **2.3. The Final Step Before the Analysis Phase: Discussion of Possible Outcomes**

16
17 It is useful for the entire team to hold some preliminary discussions, before the analytical
18 efforts of the assessment are started, about the various possibilities of the cumulative risk
19 assessment results and their implications. Given that statutory mandates, regulations, property
20 rights, or due process may constrain or define most or all acceptability criteria, what conclusions
21 of the team will be associated with various results or risk levels? For example, for a risk
22 assessment team with members from the community, industry, and the local and other
23 government entities, what would happen if the assessment shows risk levels to be “low”? Would
24 members accept this? Conversely, if “unacceptable” risks are determined, will all team members
25 accept the results and their possible responsibility to do something about that risk? Do team
26 members understand the limitations of the information to be generated?

27
28 Discussions like these will help determine if the assessment can really address the
29 questions of the team. If not, the assessment may not be worth doing as planned. If members of
30 the team will not accept the possibility of a range of results of the analysis, then it is important to
31 reopen the entire planning and scoping discussion before anything is done in the analysis phase,
32 since the planning and scoping phase has not been satisfactorily completed. Although it is not
33 necessary to have unanimity among stakeholders on the plan before proceeding, knowing where
34 some of the potential disagreements may occur after the Analysis and Interpretation phases are
35 started allows the stakeholders as a group to plan beforehand for how such disagreements will be
36 addressed, should they occur.

37
38 As an example, the Baltimore Community Environmental Partnership Air Committee
39 Technical Report (USEPA, 2000f) is a case study where the stakeholders thought they had
40 agreement on roles, responsibilities and approach, only to find that the group acrimoniously
41 splintered after the analysis results came back. The Baltimore report contains valuable lessons
42 learned in the area of stakeholder disagreements and agendas, and can provide some insight for
43 planning teams.



1 Finally, discussions just prior to the analysis phase may lead to an assessment very
2 different from the one originally envisioned. The CRI case study (box, next page) is one where
3 the original plan was to do a quantitative cumulative risk assessment, but because of the lack of
4 some critical information, the scope was changed. This led to an assessment that, while not as
5 broad as originally planned – and not even directly calculating risk – had better stakeholder buy-
6 in with a better chance of success of providing useful information.



Example: Cumulative Risk Initiative (CRI) for Cook Co., IL and Lake Co., IN (formerly *Chicago Cumulative Risk Initiative, CCRI*)

CRI BACKGROUND AND OVERVIEW

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

HAZARD SCREENING ASSESSMENT

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

PRELIMINARY LESSONS LEARNED

1. A major planning/scoping/problem formulation effort by a broad group of stakeholders narrowed the scope of the CRI Hazard Screening Assessment and seemed to increase stakeholder “buy-in” with the process. This was valuable given the complexity, expense, effort, time requirement and difficulty encountered in addressing even the narrowed scope.
2. Large data gaps make risk and hazard assessment of environmentally-relevant chemical exposures highly uncertain, even for single agents. Expanded assessments that address cumulative risk considerations (e.g. mixtures; developmental toxicity; non-chemical agents) are a better match for real-world circumstances but require acknowledgment of even more uncertainty.
3. Obtaining and managing input from a large group of technical stakeholders is cumbersome and time-consuming, but that group’s perspective and expertise greatly improved the CRI assessment.
4. Given that the NRC’s 1983 four-step “framework” required several years for broad use and acceptance in the U.S., the greater complexity of cumulative risk (for CRI, cumulative *hazard*) assessment suggests an equally long period may be needed for terminology standardization, refinement of approaches and development of consensus methods.

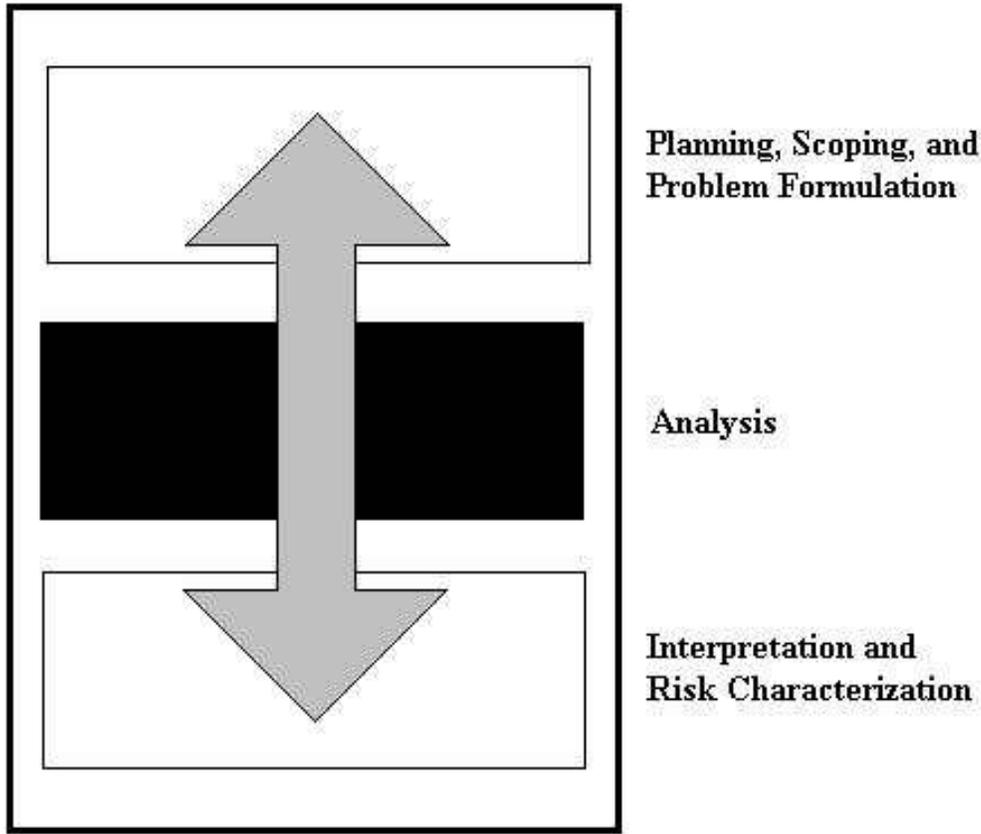
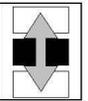


Figure 3.1. The Analysis Phase

3. THE ANALYSIS PHASE

The Analysis Phase is primarily an analytic process where risk experts apply risk assessment approaches to evaluating the problem at hand⁹. The risk assessment paradigm most widely used by risk assessors 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 conducted on single chemicals. Nevertheless, it is a useful place to start when considering cumulative risks. As a prerequisite, assessors considering cumulative risk assessments should be familiar with the 1983 NRC risk paradigm, as well as the various EPA risk assessment guidelines (see text box in section 1.1).

⁹ Although the Analysis Phase is primarily an analytic process with heavy emphasis on the role of the scientist, risk assessor, or other technical expert, other stakeholders can be involved in various ways as agreed upon before the Analysis Phase begins. Some roles stakeholders might have in the Analysis Phase include (1) suggesting sources of data, or providing data for the assessment; (2) helping clarify issues identified during Problem Formulation; (3) working alongside the risk assessment experts to see what data and assumptions are being used and why, and to better understand how the risk assessment process works; and (4) suggesting alternate scenarios that may reflect more realistic exposure conditions in the community. A variety of roles for stakeholders in the Analysis Phase can be proposed and adapted for the particular circumstances of the individual case, assuming that the roles can be agreed upon by the team.



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

3.1. General Process

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

The analysis plan should specify how data, modeling or assumptions will be obtained, performed or defined for all of the details concerning the characterization of exposure for the defined set of stressors, to the defined population and subpopulations. Additionally, the analysis plan specifies the strategy for obtaining and considering hazard and dose-response information for these stressors. And, the plan will specify the method for combining the exposure information with the hazard and dose-response information to generate risk estimates or measures. As the risk analysis is refined, it may be appropriate to revisit and refine the exposure, hazard and dose-response information in an iterative fashion.

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

The area of identifying and assessing risk to susceptible subpopulations has an increased

Example: Scope of EPA’s national scale assessment for hazardous air pollutants (also see Figure 2-3):

| | |
|-----------------------|--|
| stressors | 33 priority urban HAPs |
| sources | major industrial, small “area”, mobile (on- and off-road), & extrinsic “background” in air |
| pathways/media | outdoor air, indoor air microenvironments |
| routes | inhalation |
| subpopulations | general population only |
| endpoints | cancers, developmental, CNS, kidney, liver, respiratory effects |
| metrics | <u>for cancer</u> : distribution of high-end cancer risk estimates, predicted percent of population within predicted cancer risk ranges, predicted number of cancer cases, HAP-specific and cumulative <u>for other effects</u> : distribution of estimated hazard index values and estimated percent of population within specified ranges of index values |



1 profile in cumulative risk assessments. A variety of factors may be influential in affecting
2 population susceptibility. The extent to which these can be considered will be heavily dependent
3 on existing knowledge and available information. Section 3.2 discusses available methods for
4 identifying and estimating risk or hazard to susceptible or vulnerable subpopulations. Section
5 3.3 discusses areas of complexity and on-going work.

6 7 8 **3.2. Available Methods and Approaches**

9
10 There are many aspects of traditional risk assessment methodology which apply to
11 cumulative risk assessment. Predicting cumulative risk of multiple stressors, however, has
12 required the development of additional specific methods or approaches. Additionally, there are
13 some aspects of risk assessment, while common to both single-stressor and multiple-stressor
14 assessments, that may increase in complexity or significance, in a cumulative risk assessment.
15 Together they frame the methodological issues pertinent to the discussion of cumulative risk
16 assessment.

17
18 While these aspects common to single-stressor assessment may be many (e.g., the added
19 dimension of multiple stressors influences consideration of stressor sources, routes of exposure,
20 environmental media/pathways, and other factors), several examples are raised here. As one
21 example, the assessment of the dose-response relationship and corresponding characterization of
22 exposures in terms of duration, timing relevant to life stage and exposure history gains an
23 additional dimension with the need to consider this in some way cumulatively. The
24 consideration of population susceptibility or vulnerability, as recommended in the Agency's
25 policy and guidance on Risk Characterization (USEPA 1995a, 1995b, 2000c), also increases in
26 complexity. A third example of a complicating aspect in cumulative risk assessment is the
27 consideration of subpopulations with particularly distinctive exposures. These examples are
28 further discussed in section 3.2.1.

29
30 Although it is beyond the scope of this Framework report to describe all risk methods in
31 detail, Appendix B lists a variety of resources relevant to various exposure assessment methods.
32 Relatively speaking, there is a great deal of information on assessing human and environmental
33 exposures to chemical stressors, some information on biological and radiological stressors, but
34 relatively little information on many other types of stressors.

35
36 The most prominent aspect of cumulative risk assessment is often the prediction of the
37 combined effects of multiple stressors. Past and current activities in the development of
38 approaches for predicting risk of multiple stressors include the Agency's *Guidelines for the*
39 *Health Risk Assessment of Chemical Mixtures* (USEPA, 1986b) and *Supplementary Guidance for*
40 *Conducting Health Risk Assessment of Chemical Mixtures* (USEPA, 2000e). Concepts,
41 approaches, or methods described in these documents or elsewhere are discussed in section 3.2.2,
42 with clarification of their applicability, limitations and notable points regarding interpretation of
43 the results they produce.

44 45 3.2.1. Examples of Increased Complexity of Cumulative Risk Assessment.

46
47 Three examples of the potential for increased complexity of cumulative risk assessment



1 compared to single stressor risk assessment are described here, and related to: 1) time related
2 aspects, 2) vulnerability or susceptibility, and 3) subpopulations with special or particularly
3 distinctive exposures. All three of these aspects are relevant in single stressor assessments, but
4 have the potential to be more complicated in multiple stressor assessments.
5

6 **Time related aspects.** The issue of repeated exposures to a single stressor or exposures
7 to multiple stressors that may vary in time dimensions may have implications with regard to
8 susceptibility, which, consequently, has implications regarding the dose-response relationship.
9 Traditionally in dose-response assessment, for many stressors and effects there is an inherent
10 presumption that it is the cumulative exposure (combination of intensity and duration) to which
11 the organism responds. Thus dose-response assessments based on one pattern of exposure (e.g.,
12 6 hours per day, 5 days per week over a lifetime) are routinely applied to the assessment of risk
13 associated with a variety of patterns of exposure.
14

15 In the case of linear carcinogens, this cumulative exposure assumption has been carried as
16 an explicit assumption in the risk assessment step. Regardless of the details of the exposure
17 circumstances for the study on which the cancer potency was based, it is assumed that there is a
18 linear relationship between amounts of exposure and associated cancer risk. For non-linear
19 carcinogens¹⁰, and conceivably for linear carcinogens, if data indicate deviation from the
20 assumption that cancer risk is proportional to lifetime dose, the details and sequence of exposure
21 may be important, both in developing the dose-response relationship and in predicting risk
22 associated with exposures of interest.
23

24 As some chemicals may have the ability to affect an organism's response to other
25 chemicals, consideration of the time sequence of exposure may take on an additional layer of
26 complexity in multiple chemical cumulative risk assessments. For example, persons with
27 relevant past exposures might have increased susceptibility to the effects of a particular chemical
28 due to a previous exposure to the same – or a second – chemical.
29

30 These considerations suggest that for cumulative risk assessment, chemical exposures
31 need to be characterized in terms of which other chemicals are present, and when. As noted in the
32 *ILSI Framework for Cumulative Risk Assessment* (ILSI, 1999): “Data collected specifically to
33 support a cumulative exposure assessment should conserve the covariance and dependency
34 structures associated with the chemicals of concern.” It is important to note, however, that the
35 detail to which exposures are characterized should be closely tied to the detail of information
36 available in the dose-response assessment, since a lack of corresponding detail in the dose-
37 response assessment can pose a limitation on the interpretation and usefulness of detailed
38 exposure estimates.
39

40 Cumulative risk assessment can present challenges in matching exposure estimates with
41 dose-response relationships. Ideally, the dose-response assessment will indicate if the time
42 sequence for the chemical(s) or stressors of interest in the assessment is important for risk
43 estimation. In cumulative assessments involving chemicals where time sequence of exposure is
44 important, it may be necessary to characterize the details and sequence of exposure to the

¹⁰ The draft cancer guidelines (USEPA, 1999) 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.



1 exposed population (see text box, previous page), so there will be a match in not only the form,
 2 but also the assumptions between the dose-response relationship and the exposure/dose estimate.
 3

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 during degradation periods. Calendar based assessments maintain the integrity of the individual by capturing: the location of the exposed individual, the time of year in which he or she was exposed, and the patterns of exposure. Calendex also allows for a variety of time-breakout options for the analysis of exposure.

APEX - The Air Pollution Exposure (APEX) model is based on the 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) along with the Residential Exposure Year (RExY) model being developed by Infoscientific.com.

4 **Vulnerability.** One of the concepts that can be used in risk assessments (both for human
 5 health and ecological assessments) is that of *vulnerability* of the population or ecosystem.
 6 Vulnerability has been a common topic in socioeconomic and environmental studies. The
 7 European Commission’s TEMRAP (The European Multi-Hazard Risk Assessment Project),
 8 studying vulnerability to natural disasters such as floods, windstorms, fires, earthquakes, and
 9 others, defines “vulnerability” as “the intrinsic predisposition of an exposed element [organism,
 10 population, or ecologically valuable entity] to be at risk of suffering losses (life, health, cultural
 11 or economic) upon the occurrence of an event of [a specific] intensity” (European Commission,
 12 2000, bracketed material added).

13
 14 Vulnerability of a population places them at increased risk of adverse effect, and may be
 15 an important factor in deciding which stressors are important in doing a cumulative risk
 16 assessment. The Agency’s risk characterization policy and guidance (USEPA, 2000c) touches on



1 this concept by recommending that risk assessments “address or provide descriptions of [risk to]
2 ... important subgroups of the population, such as highly exposed or highly susceptible groups”.
3 Further, the Agency’s guidance on planning and scoping for cumulative risk assessments
4 (USEPA, 1995b) recognizes the importance of “defining the characteristics of the population at
5 risk, which include individuals or sensitive subgroups which may be highly susceptible to risks
6 from stressors or groups of stressors due to their age, gender, disease history, size or
7 developmental stage”. That guidance also recognizes the potential importance of other social,
8 economic, behavioral or psychological stressors that may contribute to adverse health effects
9 (e.g., existing health condition, anxiety, nutritional status, crime and congestion). These same
10 concepts may also be discussed as a group in terms of “population vulnerability.” The various
11 ways in which a population may be vulnerable are discussed below in four categories:
12 susceptibility, differential exposure, differential preparedness, and differential ability to recover.
13

14 The first of these is *susceptibility*. Susceptible individuals within a population have a
15 different or more pronounced dose-response relationship when confronted with a stressor.
16 Reasons for susceptibility may be related to any number of sensitivity factors, including life stage
17 (e.g., children or the elderly may be more susceptible), genetic polymorphisms (e.g., genetic
18 susceptibilities which occur in a small but significant percentage of the population), or existing
19 disease state (e.g., asthmatics). In addition, susceptibility may be related to the conditions of
20 exposures (e.g., prior exposures leading to the development of sensitization reactions, or having
21 had exposures which compromise the immune system). Confronted with equal concentrations of
22 a chemical for equal durations, for example, a biologically susceptible individual may show
23 effects while the typical individual within the population would not. Although we generally do
24 not have a lot of data available on this topic, susceptibilities or sensitivities may also exist among
25 races or genders.
26

27 The second category of vulnerability is *differential exposure*. While it is obvious by
28 examining a dose-response curve that two individuals at different exposure levels may have a
29 different likelihood of effects, this also extends to differences in historical exposure, body
30 burden, and background exposure, which are sometimes overlooked in an assessment.
31

32 The third category of vulnerability is *differential preparedness* to withstand the insult of
33 the stressor, and the fourth is the *differential ability to recover* from the effects of the stressor.
34 These last two are linked to what kind of coping systems and resources an individual, population,
35 or community has. Preparedness or recovery is often a crucial factor in ecological assessments. In
36 human health assessments, lack of access to health care, income differences, unemployment, or
37 lack of insurance, for example, may affect a community’s ability to prepare for or recover from a
38 stressor. One aspect of differential ability to recover is illustrated by differing survival rates for
39 the same disease (e.g., Lantz, et. al 1998).
40

41 Cumulative risk assessments may be uniquely suited to addressing the issues related to
42 vulnerability. In order to do that, however, there needs to be some relationship between the
43 factors discussed above and changes in risk. At the current state of the science, many of these
44 factors have not been extensively developed beyond correlations between mortality rates and
45 several socioeconomic factors such as income (e.g., Lynch, et al. 1998). Susceptibility has had
46 much more development than the other factors, and current approaches implemented by EPA and
47 others to address risk of noncancer endpoints routinely employ a 10-fold factor to address



1 heterogeneity in sensitivity. Variability with regard to susceptibility was discussed in detail by
2 NRC (1994), and the current state of knowledge concerning epidemiologically based (e.g.,
3 oncogene-specific) risk factors provides empirical data upon which at least crude estimates of the
4 magnitude of heterogeneity in susceptibility to toxic response can be based. Much research in
5 this area, however, remains to be done.

6
7 **Subpopulations with Special Exposures.** Certain subpopulations can be highly exposed
8 to stressors based on geographic proximity to sources of these stressors, coincident direct or
9 indirect occupational exposures, their activity patterns, or a combination of these factors. The
10 Agency’s Risk Characterization policy and guidance (USEPA, 2000c) includes recognition of the
11 need for risk information to include as available, information on highly-exposed subgroups.
12 Accordingly, risk assessments, including those that are cumulative, may need to include special
13 emphasis on identifying and evaluating these subpopulations.

14
15 Subpopulations at risk of high exposure due to geographic proximity could include
16 workers at a facility which is a source of a stressor or residents near such sources. Specific
17 examples might be people living downwind from a coal burning power plant, those near and
18 using a polluted water body (for example, for fishing or recreation), or along roadways with high
19 levels of vehicular traffic. Occupational exposures may be either direct (occurring in the
20 workplace) or indirect (occurring at home). Indirect occupational exposures include those
21 experienced by family members of those occupationally exposed, who may be exposed to
22 occupational chemicals brought into the house by the worker (e.g., on clothing). Thus, workers
23 or family members may be subject to greater exposures than others in the population without this
24 additional burden.

25
26 Examples of subpopulations at high exposure due to activity patterns may include people
27 who exercise heavily in polluted air, recreational or subsistence fishers or hunters who consume
28 large quantities of fish or game, farmers or others who get a large percentage of their food from a
29 location near a source of pollution and live in areas with high pesticide use, individuals with long
30 commutes in automobiles, or children (because they consume a larger amount of food, drink, and
31 air relative to their body weight, and because of additional exposure routes such as incidental soil
32 ingestion). Additionally, some subpopulations may be affected by the combined impact of high
33 geographic exposure and high exposure activity patterns (e.g., runners who run along heavily
34 traveled roadways, and those who fish for food in heavily polluted urban rivers).

35
36 It is important to recognize that some heavily exposed populations may also be
37 particularly vulnerable or susceptible to the effects associated with the stressors of concern.
38 Examples of those who could be particularly vulnerable to certain stressors include children
39 during certain stages of development, people with chronic respiratory problems, the elderly, and
40 those economically disadvantaged without access to medical care. A cumulative risk assessment
41 may need to take into account potential combinations of high exposure and high vulnerability,
42 but few, if any, methods are available and accepted today to address the combined effects of
43 exposure and vulnerability. This is an important area for further research and methods
44 development.

45 46 47 3.2.2. Approaches for Predicting Risk of Multiple Stressors.



1
2 Combination toxicology (Carpy, et al., 2000) is the study of the toxicity of mixtures. In
3 such studies, one may either measure the mixture toxicity directly (whole mixture toxicity), or
4 one may develop an estimate of the combined toxicity from information on the multiple
5 component stressors acting in concert with each other. If evaluated using its component
6 chemicals, the mixture toxicity data set should only be treated as a snapshot of a
7 multidimensional dose-response relationship, because the joint toxicity and interactions can
8 change with changes in exposure route, duration, relative proportions of the components, or the
9 effect being tracked. The application of such a data set to a specific situation then requires careful
10 matching of the test mixture composition and exposure conditions to those of the target situation.
11 In whole mixture toxicity, once the mixture toxicity is known, a risk evaluation can be done on
12 the mixture using the 1983 NRC risk assessment paradigm. On the other hand, component based
13 mixture assessments are rarely evaluated using the strict NRC paradigm, because the exposure
14 and toxicity information must be compatible, requiring some iteration to obtain toxicity
15 information that is relevant to the actual exposure estimates (USEPA, 2000e).
16

17 To address concerns over health risks from multi-chemical exposures, EPA issued
18 *Guidelines for Health Risk from Exposure to Chemical Mixtures* in 1986 (USEPA, 1986b).
19 Those Guidelines described broad concepts related to mixtures exposure and toxicity and
20 included few specific procedures. In 1989, EPA published guidance for the Superfund program
21 on hazardous waste that gave practical steps for conducting a mixtures risk assessment (USEPA,
22 1989a). Also in 1989, EPA published the revised document on the use of Toxicity Equivalence
23 Factors for characterizing health risks of the class of toxicologically similar chemicals that
24 included the dibenzodioxins and dibenzofurans (USEPA, 1989b). In 1990, EPA published a
25 Technical Support Document to provide more detailed information on toxicity of whole mixtures
26 and on toxicologic interactions (e.g., synergism) between chemicals in a two-chemical mixture
27 (USEPA, 1990a). Whole mixture assessments, toxicologic independence and similarity, and risk
28 methods using toxicologic interactions are discussed at length in the recent *Supplementary*
29 *Guidance for Conducting Health Risk Assessment of Chemical Mixtures* (USEPA, 2000e).
30

31 Risk assessment on mixtures usually involves substantial uncertainty. If the mixture is
32 treated as a single complex substance, these uncertainties range from inexact descriptions of
33 exposure to inadequate toxicity information. When viewed as a collection of a few component
34 chemicals, the uncertainties also include the generally poor understanding of the magnitude and
35 nature of toxicologic interactions, especially those interactions involving three or more
36 chemicals. Because of these uncertainties, the assessment of health risk from chemical mixtures
37 should include a thorough discussion of all assumptions and the identification when possible of
38 the major sources of uncertainty.
39

40 3.2.2.1. Single Stressor Information.

41
42 Assessments which evaluate the risk from a single stressor do not fall into the category of
43 cumulative risk assessments by the definition given in Section 1.3, whether these single-stressor
44 assessments address a single (dominant) endpoint or multiple endpoints, or whether the
45 exposures are simple or complex (e.g., multi-source, multi-pathway, multi-route exposure). Some
46 of them may be termed “aggregate risk assessments” by extension of the FQPA terminology.
47 They can, however, provide useful information for cumulative assessments.

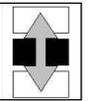


1 A cumulative risk assessment considers the joint impact of multiple stressors. Studies on
2 individual stressors can, however, provide informative qualitative information for multi-stressor
3 assessments, particularly regarding hazard identification. The collection of single stressor effects
4 can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

11
12 Exposure assessments for single stressors also need further consideration before they can
13 be used to characterize long term cumulative exposure to all the stressors by all pathways.
14 Transport and environmental transformation of a chemical can be influenced by presence of other
15 chemicals. Consequently, both the exposure levels and the relative proportions of chemicals at
16 future times may not correspond well to present measurements of a combination of chemicals
17 unless these influences are taken into account. In addition, exposure to one stressor may
18 influence the uptake of a second stressor. For example, a nonchemical stressor that increases
19 ventilation rate will increase the inhalation uptake of airborne chemicals.

20
21 **Toxicologic independence.** Two situations allow plausible approximations of the joint
22 exposure-response relationship using only the single stressor information: toxicologic
23 independence and toxicologic similarity (USEPA 2000e). In the case of toxicologic
24 independence, if the toxicity modes of action are biologically independent, then as long as there
25 are no pre-toxicity interactions (e.g., metabolic inhibition, influence on uptake), the single
26 stressor information is sufficient to approximate the joint exposure-response relationship. When
27 the effects from two or more stressors are different, the cumulative response, if toxicologically
28 independent, is merely all the single stressor responses, as if the other stressors were not present.
29 For example, joint but low exposure to heat (causing minor elevated heart rate) and toluene
30 (causing minor hearing loss) would be expected to cause both the minor heart rate elevation and
31 minor hearing loss, but to the same extent as expected for each stressor alone. If each stressor is
32 below its toxicity threshold, then for stressors exhibiting toxicologic independence, there will be
33 no estimated cumulative response, because the set of individual responses is then a collection of
34 zeros.

35
36 When the single stressor and cumulative toxicities are each represented by a frequency or
37 probability for affected individuals, also termed a probabilistic risk, then independence means
38 that “response addition,” as defined in the Agency’s *Supplementary Guidance for Conducting*
39 *Health Risk Assessment of Chemical Mixtures* (USEPA 2000e), can be applied for each adverse
40 effect that the stressors have in common. When all the single stressor risks are low, the joint risk
41 of a common effect under response addition can be approximated by the simple sum of the single
42 stressor risks. For example, if reproductive toxicity is the general effect common to the multiple
43 chemicals, the cumulative risk of reproductive effects (at low single chemical risk levels) is
44 approximately the sum of the single chemical reproductive risks. Risk addition under
45 independence places no constraints on the individual chemical dose-response curves.



1 **Toxicologic Similarity.** In the second situation, the stressors are grouped according to
2 the common mode of action for each effect of concern determined in the planning and scoping
3 phase (USEPA, 2002a). For all effects caused by that mode of action, “dose addition” (USEPA,
4 2000e) can be applied to the stressor group. Thus far, this approach has only been used with
5 combinations of toxicologically similar chemicals, not with combinations of chemicals with
6 other kinds of stressors such as radiation, physical factors or health status. With similar
7 chemicals, each chemical exposure is converted into the equivalent exposure level of one of the



An Example using Toxicological Independence: National-Scale Air Toxics Assessment

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

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

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

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

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

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

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



1 chemicals, called the index chemical. The joint toxicity or risk from the combined exposure is
2 then estimated by determining the effects or risk for that equivalent exposure level using the
3 dose-response information for the index chemical. For example, with the dioxins and furans (see
4 text box, next page), each congener exposure level is converted into its equivalent exposure as
5 the index chemical, 2,3,7,8-TCDD (USEPA, 1989b).

6
7 Although the assumption itself is not complicated, the decision to assume toxicologic
8 similarity can be complicated, depending on the level of assessment decided in the planning and
9 scoping phase and described in the analysis plan. The implementation used in Superfund
10 assessments (USEPA 1989a, Part D) is a rough approximation to dose addition where a Hazard
11 Index is determined whenever chemicals have a common target organ. The implementation by
12 the Office of Pesticide Programs in support of FQPA (USEPA, 2002a) is much more extensive
13 and requires knowledge of modes of action in order to calculate the Relative Potency Factors
14 (RPFs) for the effect of concern (see example in Appendix E). The Toxicity Equivalence Factor
15 (TEF) method used for the dioxins is a special case of the RPF method (see Appendix E); it
16 requires the most toxicologic similarity because the similarity applies to every toxic effect by any
17 type of exposure (USEPA, 2000e).

18
19 Single stressor information can also be used with dissimilar chemicals to gauge the
20 potential for toxicologic interaction. For example, chemicals with long whole body half lives, or
21 long tissue residence times, have the potential to be present in those tissues at the same time.
22 Such overlapping exposures can result in a higher effective tissue dose, altered tissue doses
23 caused by toxicokinetic interactions, or altered toxicity from interacting toxic mechanisms. When
24 a careful evaluation indicates no internal dose overlap, including metabolites, the single
25 exposures might be considered independently.

26 27 3.2.2.2. Information on Stressor Interactions and Multiple Exposures.

28
29 One important simplification that has been common in the assessment of single stressors
30 has been the separate evaluation of many of the key steps. That is, simplifying assumptions have
31 often been made regarding many characteristics of exposure (e.g., continuous vs. intermittent,
32 variations in magnitude) . For a given exposure route, for example, only one dose-response curve
33 may be used for the bounding case of setting a cleanup or action level of exposure, and also the
34 predictive case of estimating existing risk. These simplifying assumptions allow the dose-
35 response step to be performed in isolation from the exposure assessment step, with the two steps
36 executed in either order. For health-protective action levels, one may use bounds, such as the
37 upper bounds on toxic potency and exposure and lower bounds on the resulting acceptable
38 exposure level. Such bounds may be much easier to calculate, but may be more difficult to
39 interpret in terms of the uncertainties, likelihood and closeness to the best or central estimate.

40
41 The incorporation of multiple chemicals, other stressors, and multiple exposure
42 conditions obviously complicates the assessment and the use of simplifying assumptions. In
43 cumulative assessments, performing the exposure and dose-response steps of the risk assessment
44 paradigm separately is an approximation that obviously invokes a simplifying assumption. If the
45 dose response data do not represent the same conditions as the exposure being assessed, an
46 extrapolation has to be made, which introduces additional uncertainty that must be clearly stated.
47 Joint or cumulative toxicity depends on the total dose or exposure, relative exposure levels,



An Example using Toxicologic Similarity: The Dioxin Reassessment

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

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

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

1 and the many characteristics of exposure (e.g., duration, continuous vs. intermittent presence,
2 route, co-occurrence with other chemicals), and in many cases the complexities introduced by
3 multiple stressors will not allow use of some of the common simplifying assumptions of single-
4 stressor assessments. For example, toxicologic interactions have been shown to change using the
5 same doses but with a reversal of the sequence of exposure (i.e., chemical B then A instead of A
6 then B), so that the exposure and dose-response steps must be compatible and performed
7 together.

8
9 Nonchemical stressors can also cause toxicologic interactions. Biological stressors, like
10 their chemical counterparts, can interact with chemical exposures and change the overall risk in
11 non-additive ways. Ototoxic chemicals, such as toluene, can damage the auditory system and
12 have been shown to potentiate the effects of a physical stressor, noise, on hearing loss (Morata, et
13 al., 1997; Morata, 2000).

14
15 Toxicity and interaction data for the exposure-response relationship for the mixture of
16 interest that covers the full range of exposures is usually impossible because of limits on cost and
17 other resources. More feasible approaches to cumulative risk characterization, beyond that with



1 various simplifying assumptions, then require close matching of the exposure and dose-response
2 steps to minimize the data requirements. In many cases, screening level ranking may be the only
3 practical assessment. In some cases, there will be sufficient information for some quantitative
4 evaluation of cumulative health risks that reflect both the complex exposures and toxicologic
5 interactions. The issues for these cases are now presented along with their main research
6 implications, starting with the simplest case where only chemical interactions are considered.

7
8 “Joint chemical toxicity” means the outcome of exposure to multiple chemicals that
9 includes the single chemical effects along with any toxicologic interactions. Chemical
10 interactions can be divided into two major categories: those resulting from toxicokinetic and
11 those resulting from toxicodynamic modes of action (USEPA, 2000e). Toxicokinetic modes of
12 interaction involve alterations in metabolism or disposition of the toxic chemicals, for example,
13 by the induction or inhibition of enzymes involved in xenobiotic activation and detoxification.
14 Toxicodynamic modes of interaction include those processes that affect a tissue’s response or
15 susceptibility to toxic injury. A simplifying observation is that most interactions seem to involve
16 pharmacokinetics. Unfortunately, most studies of toxicologic interaction to date have only
17 involved two chemicals, and few have quantified the magnitude of the interaction or its
18 dependence on exposure conditions.

19
20 Toxicologic interactions are commonly described with terms such as *synergism* and
21 *antagonism*. These terms are only marginally useful, in part because the underlying toxicological
22 concepts are only defined for two-chemical mixtures, while most environmental and
23 occupational exposures are to mixtures of many more chemicals. Further, the mathematical
24 characterizations of synergism and antagonism are inextricably linked to the prevailing definition
25 of “no interaction,” instead of some intrinsic toxicological property (Hertzberg and MacDonell,
26 2002). The U.S. EPA has selected “dose addition” as the primary no-interaction definition for
27 mixture risk assessment, so that synergism would represent observed toxic effects that exceed
28 those predicted from dose addition (USEPA, 2000e). The EPA mixture risk guidance also
29 describes a modified Hazard Index that incorporates evidence of pairwise toxicologic interactions
30 but notes that the pairwise evidence may be specific to the exposure conditions of the study. The
31 guidance further encourages development of full biomathematical models for the joint toxicity,
32 such as those based on pharmacokinetics, so that qualitative interaction labels such as synergism
33 are replaced by quantitative estimates of mixture response that directly reflect the actual
34 environmental exposure levels.

35 36 37 3.2.2.3. Decision Indices.

38
39 The complexities with cumulative risk assessment include the frequent need to combine
40 pieces of information that differ widely from each other. Exposure data for some stressors may
41 be only as time-weighted averages, while others reflect daily human activity patterns. Toxicity
42 data for some chemicals may allow estimation of probabilistic risk for one endpoint, while only
43 providing qualitative descriptions of other endpoints. It is possible to develop the risk
44 characterization using the original information in a high dimensional matrix, but such a summary
45 will be difficult to evaluate and communicate. One approach to diverse multivariate data used
46 successfully for weather forecasting is the decision index, with examples such as the smog index,
47 the pollen count, and the mold index commonly used to assist in public and personal decisions



1 about environmental exposure. A similar approach can be taken for cumulative risk assessment
2 (Hertzberg, 2000).

3
4 The advantage of a decision index is
5 the simplicity in converting highly
6 multivariate technical information into a
7 single number. The most common example
8 used for cumulative health risk is the Hazard
9 Index (HI) for mixture risk (see box at right).
10 Although specific for a single affected target
11 organ, each HI reflects multiple studies of
12 multiple chemicals, often involving multiple
13 test animal species and test exposures, and
14 highly varied measures of toxicity.

15
16 The main disadvantage of a simple
17 index is that the uncertainties in its
18 calculation are largely hidden. Another key
19 disadvantage is in quantifying what are often
20 scientific judgments. For example, the Hazard Index implemented under Superfund (USEPA,
21 1989a) is a number whose decision threshold is usually given as 1.0, so that when the HI is
22 greater than 1, additional action is indicated. The actual value of HI is not that informative; HI=6
23 is not necessarily twice as bad as HI=3.

24
25 One alternative for addressing multiple effects is to recast these qualitative judgments in
26 terms of severity categories or levels of concern, and then use statistical methods such as
27 categorical regression that use only the ordering of the severity scores, but not their actual values.
28 The result is not a risk of a particular toxic effect, but rather a risk of exceeding a certain
29 minimum toxic severity level, or level of minimal concern (Hertzberg, 1989; Guth, et al., 1993).
30 In the best situations, such as the EPA interaction-based Hazard Index (USEPA, 2000e), the
31 decision index formula is modular so that component pieces can be evaluated separately for
32 accuracy, and so that improvements in one area can be easily incorporated to give an improved
33 index.

34
35 Another example of a decision index with more overt display of its diverse parts is the
36 Hazard Ranking System (HRS), a formula developed for characterizing the relative hazards of a
37 particular waste site. These hazards were highly diverse, including corrosivity, explosivity,
38 toxicity and soil conditions. As with the HI, different uncertainties in the components make the
39 uncertainty of the HRS index difficult to describe. Instead of merely presenting the index as a
40 number, a high dimensional graphical presentation could be used such as the star plots of
41 multivariate data (Chambers, et al., 1983; Hertzberg, 2000), where each arm of the star represents
42 one of the sub-indices. While this approach shows the relative contribution of each factor, it
43 again hides the uncertainties of the factors as well as of the HRS index itself.

44
45 Hybrid methods also have been used for complex risk assessments that combine
46 judgment with numerical descriptions of risk or dose-response. The EPA interaction-based
47 Hazard Index (USEPA, 2000e) and the mixture risk approaches of the Agency for Toxic

Example Decision Index: The Hazard Index

The Hazard Index for oral exposure is implemented by Superfund assessors by the formula:

$$HI = \sum [HQ_j] = \sum [E_j / RfD_j]$$

where E_j and RfD_j are the daily exposure and Reference Dose of chemical j .

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



1 Substances and Disease Registry (Hansen, et al., 1998) both include a judgmental weight of
2 evidence (WOE) score to reflect the strength of evidence for toxicologic interactions and
3 relevance to human health risk. The ATSDR WOE is used in communicating risks and
4 intervention options, while the EPA WOE is used to calculate a modified Hazard Index. A
5 slightly different approach is the Integral Search System data base program for combinations of
6 carcinogens (Woo et al., 1994) by which available studies on pairwise interactions of
7 carcinogenicity are used to modify the risk range of the combination from that predicted by
8 response addition (USEPA, 2000e). In all these cases, scientific judgment is used to alter the risk
9 description or quantitative estimate, but only in terms of an approximate risk interval or a
10 decision threshold.

11 3.2.2.4. Probabilistic Approaches.

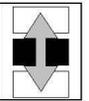
12 The recent report by Bogen (2001) illustrates an alternative probabilistic approach to
13 noncancer endpoints, in which methods used for integrated quantitative treatment of uncertainty
14 and variability are made consistent with those used for probabilistic assessment of cancer risk.
15 This report addresses many issues concerning the implementation of probabilistic methods for
16 noncancer endpoints, and cites a number of related references (e.g., Lewis, 1993; Dourson et al.,
17 1994; Slob and Pieters, 1998).

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

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

35 3.3. Areas of Complexity and Current Research

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



1 3.3.1. Interactions Between Stressors and Other Factors.

2
3 In identifying and characterizing susceptible subpopulations, it may be important to
4 consider a variety of factors such as current physical and mental health status and past exposure
5 histories, which may exacerbate the effects of the stressors of interest. Economic considerations
6 such as economic status, community property values, source of income, level of income, and
7 standard of living may also affect susceptibility and exposure of subpopulations to certain other
8 stressors. Risks associated with chemical or biological stressors may be significantly affected by
9 “vulnerability factors” such as lack of health care or genetic predisposition to some diseases and
10 effects. Community traditions and beliefs may affect activity patterns and behaviors and therefore
11 affect exposure to stressors as well as the risk management options deemed acceptable.
12 Depending on the scope of the assessment and the stressors included, “lifestyle factors” such as
13 smoking habits, nutritional habits and others may be important to susceptibility.
14

15 In what could be characterized as an exploration of how somewhat abstract factors may
16 affect susceptibility, the Agency for Toxic Substances and Disease Registry (ATSDR) held an
17 expert panel workshop in 1995 on the subject of psychological responses to hazardous substances
18 (ATSDR, 1995). In this report, the panel noted that there is “a significant lack of information”
19 about how often communities near hazardous waste sites or spills suffer chronic stress reactions,
20 but that psychological stress causes both psychological changes that can be measured by self-
21 reports and objective tests, as well as physical changes such as increased blood pressure, heart
22 rate, and biochemical parameters such as changes in stress hormones. Assessing the levels of
23 stress, and their potential contribution to risk, is difficult for a variety of reasons. The report notes
24 that “unlike the damage and injuries caused by a natural disaster, many toxic substances are
25 invisible to the senses.... In the face of no external cues and uncertain circumstances, each person
26 affected by a hazardous exposure develops their own beliefs about the nature of the resultant
27 harm. These beliefs are based on the facts available to them, pre-existing opinions, cultural
28 factors, sensory cues, and the beliefs of leaders and others in the community. . . . Unlike a natural
29 disaster, which hits and has a low point after which recovery can begin, the response to a
30 hazardous waste site can take 12 to 20 years.”
31

32 Although the ATSDR report indicates that stress related to hazardous chemicals in the
33 community can show measurable physical effects, they stopped short of saying that long-term
34 health effects from this stress can be converted to risk estimates at this time. One of the questions
35 the panel was asked to address was, “Given what is known regarding the psychology of stress,
36 are there interactions between chronic stress and exposure to neurotoxicants that could shift the
37 dose-response curve for neurotoxins?” The panel concluded:
38

39
40 “A methodology does not exist that would allow for discrimination between stress or
41 neurotoxicant-mediated effects in community-based studies. . . . Experimental animal
42 data exist to suggest that stress levels can modulate a toxic response; however, the
43 question of specificity remains. Given that stress can induce or unmask a latent effect of
44 a toxicant, there is the possibility that chronic stress could alter basal levels of
45 neurofunctioning and shift the threshold for neurotoxicity. Indeed, one may find a shift in
46 the dose response to a neurotoxicant; however, a specific effect of the neurotoxicant
47 needs to be examined in greater detail than the generalized non-specific endpoints.



1 Detecting such a shift would require the knowledge of toxicant-specific biological
2 mechanisms of actions, which most often are not known.” (ATSDR, 1995, page 30)
3

4 The ATSDR report made many suggestions for research to fill data gaps in this area, and
5 scientists may make significant progress in this area in the coming years.
6

7 Another group of factors which may influence the risk to health or the environment,
8 whose evaluation may require a different approach from the traditional NRC risk paradigm, is the
9 group of “quality-of-life” issues. Although a cumulative human health or ecological health risk
10 assessment is not a cumulative impact analysis such as is conducted under NEPA, changes in
11 quality-of-life factors may affect the vulnerability of a population to health or ecological risks,
12 and consequently may be part of the considerations in a cumulative risk assessment. Since few, if
13 any, established and accepted relationships are currently available quantitatively linking quality-
14 of-life factors and health or ecological risk, this is an area in which further research may prove
15 valuable.
16

17 To evaluate the effects on human or ecological health from these types of stressors, a
18 more deliberative approach (in the analytical-deliberative process) is needed than is used in, say,
19 cancer risk analysis. EPA’s *Guidebook to Comparing Risks and Setting Environmental Priorities*
20 (USEPA, 1993b) suggests a six-step process that may help characterize quality-of-life factors,
21 some of which may be relevant to the assessment (e.g., in considering population susceptibility).
22 An example of a set of quality-of-life criteria, and their descriptions, developed by the State of
23 Vermont’s Agency of Natural Resources (State of Vermont, 1991) is provided in Appendix F.
24

25 Quality-of-life issues can encompass much more than the criteria mentioned in Appendix
26 F as an example. Some human health or ecological cumulative risk assessments may consider
27 quality-of-life factors as having a role in susceptibility to the stressors being assessed.
28

29 3.3.2. The Promise of Biomarkers and Biomonitoring. 30

31 There are a variety of measures that are inherently cumulative. These include biomarkers
32 (they give the full effect or full exposure, regardless of source) and measures of the incidence and
33 prevalence of disease in a community. The latter give an indication of the total effect of multiple
34 sources of exposure. In light of our understanding of the multifactorial basis of disease, a public
35 health approach that says “regardless of the cause, a community has x level of disease” can be
36 informative. Such statistics can be compared across geographical areas that have different
37 sources or different groups that have different levels of vulnerability. The approach is based
38 strongly in the field of epidemiology. Indeed, the most often heard critique of epidemiology –
39 that it is the prevalence or incidence of disease documented as a function of the combined effect
40 of many exposures (over time and/or space), is exactly what makes it so well suited for
41 cumulative risk assessment. It is likely that epidemiological concepts will figure prominently in
42 cumulative risk assessment, both in identifying the underlying vulnerability of a population and
43 by generating hypotheses regarding the determination of relative contributions of multiple
44 stressors.
45

46 Sources of data include cross sectional analyses that determine prevalence levels, as well
47 as basic surveillance techniques. With respect to the latter, The Pew Environmental Health



1 Commission (<http://pewenvirohealth.jhsph.edu/html/home/home.html> then click on “reports”) has recently completed a series of reports that document the extent of national and state level
2 resources for chronic disease surveillance. Reports focus on the type of surveillance systems
3 needed, as well as the status of registries for birth defects and asthma. Health Track
4 (<http://health-track.org/> and <http://healthyamericans.org/>) is the outgrowth of that research, and is
5 devoted to tracking and monitoring of chronic disease that would help communities begin to
6 identify patterns of health problems.
7

8
9 Biomarkers are inherently cumulative risk measures. Using biological measurements –
10 biomarkers – to determine prior exposures (biomarkers of exposure) or the current health status
11 of individuals (biomarkers of effect) holds some promise for cumulative risk assessments of the
12 future. Use of biomarkers for a group of chemicals or stressors which act upon individuals in the
13 same way can give the assessor a picture of where an individual currently falls on the continuum
14 from exposure to effects, making it much easier to predict risks if additional exposure occurs.
15

16 A few biomarkers (or even a single one) can possibly represent exposure to a suite of
17 chemicals. Although this reduces the analytical burden and simplifies the process of estimating
18 cumulative risk, the approach loses some of the advantages of single-chemical assessment
19 (especially being able to quickly discern the importance of different pathways and routes of
20 exposure contributing to the risk).
21

22 Biomarkers may be the approach of choice in the future, but the state-of-the-science is not
23 developed enough to make this practicable today in an assessment with large numbers of diverse
24 stressors (although it may be possible to do this for more simple cases). Currently, biomarker
25 development is not at the stage where they can be widely applied. For example, information on
26 the cumulative risks in a local population of a group of chemicals that are toxic to the liver might
27 be provided by selective liver function tests, but causal inferences would have to take account of
28 many other factors that may affect liver function. Likewise, body burden data for chlorinated
29 dioxins and related compounds may show that exposure has occurred, but assumptions would
30 need to be made as to the pathways, route, and timing of exposures, as well as scenarios
31 developed for future exposures if risks are to be estimated.
32

33 One of the benefits of this approach, the development of data which show the actual
34 current exposure and risk status of a population, is also its major impediment: it can require
35 extensive (or for humans, possibly invasive) monitoring. This can be not only costly, but
36 difficult to obtain. This approach uses primarily measurement methods, and also can develop
37 statements of probability of adverse effects of additional incremental exposures. This approach
38 holds great promise for simplification of a cumulative risk assessment, but few methods exist at
39 this time for applying this approach in a cumulative assessment. The main drawback of the
40 biomarker approach, at least for a regulatory agency like EPA, is that a decision to act to reduce
41 risk is often dependent on separation of contributions from exposure pathways so that effective
42 policies can be determined.
43

44 3.3.3. A Single Metric for Multiple Types of Hazard.

45
46 The most complex cumulative risk assessments will evaluate both multiple exposures
47 (potentially, multiple sources, stressors, pathways and durations) and multiple effects. Ideally



1 this evaluation would provide projections regarding the potential for a particular complex
2 exposure to cause particular effects to different physiological systems, and also provide an
3 integration of these projections into a qualitative characterization of overall potential impact to
4 human health. Some applications have attempted this via approaches which range from treating
5 the assessment as a number of multi-stressor, single effect assessments, where the risks from the
6 various effects are combined or characterized at the final step, to those that are more integrated
7 throughout.

8
9 For example, cumulative ecological risk assessments such as those that have been
10 conducted in the Columbia River Basin and the Chesapeake Bay focused on a number of
11 observed adverse conditions, then determined, among all of the possible stressors, which
12 particular combination was most influential in creating the observed adverse conditions.
13 Stressors such as overharvesting of natural resources, modification of natural hydrology, land use
14 change, point-source and non-point-source pollution, including toxic chemicals, and presence of
15 exotic species are analyzed, with the goal of the assessment being to design effective restoration
16 strategies to eliminate or ameliorate the conditions (Barnthouse, et al., 2000).

17
18 If it is considered desirable to the assessment, an important cumulative risk assessment
19 activity may be determining how (if at all possible) to combine risks from different effects – or
20 the even more problematic disparate measures of risk – and present them in an integrated
21 manner. Depending on the purpose and risk management objectives (see section 2.1.1), some
22 cumulative risk assessments may employ some sort of single, common metric to describe overall
23 risk.

24
25 One, but certainly not the only, approach to simplifying this problem is to collapse this
26 “n-dimensional matrix” of hazards and risks into a few or even a single measure (Murray, 1994).
27 However, this requires converting the various measures of risk to a common metric or otherwise
28 translating them into a common scale or index. Some methods for combining disparate measures
29 of risk are briefly described below.

30 31 3.3.3.1. Creating a Common Metric.

32
33 As discussed earlier in this chapter, there are several different theoretical approaches to
34 cumulative risk assessment. Some of these require synthesizing a risk estimate (or risk
35 indication) by “adding up” risks for different parts of the risk picture. Actual mathematical
36 addition, of course, requires a “common denominator,” or a common metric. Frequently used
37 common metrics are risk, money, time, and effort. Finding a common metric for dissimilar risks
38 (cancer vs. non-cancer, human vs. ecological, etc.) is not strictly an analytic process, since some
39 judgments must be made as to how to link two or more separate scales of risks. These judgments
40 often involve subjective values, and because of this, it is a deliberative process.

41
42 As an example of combining different effects into a common metric and the consequent
43 judgment needed to achieve a common metric, the EPA Office of Pollution Prevention and
44 Toxics in 1999 released its CD-ROM called “Risk-Screening Environmental Indicators Model,



1 Version 1.0" (USEPA, 1999i)¹¹. In this model, emissions for both carcinogens and non-
2 carcinogens are weighted by a toxicity factor so that they can be combined in a risk-based
3 screening “score” for a particular geographic area. The scale for this weight for carcinogens is
4 related to the unit risk factor, and the weight for the non-carcinogens is based on the RfD.
5 According to the authors, it is possible to relate these two scales by making a judgment as to how
6 they relate. They note that in their case, “when combining cancer and noncancer endpoints, it is
7 assumed that exposure at the RfD is equivalent to a 2.5×10^{-4} cancer risk” (Bouwes and Hassur,
8 1998; USEPA, 1998h).

9
10 Obviously, as Bouwes and Hassur acknowledge, equating an HQ value of 1.0 (i.e.,
11 exposure is at the RfD) with a cancer risk of 2.5×10^{-4} is a judgment that is outside the strictly
12 analytic part of an assessment; the equating of the two points in the respective scales represents a
13 value judgment and as such can be debated. Therefore, this particular part of the assessment is
14 deliberative in nature. In most cases, construction of a single scale for different types of
15 endpoints will involve *comparative risk*, a field where different types of risks or endpoints are
16 ranked, compared, or converted to a scale based on the judgments and values of the persons
17 doing the assessments (USEPA, 1993b, 1998f, 1999j).

18
19 There have been some attempts to allow for transparent and quantitative incorporation of
20 values into a common metric. One example flows from the suggestion that “time is the unit of
21 measure for the burden of disease”; whether the disease results in disability or premature
22 mortality (Murray, 1994). Based on this premise, economic analyses of the costs and benefits of
23 disease intervention strategies have used Quality Adjusted Life Years (QALYs) and Disability
24 Adjusted Life Years (DALYs) as the metrics for the adverse effects of disease. These metrics are
25 intended to reflect the years of life spent in disease states (considering the variation in severity of
26 effects) and the years of life lost due to premature mortality resulting from disease as a surrogate
27 measure for risk from a variety of different types of effect. Even if this conversion of effects into
28 QALYs or DALYs were successful, for diseases that result in periods of morbidity and disability
29 (but not death), weighting factors (based on judgments) are used to equate time spent in various
30 disease states with years lost to mortality. In this way, dissimilar adverse effects can be
31 combined to provide a single measure of disease burden. However, it should be noted that
32 aggregation of effects in this manner obscures the meaning of the final measure. QALYs and
33 DALYs do not represent an actual shortening of the lifespan but are indicators of the overall
34 degradation of well-being that results from various disease states. Therefore, QALYs and
35 DALYs may be best suited for ranking and comparative analyses.

36
37 Experience with applying such measures as QALYs and DALYs to environmental risk
38 problems is extremely limited. Some very early methods development work has been initiated
39 which explores the use of QALYs for combining microbial and disinfection by-product risks
40 (USEPA, 1998f). However, some concerns have been raised about the adequacy of such
41 measures, especially when integrated with economic information for decision making USEPA,
42 2000g). Further methods development work is needed to improve the utility of QALYs and
43 DALYs for environmental risk assessments; especially with respect to the incorporation of
44 uncertainty (USEPA, 1999j).

¹¹ 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.



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

9 EPA has also used decision indices (see section 3.2.2.3) based on dissimilar measures,
10 and while they do not produce risk estimates, the indices can still prove useful. The approach
11 involves developing a composite score – or index – from measures of various risk dimensions .
12 Various environmental risk indices have been developed and applied to ranking and comparative
13 analyses. Often, these indices employ surrogate measures for risk rather than using actual
14 calculations of the probability of adverse effects. One such index is the Hazard Ranking System
15 (HRS) [47 *Fed. Reg.* 31219, dated July 16, 1982, and amended 55 *Fed. Reg.* 51532, dated
16 December 14, 1990], used to place uncontrolled waste sites on the National Priorities List (NPL)
17 for Superfund. This index is based on the likelihood of off-site movement of waste, the toxicity
18 of the waste, and the people and sensitive environments that may be affected. It also uses
19 corrosivity, toxicity, fire hazard and other factors, all scored and combined into one numerical
20 indicator of overall hazard potential. Such an approach for a composite index has been suggested
21 for communication of cumulative risk (Hertzberg, 2000).

22
23 Fischhoff et al. (1984) provided an example of this approach as applied to the evaluation
24 of energy technologies. In this case, disparate risks are assigned a score from a fixed scale (e.g.,
25 from 0, representing no risk, to 100, representing the worst risk for that dimension). The scores
26 are then weighted to reflect value judgments about the importance of the various risk dimensions
27 and the composite score is calculated by summing the individual weighted scores. Again, the
28 aggregation of dissimilar adverse effects obscures the meaning of the final score making it more
29 appropriate for ranking and comparative analyses.

30
31 Recently, EPA has been working on several index-based approaches to dealing with
32 cumulative risk issues. EPA Region III and the Office of Research and Development have been
33 jointly working to develop a Potential Risk Indexing System (USEPA, 1993c, 1995d, 1997c).
34 This index also uses a vulnerability index, and gauges the overall well-being of a locale and
35 various subpopulations. Again, the volume and toxicity of released stressors serve as surrogate
36 measures of risk in developing this index.

37
38 Combining diverse effects and risk using either common metrics or indices each have
39 pros and cons. A weakness of the index approach is that information is “lost,” and the meaning
40 of the final score can be obscured, by aggregating dissimilar information. One strength, however,
41 is common to both approaches. Both techniques have the ability to incorporate social values in
42 an explicit and quantitative manner in the risk assessment. For example, in the derivation of
43 DALYs, weights can be used to reflect the different social roles people play as they age (Murray,
44 1994). In the composite scores developed by Fischhoff (1984), public concern was incorporated
45 as an adverse effect. This is an important feature for methods that will be applied to cumulative
46 risk assessments, especially for communities. Given that cumulative assessments have a
47 community/population focus, the ability to incorporate social values in an overall assessment of



1 well-being will be critical.
2
3

4 3.3.3.2. General Issues with a Single Metric. 5

6 As described above, each approach to portraying the results of a cumulative risk
7 assessment has desirable and undesirable features. While common metrics and indices can
8 incorporate social values in an explicit and quantitative manner, the meaning of the final measure
9 can be obscured by aggregation of dissimilar effects. The abstract meaning of the final measure
10 could lead to difficulties when communicating the results of the cumulative risk assessment to
11 the public. Graphical and mapping techniques do not necessarily overcome such problems with
12 communication. While these techniques may avoid some of the problems associated with the
13 mathematical aggregation of dissimilar effects, it can be difficult to accurately describe the
14 information that a graphic is intended to convey.
15

16 Because we have relatively little experience in combining different types of risk, a key
17 issue is *the need for methods development* in this area. The approaches described above indicate
18 a beginning. Additional exploratory work is needed, however, to further develop existing
19 methods and to find additional methods that are flexible, can incorporate social values, are easy
20 to communicate, and provide an integrated portrayal of the overall well-being of a community
21 and its various subpopulations.
22

23 3.3.4. Qualitative approaches. 24

25 There will be cases where cumulative risk cannot be quantified in any meaningful or
26 reliable way. Qualitative approaches can be valuable for cumulative risk assessment and, in the
27 near-term, may be the only practical way to address many of the complexities involved.
28 Qualitative approaches may be used as a way to overcome the complexity and data deficiencies
29 that hinder quantitative approaches. In many assessments, risk may not be a quantifiable
30 variable.
31

32 For these cases, there may be qualitative approaches that provide some insight. Broad
33 indicators related to exposure in complex ways (e.g., production volumes, emissions inventories,
34 environmental concentrations, etc.) and indicators of toxicity can be communicated using
35 geographic information systems. Displaying complex multi-dimensional matrices in a map can
36 help visualize locations of areas with multiple stressors. Furthermore, geographically based
37 measures of hazard are potentially useful cumulative measures – although they do not provide
38 information on the risks, the locations of hazards can be used as an indicator of cumulative
39 exposures, thus risks from all of the potential chemicals associated with that site. The
40 environmental justice literature has used this approach.
41

42 Quantitative results might eventually be reduced to a more qualitative scale (High,
43 Medium or Low), or the qualitative results could provide “comments” tacked to the quantitative
44 results. The assessment might simply raise “red flags” associated with specific issues (e.g.
45 density of emitters in a community; presence of minority populations; special exposure
46 pathways; etc); a high number of such flags would indicate unacceptable cumulative risk, even if
47 this isn’t quantified. This approach has been used in the European Union, and their experience

[ref needed] in using qualitative methods for permitting suggests that “qualitative” is not “irrational”. Other relevant tools include expert judgment techniques, focus groups, opinion surveys, citizen juries, alternative dispute resolution, and others.

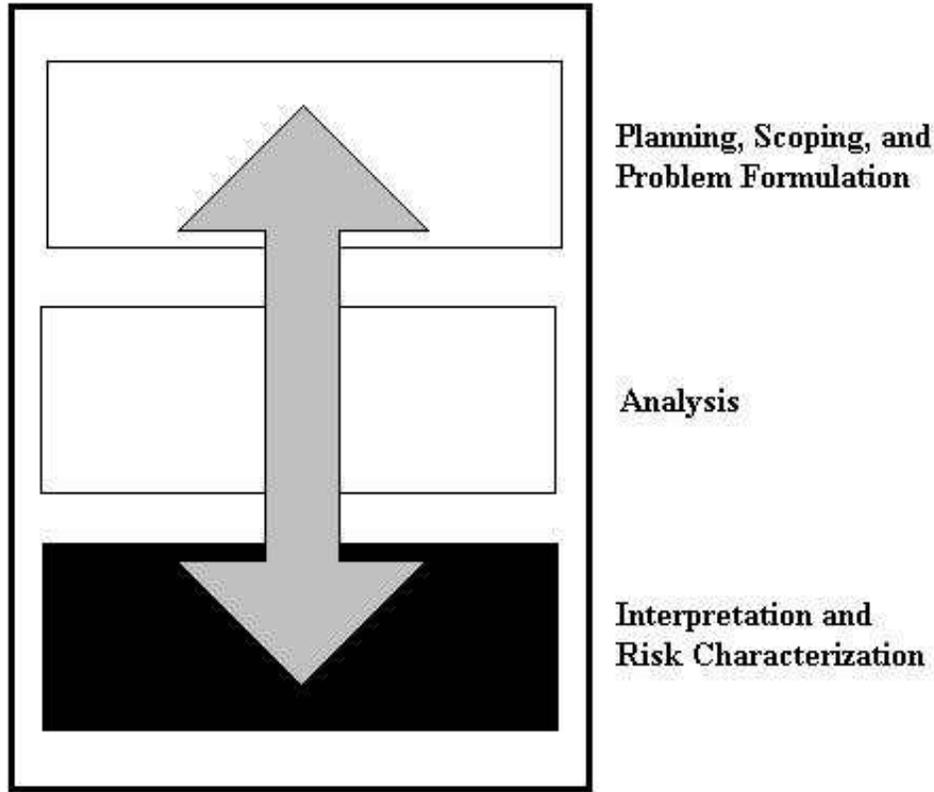


Figure 4.1. The Interpretation and Risk Characterization Phase.

4. THE RISK CHARACTERIZATION PHASE

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

As in the Analysis Phase, there is a substantial analytical component of the Interpretation



1 Phase, but there is also a considerable need for deliberation. At a minimum, stakeholders in this
 2 phase should (1) understand the outcome of the cumulative risk assessment; (2) ask questions
 3 about how best to frame the interpretation; (3) confirm that the cumulative risk assessment met
 4 the goals set in the Problem Formulation, or if not, why not. As in the previous phase, the
 5 stakeholders' role is only limited by what is proposed and agreed upon in the individual case
 6 being assessed.

7
 8 Risk estimation in a cumulative risk assessment will involve some combination of risks,
 9 either risks from various stressors causing similar effects, or risks from various stressors causing
 10 different types of effects. The stressors may be similar or widely different. Combinations of many
 11 types of stressors with different endpoints in a single assessment will quickly cause the risk
 12 estimation step to become very complex and difficult.

13
 14 Because of its potential complexity, and because in some cases cumulative risk
 15 assessments will be dealing with “uncharted territory” methodologically, it is very important that
 16 the planning, conduct, analysis, and characterization of a cumulative risk assessment be
 17 transparent. As stated by OMB (OMB,
 18 2002), the “benefit of transparency is that
 19 the public will be able to assess how much
 20 an agency's analytic result hinges on the
 21 specific analytic choices made by the
 22 agency.” The process, methodology, data,
 23 assumptions, and selection among alternate
 24 interpretations must be very carefully
 25 documented and very clearly stated. This is
 26 noted again in the next section.

27 28 **4.1. Risk Description**

29
 30 The ultimate product in the risk
 31 assessment process is the risk
 32 characterization, in which the information
 33 from all the steps is integrated and an
 34 overall conclusion about risk is synthesized
 35 that is complete, informative, and useful for
 36 decision-makers. The nature of the risk
 37 characterization will depend on the
 38 information available, the regulatory
 39 application of the risk information, and the
 40 resources (including time) available. It is
 41 important to identify and discuss all major
 42 issues associated with determining the
 43 nature and extent of the risk. Further, the
 44 EPA Administrator's March 1995 *Policy for*
 45 *Risk Characterization* (U.S. EPA, 1995a)
 46 specifies that a risk characterization “be
 47 prepared in a manner that is clear,

Risk Characterization Guiding Principles

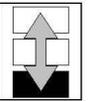
Regarding information content and uncertainty aspects:

- 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 a other 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.

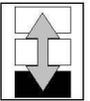


1 transparent, reasonable, and consistent with other risk characterizations of similar scope prepared
2 across programs in the Agency.” In short, estimates of health risk are to be presented in the
3 context of uncertainties and limitations in the data and methodology.
4

5 The 1995 *Guidance for Risk Characterization* (USEPA, 1995b) lists several guiding
6 principles for defining risk characterization in the context of risk assessment (see text box), both
7 with respect to information content and uncertainty aspects and with respect to descriptions of
8 risk. EPA has recently published a handbook on risk characterization (USEPA, 2000c).
9

10 Risk assessments are intended to address or provide descriptions of risk to one or more of
11 the following: (1) individuals exposed at average levels and those in the high-end portions of
12 the risk distribution; (2) the exposed population as a whole; and (3) important subgroups of the
13 population such as highly susceptible groups or individuals (e.g., children), if known. Risk
14 predictions for sensitive subpopulations are a subset of population risks. Sensitive
15 subpopulations consist of a specific set of individuals who are particularly susceptible to adverse
16 health effects because of physiological (e.g., age, gender, pre-existing conditions),
17 socioeconomic (e.g., nutrition), or demographic variables, or significantly greater levels of
18 exposure (USEPA, 1992a). Subpopulations can be defined using age, race, gender, and other
19 factors. If enough information is available, a quantitative risk estimate for a subpopulation can
20 be developed. If not, then any qualitative information about subpopulations gathered during
21 hazard identification should be summarized as part of the risk characterization.
22

23 The 1996 book *Understanding Risk* (NRC, 1996) devoted a great deal of discussion to risk
24 characterization. Risk characterization is most efficiently conducted by early and continued
25 attention to the “risk characterization” step in the risk assessment process (NRC, 1996; USEPA,
26 2000c). The box on the following page summarizes some of the points made in *Understanding*
27 *Risk*.
28
29



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: (1) diagnose the kinds of risk and the state of knowledge, (2) describe the legal mandate, (3) describe the purpose of the risk decision, (4) describe the affected parties and anticipate public reactions, (5) estimate resource needs and timetable, (6) plan for organizational needs, (7) develop a preliminary process design, and (8) summarize and discuss the diagnosis with the responsible organization.

1
2
3
4

4.2. Uncertainty Analysis



1 In their 1990 book *Uncertainty: A Guide to Dealing with Uncertainty in Quantitative*
 2 *Risk and Policy Analysis*, Morgan and Henrion (1990) note that historically, the most common
 3 approach to uncertainty in policy analysis (including in risk assessment) has been to ignore it. In
 4 a section titled “Why Consider Uncertainty?” they advance three primary reasons, all of which
 5 are especially relevant to an analytic-deliberative process such as cumulative risk assessment.
 6 They suggest that it is important to worry about uncertainty:

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

18 Morgan and Henrion provide
 19 “ten commandments” for good policy
 20 analysis, and although all are
 21 commendable, and several have been
 22 discussed elsewhere in this Framework
 23 report, we should look more closely at
 24 numbers 6-8 in the box at right for
 25 some insight into uncertainty analysis.
 26 There are many resources available
 27 which talk in detail about how to
 28 perform uncertainty analysis (e.g.,
 29 USEPA, 1997b, Morgan and Henrion,
 30 1990). While detailed instruction on
 31 how to perform uncertainty analysis is
 32 beyond the scope of this Framework
 33 report, we believe that a discussion of some general principles is in order.

Morgan & Henrion’s “Ten Commandments” for Good Policy Analysis

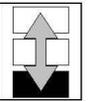
1. Do your homework with literature, experts, and users.
2. Let the problem drive the analysis.
3. Make the analysis as simple as possible, but no simpler.
4. Identify all significant assumptions.
5. Be explicit about decision criteria and policy strategies.
6. Be explicit about uncertainties.
7. Perform 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.

4.2.1. Assumptions in the Assessment

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

- 43 • the main policy concerns, issues, or decisions that prompted the assessment;
- 44 • the evaluation criteria to be used to define issues of concern or options;
- 45 • the scope and boundaries of the assessment, and ways in which alternate selections might
 46 influence the conclusions reached;
- 47 • soft or intangible issues that are ignored or inadequately dealt with in the quantitative



- 1 analysis (e.g., intrinsic value of wilderness, equity of distribution of risks and benefits);
2 • approximations introduced by the level of aggregation or by level of detail in models;
3 • value judgments and tradeoffs; and
4 • the objective function used, including methods of combining ratings on multiple criteria
5 (or combining risk scales). [adapted from Morgan and Henrion, 1990]
6

7 Identifying significant assumptions can often highlight “soft” uncertainties that are not
8 easily quantified, and are therefore often left out of a quantitative uncertainty analysis.
9 Nevertheless, these “soft” assumptions can often contribute more to the overall uncertainty of the
10 assessment than the factors more easily quantified.
11

12 In item #7 in Morgan and Henrion’s “ten commandments,” they list three types of
13 uncertainty that analysts should explicitly include:
14

- 15 • uncertainty about technical, scientific, economic, and political quantities (e.g., quantities
16 like rate constants often lend themselves to quantitative uncertainty estimates relatively
17 easily);
18 • uncertainty about the appropriate functional form of technical, scientific, economic, and
19 political models (e.g., are the models used, such as dose-response models, biologically
20 sound?);
21 • disagreements among experts about the values of quantities or the functional form of
22 models (e.g., different health scientists using different forms of dose-response models).
23

24 In Item #8 in the box on the previous page, Morgan and Henrion suggest that an assessor
25 needs to find out which assumptions and uncertainties may significantly alter the conclusions,
26 and that process can be conducted using sensitivity and uncertainty analysis. Techniques for these
27 include:
28

- 29 • deterministic, one-at-a-time analysis of each factor, holding all others constant at nominal
30 values;
31 • deterministic joint analysis, changing the values of more than one factor at a time;
32 • parametric analysis, moving one or a few inputs across reasonably selected ranges to
33 observe the shape of the response; and
34 • probabilistic analysis, using correlation, rank correlation, regression, or other means to
35 examine how much of the uncertainty in the conclusions is attributable to which inputs.
36

37 Finally, Morgan and Henrion answer the question of why we should consider uncertainty
38 analysis with the following point. “Policy analysts have a professional and ethical responsibility
39 to present not just “answers” but also a clear and explicit statement of the implications and
40 limitations of their work. Attempts to fully characterize and deal with important associated
41 uncertainties help them to execute this responsibility better.” (Morgan and Henrion, 1990)
42
43
44
45

46 4.2.2. Uncertainty and Variability 47



1 In their 1994 report *Science and Judgment in Risk Assessment* (NRC, 1994), the National
 2 Research Council noted a clear difference between uncertainty and variability, and recommended
 3 that the distinction between these two be maintained:
 4

5 “A distinction between uncertainty (i.e., degree of potential error) and inter-individual
 6 variability (i.e., population heterogeneity) is generally required if the resulting
 7 quantitative risk characterization is to be optimally useful for regulatory purposes,
 8 particularly insofar as risk characterizations are treated quantitatively. The distinction
 9 between uncertainty and individual variability ought to be maintained rigorously at the
 10 level of separate risk-assessment components (e.g., ambient concentration, uptake, and
 11 potency) as well as at the level of an integrated risk characterization.” (NRC, 1994, page
 12 242)
 13

14 Variability and uncertainty have been treated separately and distinctly in single-chemical
 15 assessments such as the assessment of trichloroethylene in ground water at Beale Air Force Base
 16 in California (Bogen, 2001). The treatment of variability and uncertainty will be an important
 17 issue in cumulative risk assessments, also, although at the time of this writing there are no good
 18 examples available of an elegant treatment of this issue for cumulative risk.
 19
 20

21 4.2.3. Uncertainty and Risk Addition

22
 23 Calculating individual stressor risks,
 24 and then combining them, presents largely the
 25 same challenges as combination toxicology,
 26 but also adds some statistical stumbling
 27 blocks. Toxicity addition, independence,
 28 synergism, or antagonism still need to be
 29 evaluated, but since risk estimates for various
 30 stressors are often presented as values on the
 31 same numeric scale (e.g., as cancer
 32 probabilities), cancer risks are often just
 33 added together.
 34

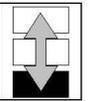
35 Since most cancer slope factors are
 36 not “most probable estimates,” but 95% upper
 37 confidence levels, adding traditional risk
 38 levels can cause the resulting sum to
 39 overestimate a 95% upper confidence level
 40 risk for a mixture. There have been several
 41 recent papers discussing this problem and
 42 how it may effect the resulting estimates. Kodell and Chen (1994) looked at several binary
 43 mixtures and calculated that the summation of individual upper 95% confidence intervals for
 44 chlorobenzene and hexachlorobenzene would overestimate the upper-bound risk of a binary
 45 mixture of these compounds by 2-6%, while for chlorobenzene and trichloroethylene, the
 46 overestimate would be in the range of 12-15%. Seed, et al. (1994) noted that, “in most cases, the
 47 magnitude of the difference in cancer risk estimates calculated by [Kodell and Chen’s] various

Uncertainty Analysis Example: The Cumulative Exposure Project

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

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

Source: Woodruff, et al., 2000



1 methods will be greatest for mixtures of equipotent compounds. However, even for mixtures of
2 equipotent compounds, the differences in joint risk estimated by summing the upper 95%
3 confidence levels. . .are not great.” After analyzing four cases, Cogliano (1997) concluded that
4 “as the number of risk estimates increases, their sum becomes increasingly improbable, but not
5 misleading.” For example, in adding 20 different cancer risk estimates based on a 95% upper
6 bound, the resulting sum of the upper bounds was no more than 2.2 times the true upper bound.
7 Cogliano goes on to suggest that, for certain cases not involving synergistic or antagonistic
8 interactions, “depending on the number of carcinogens and the shape of the underlying risk
9 distributions, division by a factor of 2 can be sufficient to convert a sum of upper bounds into a
10 plausible upper bound for the overall risk” (Cogliano, 1997).

11
12 The assumption of toxicologic independence (see section 3.2.2) may not be a bad
13 assumption if other evidence supports it, but it should be addressed in the assessment if used
14 (i.e., if risks are added). Although there are some scientists who believe that toxicologic
15 interactions are of minor consequence at concentrations observed in the environment (see
16 discussion in USEPA, 2000e), the scientific evidence for such an assumption has not been firmly
17 established.

18
19 Notwithstanding the statistical limitations of adding traditional risk estimates, and the
20 implicit assumption that the toxicities will be additive¹² (i.e., no interactions such as synergism or
21 antagonism occur), the numerical ease for combining risks in this way may make it the most
22 popular method for approximating cumulative risks in the short term, at least at a screening level
23 of assessment.

24 25 **4.3. The Information Provided by Cumulative Risk Assessment**

26
27 It is important to clarify how cumulative risk assessment and this Framework report relate
28 to community assessments and community decision making. Certainly, the Agency’s *Risk*
29 *Characterization Handbook* (USEPA, 2000c) emphasizes that whatever information is imparted,
30 it be transparent, clear, consistent, and reasonable. For example, if it is known that the results of a
31 particular cumulative risk assessment will be severely limited because of a lack of data or
32 available methods, it may be advisable to start with a screening analysis to set priorities for a
33 subsequent more detailed, focused study. In simple terms, what can a cumulative risk assessment
34 tell us, and what can’t it tell us?

35 36 **4.3.1. Making Sense of Multiple Stressor Effects**

37
38 The information provided by cumulative risk assessment is only a portion of the
39 information that communities and governments need to make informed decisions about risks.
40 There are almost always a multitude of factors that affect health in a community (e.g., crime,
41 drugs, health care access, vehicle safety, climate, infectious disease, diet. . .), some of which may
42 not have been considered within the scope of any given cumulative risk assessment. Community
43 decision-making will typically take risks to the environment into account, as well as

¹² At risk levels often seen with pollutant concentrations observed in the environment, the combined risks calculated assuming “response additivity” (that is, each component acts as if the other were not present) are approximately the same as with dose additivity (USEPA, 2000e).



1 consideration about historical and cultural values, and questions of fairness and distribution of
2 risks. The methodology is not currently available to understand how these factors (or stressors)
3 may affect cumulative health risk.
4

5 Additionally, benefits that may be associated with chemical or other stressor exposures –
6 benefits such as jobs and useful products or services – may be important contexts for decisions
7 on the risks considered in cumulative risk assessments.
8

9 This Framework report is not an attempt to lay out protocols to address all the risks or
10 considerations that are needed to adequately inform community decisions. Rather, it is focused
11 on describing various aspects of cumulative risk, *whether or not the methods or data currently*
12 *exist to adequately analyze or evaluate those aspects of the assessment.* The Framework report
13 devotes considerable time to a discussion of improving the methods for a single part of the
14 broader picture -- characterizing health risks associated with exposures to multiple chemicals via
15 multiple routes. Because of the limitations of the current state of the science, cumulative risk
16 assessments in the near future will not be able to adequately answer all questions posed by
17 stakeholders or interested parties. This does not mean, however, that they can't be useful in
18 providing insights to *some* of the questions asked; in fact, cumulative risk assessment may be the
19 best tool available to address certain questions dealing with multiple stressor impacts.
20

21 4.3.2. Cumulative Risk Assessments in a Public Health Context 22

23 The public, in a variety of forms, continually draws attention to health statistics, asking
24 for clarification of the relationship between environmental pollution (and risk assessments
25 concerning it) and public health. It is important to clarify that to draw relationships between
26 environmental pollutant exposures and disease incidence, a body of epidemiological study is
27 necessary, and trying to “work backwards” from health statistics to risk factors requires full
28 knowledge of the risk factors associated with the relevant disease(s).
29

30 Health statistics, including death rates and incidence of various diseases, illustrate the
31 impact of a variety of risk factors (e.g., smoking as well as environmental pollutants) and risk
32 reduction factors (e.g., exercise and good nutrition, as well as pollution control measures).
33 Indeed, population health statistics are reflective of *all* risk and risk reduction factors in a
34 population's history-to-date. Even the best cumulative risk assessment given today's state of the
35 science would fall short of being able to include an evaluation of the magnitude and interactions
36 of *all* stressors and effects. At best, the risk estimates of a cumulative risk assessment will reflect
37 *some* of the risks which may be reflected in community health statistics. With rare exceptions¹³,
38 cumulative risk assessment estimates would not be expected to match exactly with community
39 health statistics, even for specific health endpoints such as specific cancers.
40
41
42

43 4.3.3. How Scope and Purpose of the Assessment Affect Results

¹³ 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 coincidental, a substantial effort to match risk assessment scenarios with actual histories or exposures would have to be made.



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

11
12 The Agency is doing more place-based human health and ecological assessments (i.e.,
13 compared to source- or media-specific assessments) than in the past, but it will be some time
14 before place-based assessments become commonplace. Consistent with good practices for
15 planning and scoping, these often may be driven by specific risk management needs. To the
16 extent there are parties that were outside the process, their desired objectives and purpose may
17 differ from those for which the assessment was designed. For this reason, users of cumulative
18 risk assessments are advised to carefully study the scope and purpose of the assessment at hand,
19 as well as the analysis plan and resulting characterization, in order to determine whether it is
20 suitable (or partly suitable) to answer questions outside its stated objectives and purpose.

21 22 23 **4.4. Using the Results of the Assessment**

24
25 Once the results of an assessment are in hand, the assessment participants will usually
26 focus primarily on the use of those results. The intended use of the assessment was considered at
27 the beginning, in the Problem Formulation Phase, both to plan the assessment work and to set the
28 stage for what possible actions might be taken at this point.. A detailed discussion of the use of
29 the results of a cumulative risk assessment is beyond the scope of this document, but in deciding
30 on a course of action, other considerations will need to be taken into account along with the
31 results of the cumulative risk assessment.

32
33 If the goals of a cumulative risk analysis are to estimate the risk from multi-chemical and
34 multi pathway exposure to individuals living within a geographical area of concern, then an
35 important objective in presenting the results is to identify the major risk contributors in order to
36 understand the sources, pathways, and stressors which contribute most to that overall risk. The
37 results of a cumulative risk assessment provide an additional tool for the risk manager, one that
38 permits a more complete accounting and more explicit analysis to target follow-up risk
39 mitigation strategies toward those stressors which most contribute to the population’s risk.

40
41 If action to mitigate or prevent risk is the goal of the stakeholders, then options for action
42 discussed in the planning of the assessment can be re-evaluated in light of the results of the
43 assessment. Some of the issues after re-evaluating the action alternatives might include: “Is
44 regulatory authority available to address concerns or are voluntary actions better suited to address
45 the risks?” or “Can the concerns be addressed by the stakeholders involved in the assessment or
46 are the options for mitigation and prevention beyond the scope of their control?” In the latter
47 case, for example, siting issues are usually decided locally and may be within the authority of the



1 participants of a local assessment. In contrast,
 2 risk from mobile sources or acid rain are likely
 3 to require action beyond the scope of a single
 4 local community. In that case, taking action
 5 will require working with other communities
 6 and is likely to take more time. Discussion of
 7 the options available for addressing results of
 8 a risk assessment will help to keep
 9 expectations in line with possibilities.

10
 11 In taking action – or not taking action –
 12 after a cumulative risk assessment has been
 13 interpreted, the team may benefit from lessons
 14 learned by others, just as in the planning,
 15 scoping, and problem formulation phase. The
 16 European Environment Agency (EEA) in early
 17 2002 released an extensive study of twelve
 18 classic case studies in human and
 19 environmental health protection, and the
 20 lessons learned from them (EEA, 2001). The
 21 report is available on the internet and should
 22 be “food for thought” for any group
 23 contemplating protective actions, but
 24 particularly for community assessments.
 25 Twelve of the EEA’s “late lessons learned” are
 26 reproduced in the box at right.

27
 28 Finally, it is important to keep in mind
 29 that the results of the risk assessment will be
 30 only one of the factors that will need to be considered in making a decision on action to address
 31 the risk. Risk information can make an important and valued contribution to the decision-
 32 making process, but risk information, by itself, can not determine the decision. Factors such as
 33 the availability of resources for change, fairness and other community values, politics, business
 34 and employment considerations, quality of life issues, or concern for future generations will also
 35 influence any decision made. In the siting example mentioned above, the assessment may
 36 determine that the new facility does not significantly increase risk to the community and a
 37 decision not to site the facility might still be made on the basis of a quality of life issue unrelated
 38 to risk. Or, in contrast, a community may decide that the economic and employment benefits
 39 outweigh the risks associated with the siting. Other risk factors not considered in the assessment
 40 may also enter into the decision-making process. This can include both the environmental risks
 41 not covered in the cumulative risk assessment as well as the non-environmental risks that may
 42 affect a community. With limited resources, a community may use all available risk information
 43 to most effectively target its resources.

EEA’s 12 Late Lessons Learned

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

Source: EEA, 2001

1 **5. GLOSSARY**
2

3 **Adverse effect** - A biochemical change, functional impairment, or pathological lesion that either
4 singly or in combination adversely affects the performance of the whole organism or reduces an
5 organism's ability to respond to an additional environmental challenge.
6

7 **Agent** - a chemical, radiological, mineralogical, or biological entity that may cause deleterious
8 effects in an organism after the organism is exposed to it.
9

10 **Aggregate exposure** - The combined exposure of an individual (or defined population) to a
11 specific agent or stressor via relevant routes, pathways, and sources.
12

13 **Aggregate risk** - The risk resulting from aggregate exposure to a single agent or stressor.
14

15 **Benchmark dose (BMD)** - The dose producing a predetermined, altered response for an effect.
16 A BMD₁₀, for example, would be calculated based on a benchmark response of 10%.
17

18 **Benchmark response (BMR)** - A predetermined level of altered response or risk at which the
19 benchmark dose is calculated. Typically, the BMRs used are 1%, 5%, or 10%.
20

21 **Conceptual model** - Both a written description and a visual representation of actual or predicted
22 relationships between humans or ecological entities and the chemicals or other stressors to which
23 they may be exposed.
24

25 **Cumulative risk** - The combined risks from aggregate exposures to multiple agents or stressors.
26

27 **Cumulative risk assessment** - An analysis, characterization, and possible quantification of the
28 combined risks to health or the environment from multiple agents or stressors.
29

30 **Dose additivity** - In a mixture, when each chemical behaves as a concentration or dilution of
31 every other chemical. The response of the combination of chemicals is the response expected
32 from the equivalent dose of an index chemical (the chemical selected as a basis for
33 standardization of toxicity of components in a mixture). The equivalent dose is the sum of
34 component doses scaled by their toxic potency relative to the index chemical. For example, for
35 chlorinated dibenzodioxins (CDDs), 2,3,7,8-TCDD is selected as the index chemical, and other
36 CDD concentrations are adjusted for their potency relative to 2,3,7,8-TCDD, then treated as if
37 they were 2,3,7,8-TCDD "equivalents."
38

39 **Dose-response relationship** - A relationship between (1) the dose, either "administered dose" or
40 absorbed dose, and (2) the extent of toxic injury produced by that chemical or agent. Response
41 can be expressed either as the severity of injury or proportion of exposed subjects affected.
42

43 **Endpoint** - An observable or measurable biological or chemical event used as an index of the
44 effect of a stressor on a cell, tissue, organ, organism, etc.
45

1 **Lowest observed adverse effect level (LOAEL)** - The lowest dose or exposure level in a study
2 which there is a statistically or biologically significant increase in the frequency or severity of an
3 adverse effect in the exposed population as compared with an appropriate, unexposed control
4 group.
5

6 **Model** - A mathematical representation of a natural system intended to mimic the behavior of the
7 real system, allowing description of empirical data and predictions about untested states of the
8 system. Use of models is usually facilitated by computer programming of the mathematics and
9 construction of a convenient input and output format.
10

11 **No observed adverse effect level (NOAEL)** - An exposure level at which there are no
12 statistically or biologically significant increases in the frequency or severity of adverse effects
13 between the exposed population and its appropriate control; some effects may be produced at this
14 level, but they are not considered to be adverse or precursors to adverse effects. In an experiment
15 with several NOAELs, the common usage of the term NOAEL is the highest exposure without
16 adverse effects.
17

18 **Ototoxic stressor** - A stressor which causes damage to the ear or the sense of hearing.
19

20 **Reference Concentration (RfC)** - An estimate (with uncertainty spanning perhaps an order of
21 magnitude) of a continuous inhalation exposure to the human population (including sensitive
22 subgroups) that is likely to be without an appreciable risk of deleterious noncancer effects during
23 a lifetime.
24

25 **Reference Dose (RfD)** - An estimate (with uncertainty spanning perhaps an order of magnitude)
26 of a daily exposure to the human population (including sensitive subgroups) that is likely to be
27 without an appreciable risk of deleterious noncancer effects during a lifetime.
28

29 **Response additivity** - In a mixture, when the toxic response (rate, incidence, risk, or probability
30 of effects) from the combination is equal to the conditional sum of component responses as
31 defined by the formula for the sum of independent event probabilities. For two chemical
32 mixtures, for example, the body's response to the first chemical is the same whether or not the
33 second chemical is present.
34

35 **Risk** - *Absolute risk*: The probability of injury, disease, or death under specific circumstances. In
36 quantitative terms, risk is expressed in values ranging from zero (representing the certainty that
37 there is no chance of harm), to one (representing the certainty that harm will occur). *Incremental*
38 *risk*: The probability of injury, disease, or death under specific circumstances, relative to the
39 background probability. In quantitative terms, risk is expressed in values ranging from zero
40 (representing the certainty that the probability of harm is no greater than the background
41 probability), to one (representing the certainty that harm will occur).
42

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

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

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1 **APPENDIX A: RESEARCH AND DEVELOPMENT NEEDS**
2

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

10
11 EPA and other scientists are currently investigating the use of similar approaches for
12 cancer and noncancer assessments. Although we will not discuss this research need here, it
13 would be useful to cumulative risk assessment to have similar approaches, and it is a topic of
14 current discussion within scientific circles (e.g., Albert, 1999).

15
16 *Understanding the Timing of Exposure and its Relationship to Effects*
17

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

29
30 In addition to gaining a better understanding of the sequence and timing of exposures and
31 their relationship to effects, it is important to understand how acute, non-lethal exposures from
32 accidents contribute to chronic or long-term effects.

33
34 *Understanding the Composition and Toxicity of Mixtures*
35

36 Chemical mixtures can change or degrade over time and space making the assessment of
37 exposure a particular challenge. For cumulative risk assessment, the composition of the mixture
38 at the point of contact with the receptor needs to be well characterized. Both measurement
39 techniques (at the receptor) and predictive models are applicable in this characterization.

40
41 EPA's *Guidance for the Health Risk Assessment of Chemical Mixtures* (USEPA, 2000e)
42 presents approaches for combining the toxicities of multiple chemical stressors. These
43 approaches necessarily involve a number of simplifying assumptions when the mixtures are
44 complex. Although the current methods provide a valuable resource for assessing cumulative
45 risks, future cumulative risk assessment will need a more complete understanding of the

1 interactions among chemicals in complex mixtures. Some current research efforts are seeking to
2 identify toxicologic principles of joint action that are applicable to mixtures involving many
3 chemicals.

4
5 *Applying the Risk Factor Approach to Environmental Health Risks*
6

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

16
17 *Using Biomarkers and Biomonitoring*
18

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

23
24 *Considering Hazards Presented by Non-Chemical Stressors*
25

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

33
34 *Considering Psychological Stress as Part of Cumulative Risk*
35

36 Psychological stress causes both psychological and physiological changes that can be
37 measured. Assessing levels of stress and their potential contribution to risk, however, is difficult
38 for a variety of reasons. The Agency for Toxic Substances and Disease Registry (ATSDR) began
39 the process of identifying research needs in this area through an expert panel workshop held in
40 1995.

41
42 *Considering All Aspects of Vulnerability*
43

44 The issue of the vulnerability of a population can be thought of as having four
45 components: susceptibility of individuals, differential exposures, differential preparedness to

1 withstand the insult, and differential ability to recover from effects. Traditional risk assessment
2 may consider one or more of these categories but rarely are all considered. The overall
3 consideration of all four categories may be more important in cumulative risk assessment than in
4 traditional one-chemical assessments. A cumulative risk assessment, for example, may need to
5 consider potential combinations of high exposure and high vulnerability across stressors.
6 Methods development work is needed in this area.

7
8 *Methods for Combining Different Types of Risk*

9
10 Another key concept in the definition of cumulative risk assessment is that it represents
11 the combined risk from multiple stressors. This implies that, in some cases, it may be necessary
12 to combine disparate measures of risk (i.e., different types of effects) to simplify the expression
13 of cumulative risks. There have been some attempts to collapse complex arrays of risk into a few
14 or even a single measure. These approaches have involved the use of common metrics (e.g.,
15 Quality Adjusted Life Years, Disability Adjusted Life Years, Loss of Life Expectancy, etc.),
16 indices (e.g., Hazard Ranking System, etc.), and the categorization of effects (e.g., as for
17 categorical regression). Alternatively, Geographic Information Systems (GIS) and mapping
18 techniques can be used to graphically portray integrated information on risks without
19 mathematically combining disparate measures. Much methods development work remains to be
20 completed in each of these areas.

21
22 *Development of Default Values for Cumulative Risk Assessments*

23
24 Just as conventional risk assessments use a series of default values for screening or other
25 applications, it may be necessary to investigate whether certain defaults need to be established
26 specifically for cumulative risk assessments.

27
28 *Development of Case Studies and Issue Papers on Specific Cumulative Risk Topics*

29
30 The more detailed technical issues and methodologies should be developed as a series of
31 issues papers that would augment the *Framework* report. The level of detail would, of course,
32 vary depending on the topic, and may include the generic material from other guidance
33 documents. The issues papers (or white papers) should also include details on additional
34 approaches to cumulative risk assessment that are currently being explored (including screening-
35 level analyses, place-based assessments, comparative risk assessments, NEPA cumulative effects
36 analyses, and hazard assessments). In addition, the issues papers could include summaries of
37 case studies of cumulative risk projects that would extend the *Framework* from theoretical to
38 practical approaches and applications.

1 **APPENDIX B: SELECTED RESOURCES FOR EXPOSURE AND RISK ASSESSMENT**

2
3 **B.1. Resources Relevant to Chemical Exposures**

4
5 *EPA Guidelines:*

6
7 Most of EPA’s general guidelines are listed in the text box in section 1.1, page 5.

8
9 *Air-related sources and activities:*

10
11 EPA’s Clearinghouse for Inventories and Emission Factors (CHIEF) website
12 (www.epa.gov/ttn/chief/) is an excellent starting place that has many of the relevant
13 documents on methods and data for constructing emissions inventories available for
14 download. These include *Handbook for Criteria Pollutant Inventory Development: A*
15 *Beginner’s Guide for Point and Area Sources* (USEPA, 1999k), *Handbook for Air Toxics*
16 *Emission Inventory Development, Volume I: Stationary Sources* (USEPA, 1998i), and
17 *Compilation of Air Pollutant Emission Factors* (for both stationary and mobile sources)
18 (USEPA, 1995e, 1996d, 1997d, 2000h), as well as many other documents and software.

19
20 EPA’s Support Center for Regulatory Air Models (SCRAM) website
21 (www.epa.gov/ttn/scram/) provides extensive information on the models discussed in
22 *Guideline on Air Quality Models* (USEPA, 1999e), including downloadable software and
23 users guides for many of the models.

24
25 The Ambient Monitoring Technology Information Center (AMTIC) website
26 (www.epa.gov/ttn/amtic/) contains information on monitoring programs, monitoring
27 methods, and other monitoring-related information.

28
29 The umbrella website for all three of the above is the Technology Transfer Network
30 (www.epa.gov/ttn/), which also has other useful information and links in addition to those
31 noted above.

32
33 *Sources to land, and waste-related activities:*

34
35 The EPA Office of Solid Waste and Emergency Response has published an extensive
36 catalog summarizing their publications (USEPA, 2000i). They have also published a
37 “peer review draft” document called *Human Health Risk Assessment Protocol for*
38 *Hazardous Waste Combustion Facilities* (USEPA, 1998j) which deals with how to assess
39 risks from hazardous waste incinerators. These reports are available on-line.

40
41 *Chemical accidents, transportation-related spills:*

42
43 There are several steps in assessing an accidental chemical release exposure. The typical
44 analytical steps in an overall accidental chemical release risk assessment are process
45 analysis, likelihood or frequency of accidents, source term modeling, dispersion or

1 consequence modeling, and the exposure assessment.
2

- 3 ▶ The *process analysis* is a formal, systematic analysis of the process where a
4 chemical is handled to determine the probabilities and consequences of acute,
5 catastrophic failures of engineered systems leading to an accidental release of the
6 chemical. This analysis is often called a Process Hazards Analysis (PHA).
7 Several formal PHA evaluation techniques are available including “What-If,”
8 “Failure Mode and Effect Analysis,” “Event-Tree”, and “Fault-Tree” analysis
9 (USEPA 1998e, AIChE, 1992).
10
- 11 ▶ The *likelihood or frequency of accidents* step is an evaluation of each of the
12 scenarios uncovered in the process analysis step for likelihood or frequency of
13 occurrence.
14
- 15 ▶ *Source term modeling*, which estimates the amount or rate of release in case of
16 accident, is performed once the failure scenarios are determined. A wide variety of
17 published calculation methods or models are available (USEPA 1998e, USEPA
18 1999d) to determine the source terms for an accidental chemical release.
19
- 20 ▶ *Dispersion or consequence modeling* is performed once the source terms (rate and
21 duration of the release) are known. A wide variety of dispersion and consequence
22 modeling tools, ranging from simple screening models to sophisticated and
23 complex computer applications, are available for this step (USEPA 1999d, AIChE
24 1996, USEPA 1993a). In addition to the source terms generated above, several
25 other data elements are needed, such as physical/chemical properties (e.g.,
26 whether the vapor cloud is heavier than air or water reactive), meteorological
27 conditions (e.g., wind speed and direction, temperature, humidity), and terrain
28 surrounding the facility (e.g., buildings or valleys that may channel or disperse a
29 vapor cloud). Physical/chemical properties can be found in chemical reference
30 texts such as *Kirk-Othmer’s Encyclopedia of Chemical Technology* (Kroschwitz
31 and Howe-Grant, 1994), *Perry’s Chemical Engineers’ Handbook* (Perry, et al.,
32 1997), on Material Safety Data Sheets (MSDS)¹⁴, or in the *Guidance for Offsite
33 Consequence Analysis* (USEPA 1999d). Meteorological conditions are often
34 collected on-site or at local airports. Information about terrain can be collected
35 from topological maps or by visual inspection. Guidance on all these parameters is
36 available in USEPA 1999d.
37

38 The final step in a chemical accident exposure analysis is the *exposure assessment*. The
39 exposure assessment is related to, and builds from, the dispersion or consequence
40 modeling step. The dispersion or consequence modeling depends on a health endpoint
41 and the exposure level related to that endpoint. Besides lethality, concentrations for
42 certain health effects (e.g., odor thresholds, eye irritation) are available for several

¹⁴ There are many searchable MSDS data bases on-line that can be located with most search engines.

1 common toxic substances (NIOSH 1997, ACGIH 1998, AIHA 2000).
2
3

4 **B.2. Resources Relevant to Exposures to Non-Chemical Stressors**

5

6 *Biological stressors:*

7

8 The ILSI Risk Science Institute recently published a workshop report entitled “Revised
9 Framework for Microbial Risk Assessment” (ILSI, 2000), which looks at methods for
10 assessing risks to microorganisms such as *Cryptosporidium*, which has caused disease
11 outbreaks when it contaminates drinking water. The methodology is superficially similar
12 to a risk assessment conducted for a chemical pollutant, but only at the most general
13 level. How exposure is characterized, for example, includes many differences from
14 environmental chemical exposure assessment. Under “characterization of exposure,” for
15 example, the framework includes (1) pathogen characterization, (2) pathogen occurrence,
16 (3) exposure analysis, and finally developing (4) an exposure profile.
17

18 *Radiological stressors:*

19

20 EPA’s Office of Air and Radiation maintains a web page at
21 <http://www.epa.gov/radiation/assessment/>. This page provides (or cites) much of the
22 needed documentation for performing risk assessments for radionuclides. This includes
23 the *Radiation Exposure and Risk Assessment Manual (RERAM)* (USEPA, 1996e) and
24 several Federal Guidance Reports (USEPA, 1988, 1993d, 1999l).
25

26 *Noise, vibration, and congestion:*

27

28 The U.S. Department of Housing and Urban Development has issued *The Noise*
29 *Guidebook* (HUD, 1991), which implements the existing noise regulations [24 CFR 51-
30 B] and includes the HUD Noise Assessment Guidelines. (The *Guidebook* is available in
31 hard copy only.)
32

33 The Federal Railroad Administration has developed a manual called *High-Speed Ground*
34 *Transportation Noise and Vibration Impact Assessment* (DOT, 1998) which provides the
35 theory, equations, and applications of noise and vibration analysis for high-speed
36 railroads. Much of the theory and information is also applicable to other noise and
37 vibration problems. Appendix A of the DOT *Guide* is a general discussion of noise
38 concepts, with references. The *Guide* is available on-line.
39

40 The National Institute of Occupational Health and Safety has done much research on the
41 interaction of noise with chemical exposures (Morata, 2000).
42

43 *Odor:*

44

45 EPA’s Office of Wastewater Management has issued a report called *Guide to Field*

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1 *Storage of Biosolids* (USEPA, 2000j) which contains an appendix on “Odor
2 Characterization, Assessment, and Sampling.” Odor assessment is an analytic-
3 deliberative process, involving both science-based analytical methods and more
4 subjective analysis. The appendix of the *Guide* discusses sensory characterization of
5 odors (character, intensity, pervasiveness, quantity), some practical options for assessing
6 odors in a community, and the chemistry of odors (including range of odor thresholds). It
7 also discusses odor sample collection and analysis, and has several dozen references for
8 further information. This report is available on-line.

1 **APPENDIX C: SOME THOUGHTS ON BACKGROUND EXPOSURES**

2
3 When looking at aggregate exposures or cumulative risks of citizens, “background
4 exposures” to specific chemicals are no less “real” exposures than the pollution usually studied
5 for regulatory purposes. Whereas in historical single-chemical assessments conducted for
6 limiting pollution, background sources of the chemical were often irrelevant to the questions
7 being asked of the assessment (or ignored as having negligible effect on risk), background
8 sources are rarely irrelevant with cumulative risk assessments¹⁵.

9
10 Background concentrations can be categorized as either *naturally-occurring*, that is,
11 chemicals which are naturally present in the environment before it was influenced by humans, or
12 *anthropogenic*, that is, present in the environment due to historical human-made sources.
13 Naturally-occurring background chemicals may be either localized or ubiquitous. Anthropogenic
14 background sources can be either localized from a point source, or generalized from unidentified
15 sources or non-point sources.

16
17 Assessments of morbidity incidence and death rates, market basket surveys, and pesticide
18 residue surveys also provide information which can be reflective of background chemical
19 concentrations as well as overt pollution. Background issues extend across all media, beyond
20 regulated sources, and beyond direct exposure. Many chemicals are naturally present in the
21 environment (e.g., soils, water, vegetation and other biota) and are consequently part of dietary,
22 dermal and inhalation exposures. In some cases, naturally-occurring substances may occur at
23 levels that exceed health-based or risk-based regulatory standards (e.g., drinking water
24 standards), or other levels established to protect human health and the environment. Since
25 cumulative risk assessments are population based, exposures due to naturally-occurring
26 background concentrations should typically be considered to be of importance.

27
28 There are several important issues related to natural or anthropogenic background
29 concentrations in cumulative risk assessment. First, if the risks posed by “background”
30 concentrations of certain chemicals are significant (and some may approach or exceed health
31 reference levels), their exclusion from the cumulative risk estimates and characterization may
32 seriously distort the portion of the total estimated risk thought to be posed to the population by a
33 specific evaluated source. A second issue is the problem of whether background chemical
34 exposures can be clearly distinguished from specific source-related chemicals, and how to
35 quantify these exposures. It may be important in a cumulative risk assessment to estimate
36 background exposures separately from specific source-related exposures, so that the risk assessor

¹⁵ The word “background” is often used to describe exposures to chemicals or other stressors that derive from sources other than the sources being assessed. For example, in the Agency’s assessment of residual risk associated with hazardous air pollutant emissions from particular categories of sources that remain after the implementation of technology-based controls, “background” is defined as all hazardous air pollutant exposures (via inhalation or other routes) not associated with the source(s) being assessed. At a Superfund site, “background contamination” refers to contamination that is not related to the site release of chemicals, as defined by *Comprehensive, Environmental Response, Compensation and Liability Act* (CERCLA).[P.L. 96-510, December 11, 1980, as amended by P.L. 98-802, August 23, 1983, and P.L. 99-499, October 17, 1986] Such focusing or segregation in a risk assessment can be useful to decisions involving pollution sources covered by particular statutory authorities, but it is typical of a chemically-focused assessment rather than a population-focused assessment such as a cumulative risk assessment.

1 can provide the community with a more complete picture of both total and known source-related
2 risks. This also provides a clearer, more complete picture for making risk management
3 decisions. Finally, there may be problems in identifying representative geographic areas for
4 determining “background levels” for comparison.
5

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

1 **APPENDIX D: EXAMPLES OF ANALYSIS PLANS**

2
3 **D.1. Human Health Analysis Plan for Pesticides under FQPA**

4
5 Risk management /regulatory goal: Protection of the general human population and susceptible
6 subpopulations to adverse effects from exposure to pesticide “X” under the 1996 Food Quality
7 Protection Act (FQPA)

8
9 Assessment endpoints:

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

12
13 Measures of Effects:

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

20
21 Measures of Exposure:

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

25
26 What Can and Cannot be Done Based on Planning and Scoping

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

30
31 Methods for Conducting Risk Analysis

- 32 - RfD
33 - Margin of Exposure (MOE)
34 - probabilistic risk assessment based on dose-response or exposure parameters
35 - quotients (e.g., ratio of exposure level to toxicity threshold)
36 - narrative discussions
37 - other considerations (e.g., mechanisms of action, toxicokinetic models, timing of dose,
38 sensitive population characteristics)

39
40 Data Needs and Uncertainties

41
42 **D.2. Ecological Analysis Plan**

43
44 Risk management/regulatory goal: Viable, self-sustaining coho salmon population that supports
45 a subsistence and sport fishery.

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

2
3 Measures of Effects:

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

8
9 Measures of Ecosystem and Receptor Characteristics:

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

15
16 Measures of Exposure:

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

21
22 What Can and Cannot be Done Based on Planning and Scoping

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

26
27 Methods for Conducting Risk Analysis

- 28 - quotients
- 29 - narrative discussions
- 30 - stressor-response curves with probabilities

31
32 Data Needs and Uncertainties

APPENDIX E: TOXICOLOGIC SIMILARITY: ORGANOPHOSPHORUS PESTICIDES

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

Shortly after enactment of FQPA, EPA began developing new methods and tools that would allow the consideration of combined risks from exposure to several pesticides via several pathways and routes of exposure. Actual data sets for organophosphorous pesticides were used in pilot analyses to test these methods. The methods and pilot analyses were subjected to peer review through the FIFRA Scientific Advisory Panel (SAP) to ensure the use of sound science. As part of this ongoing effort, on December 28, 2001 EPA’s Office of Pesticide Programs (OPP) announced the availability of the Preliminary Organophosphorus Cumulative Risk Assessment [66FR67249-67250]. The risk assessment is available electronically at: <http://www.epa.gov/pesticides/cumulative>. In preparing the cumulative risk assessment for the organophosphorous (OP) pesticides, OPP followed 5 major steps.

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

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

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

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

To determine the combined risk from multiple OP pesticides, EPA used the Relative Potency Factor (RPF) approach [for additional examples of comparative potency approaches, also see Albert, et al., 1983; Lewtas, 1985, Lewtas, 1988]. The index chemical was selected based on the quality of the dose-response data. Then the relative

1 potency of each OP pesticide was estimated by taking the ratio of its toxic potency to that
2 of the index chemical.

3
4 In selecting studies for evaluating toxic potencies, EPA used relative potency factors and
5 points of departure developed from cholinesterase inhibition in rats exposed to pesticides
6 for 21 days or more. This practice was adopted to reflect cholinesterase inhibition at a
7 point in the treatment schedule at which a steady state had been achieved. OPP elected to
8 use data reflecting a steady state in the interest of producing relative potency factors that
9 are reproducible and reflect less uncertainty due to rapidly changing time-sensitive
10 measures of cholinesterase.

11
12 Also, EPA considered that people generally have had some level of prior exposure to OP
13 pesticides. Further, the effects of exposure can persist for several days to weeks.
14 Therefore, people may be more vulnerable to subsequent exposures to OP pesticides than
15 might be predicted by not considering these prior exposures.

16
17 *3. Estimation of the risks associated with all pertinent pathways of exposure in a manner that is*
18 *both realistic and reflective of variability due to differences in location, time, and demographic*
19 *characteristics of exposed groups.*

20
21 Evaluation of the OP pesticide use profiles allowed for the identification of exposure
22 scenarios that may overlap, co-occur, or vary between chemicals. In addition, the use
23 profiles allowed for the identification of populations of potential concern. Based on this
24 analysis, EPA considered exposure to OP pesticides in food to be uniform across the
25 nation (i.e., there are no significant differences in food exposure due to time of year or
26 geographic location). For the residential and drinking water pathways of exposure, EPA
27 divided the nation into 12 regions for assessment. This allowed for the consideration of
28 such factors as the location of vulnerable surface watersheds and region specific pest
29 pressures. To estimate risks, EPA used a calendar based computer model titled Calendex.
30 This model integrates the various pathways of exposure while simultaneously
31 incorporating the time dimensions of the data. The model produces a detailed profile of
32 the potential exposure to individuals across a calendar year.

33
34 *4. Identification of the significant contributors to risk.*

35
36 Although interpretation of the preliminary organophosphorous cumulative risk
37 assessment is ongoing, there are some early indications concerning contribution to risk.
38 The drinking water pathway for exposure does not appear to be a major contributor to the
39 total cumulative risk. Residential exposure appears to be a contributor to risk,
40 particularly inhalation exposures from certain no-pest strips and crack and crevice
41 treatments. Childhood exposure from mouthing hands also appears to be a contributor
42 but there is a great deal of uncertainty associated with the estimates.

43
44 *5. Characterization of the confidence in the results and the uncertainties encountered.*
45

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1
2
3
4

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

APPENDIX F: OTHER TYPES OF CUMULATIVE ASSESSMENTS

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

F.1. Quality-of-Life Assessments

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

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

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

Vermont’s Quality of Life Criteria

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

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

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

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

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

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

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

Source: State of Vermont, 1991

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

7
8 Quality-of-Life impacts are determined by analyzing a set of criteria developed for each
9 community, depending on what they value. Stressors are those things that threaten to degrade the
10 quality-of-life criteria for that community. An example of a set of quality-of-life criteria, and
11 their descriptions, is in the box on the previous page. These criteria were developed by the State
12 of Vermont’s Agency of Natural Resources (State of Vermont, 1991). Vermont’s experience in
13 evaluating these criteria was described as a qualitative description of harm, or in their terms,
14 “risk.”

15
16 “Because most of these seven criteria are intangible, they are extremely difficult to
17 measure or quantify. The Quality-of-Life Work Group described how each problem area
18 affects each criterion and how widespread or intense the effects are. Although these non-
19 quantitative descriptions of risk often lack precision and scientific objectivity, they focus
20 attention on specific critical issues and thus are useful tools for comparing the problems
21 systematically and consistently.” (State of Vermont, 1991)

22
23 Quality-of-life issues can encompass much more than the criteria used here as an
24 example. Ultimately, such an analysis may introduce much additional complexity into the
25 analysis. There may, for instance, be feedback loops not easily evaluated (e.g., loss of property
26 value, aesthetics, etc., tend to negatively affect the socioeconomic system, which in turn tends to
27 increase rates of crime, traffic accidents, and communicable-pathogen transmission, all
28 ultimately reflecting on overall community
29 health or ecological risk). Some cumulative
30 risk assessments may consequently include
31 quality-of-life impacts as indirect measures of
32 health effects if sufficient links can be
33 established between the two.

34 **F.2. Cumulative Impact Assessments**

35
36 The National Environmental Policy
37 Act (NEPA) has certain requirements for
38 “cumulative impacts” assessment (see box at
39 right), which looks at various stressors
40 leading to a variety of impacts or effects on
41 the environment. Although the Council on
42 Environmental Quality’s guidelines for cumulative impact analysis (CEQ, 1997) take a primarily
43 qualitative approach to the analysis, this is a multiple stressor, multiple effect assessment.
44
45

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

1 The projects or actions that NEPA addresses can be viewed as sources of stressors.
2 Environmental impact assessment under NEPA contains a description of the affected
3 environment that contains four types of information: (1) data on the status of important natural,
4 cultural, social, or economic resources and systems; (2) data that characterize important
5 environmental or social stress factors; (3) a description of pertinent regulations, administrative
6 standards, and development plans; and (4) data on environmental and socioeconomic trends.
7 Health effects on populations and susceptible individuals are part of the affected environment as
8 considered by the NEPA cumulative effects analysis, but the NEPA analysis may also consider
9 effects on historic and archaeological resources, socioeconomic factors like employment, human
10 community structure, and quality of life changes. Although there is not always a clear
11 relationship between these NEPA cumulative impacts and effects relevant to human health, the
12 NEPA methods and tools for cumulative impact analysis may be useful for cumulative risk
13 assessments. For example, cumulative impact analysis begins with an extensive scoping process
14 and relies on conceptual models to plan the analysis. NEPA effects data may help risk assessors
15 identify susceptible subpopulations, environmental pathways, or exposure patterns.
16

17 EPA’s Region VI has developed a system called the Cumulative Risk Index Analysis
18 (CRIA), primarily for NEPA-type assessments (Osowski, et al., 2001). The CRIA contains some
19 90 criteria to evaluate the health of an area and its ecosystem/human populations. These criteria
20 help evaluate factors as diverse as human health, ecosystem health, and environmental justice
21 considerations. Each criterion, which leads to an indexing of 1-5, has been through the
22 deliberative process, peer review, and is well documented.
23

24 We also acknowledge that other Federal Agencies have been preparing “cumulative risk
25 analyses” for various purposes related to their own mission as part of environmental impact
26 statements (e.g., NOAA, 1999).
27

28 **F.3. Empirically-Derived Medical Models**

29
30 The medical profession has long used empirically-derived models to predict the chances
31 of particular health effects in individual patients. In this approach, the characteristics of
32 individuals within the population are correlated with the incidence of specific diseases or effects.
33 For example, the risk factors for stroke are: increasing age, heredity (family history) and race,
34 prior stroke, high blood pressure, cigarette smoking, diabetes mellitus, carotid and other artery
35 disease, heart disease, transient ischemic attacks (TIAs), high red blood cell count, sickle cell
36 anemia, socioeconomic factors, excessive alcohol consumption, and certain types of drug abuse
37 (American Heart Association, 2000). Each of these risk factors can be correlated with stroke
38 incidence, and then the risk of stroke from various combinations of these factors can be explored.
39 In this way, the analysis is “cumulative,” but “risk factors” are not always synonymous with
40 “stressors.”
41

42 Physicians use models containing effect-specific risk factors to advise patients of the
43 probabilities of future effects (e.g., stroke, breast cancer) based on their medical history.
44 Although the medical data upon which these factors are based have been well developed for
45 many effects in humans, there are substantial data gaps remaining in terms of the role played by

1 exposures to many chemicals in the environment in the development of human disease. This
2 approach may be built on links between risk factors and effects for better studied stressors, but
3 may be limited or nonexistent for less robust health effects data bases. Although this approach
4 may some day be applicable to human health and environmental risk assessment such as EPA
5 conducts, at present the data and methods are not available.
6

7 8 **F.4. Risk Surrogates**

9
10 Geographic Information Systems (GIS) and related mapping techniques (e.g.,
11 Environmental Defense, 2001) appear to hold some promise as tools for presenting integrated
12 information concerning cumulative risks without mathematically combining disparate measures.
13 Considerable methods development work remains to be completed.
14

15 Not all statements of probability of harm are expressed as probabilities of specific health
16 effects. Bernard Cohen, in his *Catalog of Risks Extended and Updated* (Cohen, 1991), uses
17 mortality ratios to derive “loss of life expectancy” (LLE) estimates for a wide variety of risk-
18 related activities. For example, workers in all occupations have a 60 day LLE as a result of
19 working, but workers in agriculture have a 320 day LLE, construction workers a 227 day LLE,
20 etc., as a result of their particular occupation. These types of statements are empirically derived,
21 probability-based statements of harm that do not use “probability of adverse health effect” as the
22 basis for the risk statement. For estimates such as LLEs, one could theoretically add up the
23 various activities and the corresponding LLEs in days to estimate a cumulative risk in terms of
24 loss of life expectancy. These “other” types of risk-surrogate probability statements could
25 conceivably be used in cumulative risk assessment, although there is apparently no methodology
26 currently being used to do so.