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# Summary Report of the Peer Consultation Workshop on the Draft *Framework for Cumulative Risk Assessment*

U.S. Environmental Protection Agency
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This report was prepared by Versar, Inc, an EPA contractor (Contract No. 68-C-99-238, Task Order No. 50), as a summary of the discussion held at the Peer Consultation Workshop on the Draft *Framework for Cumulative Risk Assessment* (August 22-23, 2001). 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 Consultation Workshop on the Draft *Framework for Cumulative Risk Assessment* was held on August 22 and 23, 2001, in Arlington, VA. The purpose of the meeting was to provide interested stakeholders with an opportunity to see an early draft of the *Framework* and to obtain early input from these stakeholders that will assist EPA with further development of the *Framework* document.

After opening presentations by EPA staff providing background information on the draft *Framework*, the participants engaged in discussions organized around three topic categories: (1) over-arching issues, (2) process issues, and (3) technical issues. Most of the remainder of the first day was devoted to such over-arching issues as the scope and organization of the draft *Framework* report. Discussion on process issues began late in the afternoon of the first day and included considerable discussion of stakeholder involvement in the cumulative risk assessment process. The technical discussion, on about ten topics, was completed on the second day. Time was set aside on both days of the workshop for comments to be made by observers.

## Summary of Comments on Over-arching Issues

- Many experts stated that the draft *Framework* represents a good start and it is expected to be a useful document (after a lot of revisions) that will help to promote consistency in cumulative risk assessment.

- Several individuals commended EPA for writing a concise document that maintains a broad perspective, which will allow users flexibility in planning and implementing cumulative risk assessments.

- Some thought that the document is too generic and needs to better present the essence of a "framework" and highlight the unique aspects of cumulative risk assessment, particularly tying in environmental health issues, vulnerability of populations, and related issues.

- Many individuals commented that the document needs editing/reorganization because the current draft is unbalanced, where some topics receive too much detail, while other issues deserve more information.

- The document would benefit from diagrams to illustrate the concepts and flow of information within the three steps: Planning and Problem Formulation, Analysis, and Interpretation.

- The document should include a better representation of the scientific literature by citing additional papers published in peer reviewed journals.

**Summary of Comments on Process Issues**

- Discussion on process issues mostly focused on stakeholder issues, with some commentary on the use of cumulative risk assessment in decision making. Most of the stakeholder involvement comments concentrated on the level of stakeholder discussion in the document, how to get stakeholders involved, and the role of stakeholders in cumulative risk assessment.

- Comments on the draft *Framework's* stakeholder involvement discussion were generally positive with some suggestions on possible changes. Several participants thought that the discussion was too general and should be reduced to focus on those issues that are specific to cumulative risk assessment.

- Extensive comments were provided on how to promote stakeholder involvement in cumulative risk assessment projects, particularly with respect to providing a level playing field for communities and other groups that may not have technical resources available to them. In particular, it was noted that significant stakeholder involvement will require not only a "place at the table" for these groups, but access to resources needed to participate in what can be dauntingly scientific processes.

- Several people suggested that the document provide a clearer picture of the potential role of stakeholders throughout all three phases of the cumulative risk assessment process. The document should clarify that stakeholders may be involved in the management team throughout the life of an assessment, which may often require considerable time commitments.

- Several individuals raised the issue of EPA developing trust with stakeholders, through up front planning and discussion of the expectations and possible outcomes from an assessment. Specifically, it is important at the beginning phases of a project to clearly articulate the objectives and discuss the possible end results, including uncertainties and the required level of confidence in the conclusions.

- Discussion on the use of cumulative risk assessment in the larger context of decision making mostly focused on adding narrative to the document on when it might be appropriate to use cumulative risk assessment and how to maximize the utility of the assessment in the larger decision making process. The document could provide further detail on the kinds of questions that may be addressed legitimately by a cumulative risk assessment, and the kinds of questions for which such an assessment is not suited. This discussion could also mention the ways in which the quality of data needed in the assessment might affect the kinds of questions that can be addressed. These are not

purely policy issues, but ones that involve an understanding of the quality of the science underlying an assessment.

- Suggestions were made to present examples of the types of decisions that cumulative risk assessment can support. Several experts noted that this tool appears to be particularly applicable to permitting and siting issues where it can be used in a proactive manner to determine potential risks from new facilities or activities.

**Summary of Comments on Technical Issues**

- Several individuals thought that the draft *Framework* document needs to address qualitative risk to the same extent as quantitative risk. They felt an increased emphasis on qualitative risk assessment is important since it allows for the evaluation of a broader range of stressors.

- There was general agreement that combining different types of stressors (e.g., chemical and non-chemical) can be problematic. Various approaches were discussed to address this issue including developing a matrix and using comparative risk assessment. Although there was no general consensus regarding appropriate methodology, it was recommended that the document should maintain a broad scope and include all stressors even though certain stressors cannot be evaluated quantitatively by existing methods.

- An individual noted that the document should emphasize that some kinds of uncertainty analyses cannot be done quantitatively. The current section in the document should be expanded to show that the limitations of the analysis include more than just statistical uncertainties, broadening the concept of uncertainty from just quantitative uncertainty to actual level of confidence in the assessment.

- It was suggested that the technical sections of the document be modified so that they are more specific to cumulative risk assessment. For example, when discussing vulnerability, it would be helpful to mention the synergy or antagonism that can occur when several different stressors are combined. Similarly, when combining chemical and non-chemical stressors, the reader should be informed that interactions may result and influence the level of the effect(s).

- Many individuals commented throughout the technical discussion on the importance of defining the scope of issues to be addressed early on in the cumulative risk assessment process to help determine the types of analyses that can be done and take into consideration the resulting level of uncertainty.

# 1.0 INTRODUCTION

## 1.1 Workshop Purpose

The Peer Consultation Workshop on the Draft *Framework for Cumulative Risk Assessment* was held on August 22 and 23, 2001, in Arlington, VA. The workshop was sponsored by the U.S. Environmental Protection Agency's (EPA's) Risk Assessment Forum and was facilitated by Versar, Inc. The purpose of the meeting was to provide interested stakeholders with an opportunity to see an early draft of the *Framework* and to obtain early input from these stakeholders that will assist EPA with further development of the *Framework* document.

## 1.2 Workshop Participants

A group of 12 experts, from different disciplines and types of organizations, was assembled by Versar for this peer consultation workshop. These individuals have experience related to cumulative risk assessment from a variety of perspectives: academia, consulting, industry, environmental groups, and community activist groups. In addition, the experts were selected such that the following topic areas would be covered at the meeting: 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. The list of experts is presented in Appendix A. In addition to these individuals, about 25 observers attended the workshop. The list of observers is presented in Appendix B.

## 1.3 Discussion Topics

A list of discussion topics, presented in Appendix C, was distributed to the participants prior to the meeting to help stimulate dialogue on technical issues related to the draft *Framework* document. These discussion topics were categorized as (1) over-arching issues, (2) process

issues, and (3) technical issues and represented those topics which have been under deliberation within the EPA Risk Assessment Forum Technical Panel. This peer consultation, as opposed to a peer review, was held to obtain input from scientists earlier in the document development process so the draft *Framework* can be expanded and improved as it moves forward. The discussion topics listed were a starting point for the dialogue and participants were encouraged to raise other issues or topics. However, regulatory policy issues were beyond the scope of the meeting.

### 1.4 Agenda

The workshop agenda is presented in Appendix D. The meeting began with opening remarks including an overview of the agenda for the two-day meeting, presentations from EPA staff on the background of the draft *Framework* document, and review of the objectives of the meeting by the chair. Consistent with the more informal nature of a peer consultation, the agenda was purposely designed to be flexible to accommodate discussion of new ideas as they arose. The agenda was organized around the three main discussion topic categories (1) over-arching issues, (2) process issues, and (3) technical issues. After the morning presentations, most of the remainder of the first day was devoted to such over-arching issues as the scope and organization of the draft *Framework* report. Discussion on process issues began late in the afternoon of the first day and included considerable discussion of stakeholder involvement in the cumulative risk assessment process. The technical discussion, on about ten topics, was completed on the second day. This discussion included such topics as approaches to cumulative risk assessment, uncertainty/variability analysis, epidemiology, and combining different types of risk. Time was set aside on both days of the workshop for comments to be made by observers.

## 1.5 Workshop Summary Report

This report summarizes the workshop presentations and discussion, with appendices that provide handouts, other materials used in presentations, and post-meeting written comments from the participants. 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.
- Sections 3, 4, and 5 provide summaries of the comments and suggestions of the participants, with supporting dialogue, organized by the three main discussion topic categories.
- The appendices to this report present the handouts from the meeting (e.g., agenda, list of discussion topics, slides, and other materials) as well as post-meeting written comments from the participants.

# 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 workshop was a peer consultation, not a peer review, and was intended to promote dialogue and provide input on technical issues associated with the draft *Framework* document earlier in the process than would be done in a peer review. Mr. Bottimore talked about the effort to assemble a group of experts with diverse backgrounds and expertise to contribute new ideas to 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 going around the room for introductions of the participants and observers.

## 2.2 Background on Risk Assessment Forum and Framework Development

Bill Wood, Executive Director of EPA's Risk Assessment Forum (RAF), provided a short overview of the RAF and its activities working toward issuing cumulative risk assessment guidelines. He stated that this peer consultation will be helpful to the Cumulative Risk Assessment Technical Panel writing the *Framework*, particularly obtaining input on community-based risk assessment issues. His presentation began with background on the RAF. He explained that the RAF's mission is to promote consensus across the agency and apply the best-available science in risk assessments. 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 papers. Major

previous efforts included the cancer risk assessment guidelines and the ecological risk assessment guidelines.

Development of the *Framework* began 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 about ten Agency program 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 recently meeting with other Federal and State government scientists, to obtain early input for the *Framework*. Bill Wood emphasized that developing a framework is the first step in the overall process of developing guidelines on cumulative risk assessment. Publication of the final *Framework* in FY 2002 is anticipated, contingent on the outcome of peer review (perhaps by the SAB). Future guideline development efforts will include activities to identify and develop case studies and issue papers on various cumulative risk assessment topics. EPA anticipates issuing proposed guidelines within the next several years. Bill Wood noted that this process is similar to that used by other Agency efforts, most notably the ecological risk assessment guidelines, which were started in 1991 and finalized in 1998.

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 principles to promote a common language and furthering development of the approaches. He stressed that the *Framework* is not intended to present substantive technical guidance, but rather provide a general overview of issues, topics, and approaches that can be considered in conducting a cumulative risk assessment.

### 2.3 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 reflecting that cumulative risk assessment is a wonderfully challenging and exciting scientific topic. The Panel has been working diligently on the *Framework* and it is helpful to get technical input from other scientists, such as those assembled for this peer consultation. The *Framework* document is intended to present options and possible approaches to cumulative risk assessment and is not a protocol or a guideline on how to perform such an assessment. EPA will be developing the guidelines over the next several years, building on the *Framework* and other subsequent efforts. Cumulative risk assessment is not a replacement for traditional risk assessment techniques. Rather, it addresses specific issues growing out of the need to focus on populations or communities, rather than on sources of pollution. He noted 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 Air Toxics Assessment - NATA). As in Bill Wood's presentation, Mike Callahan emphasized that the RAF effort is focused on the scientific issues, not policy or regulatory issues.

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, including the three main phases: (1) problem formulation (planning and scoping), (2) analysis, and (3) interpretation. Cumulative risk assessment is not appropriate for every task but it is a tool available to help risk assessors and decision makers. The process includes both analytical and deliberative aspects that are useful in answering questions, particularly in circumstances involving multiple stressors and multiple chemicals. It is important to recognize what a cumulative risk assessment can and cannot do, so people have realistic expectations. This is also something that groups performing assessments should discuss during the front end 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 and many of the challenges in cumulative risk assessment arise from limitations in methods to aggregate and/or compare risks from different chemicals and types of stressors. The *Framework* describes methods that the Agency is aware of, recognizing the strengths and limitations of the different approaches. Mike Callahan's presentation

introduced many of the scientific issues related to combining different types of risks, concepts of vulnerability and susceptibility, and evaluating uncertainty in cumulative risk assessments so the results will be more meaningful to decision makers.

Mike Callahan concluded his presentation by noting that EPA is already performing cumulative risk assessments in certain situations and needs to continue to improve methods in the future. He reiterated that guidelines are four to six years away, but the *Framework* will help Agency risk assessors and programs in the near term to apply more consistent techniques in cumulative risk assessments. The *Framework* should be completed in early 2002 following peer review, perhaps by the SAB. Mike Callahan again stated that policy issues are being addressed on a separate track by the Science Policy Council, and will not be part of the final *Framework* document. He noted that case studies and issue papers will be developed following completion of the *Framework* as part of the guidelines development process, which will start in 2002. He thanked everyone for participating in the peer consultation and looked forward to hearing the experts' thoughts and ideas for improving the *Framework*.

### 2.4 Discussion on Opening Presentations

During the opening presentations by Bill Wood and Mike Callahan, several participants raised issues and asked questions about the draft *Framework*. Norris McDonald asked Bill Wood about the extent of industry involvement in the preparation of the draft *Framework* document. Bill Wood commented that this is an open process and comments from all sectors of the public would be welcome here at this meeting, by written comments in response to the Federal Register notice, or at future peer review meetings. Later, it was clarified that the current draft of the *Framework* document was developed by EPA scientists with some input from other Federal and State government scientists obtained through recent meetings. This peer consultation meeting provides the first opportunity for broader public input on the *Framework* document. Amy Kyle, at the end of Bill Wood's talk, encouraged EPA to write the *Framework* so that cumulative risk assessments can be as broad and inclusive as possible, because current risk assessments tend to

have a narrow focus. She hoped that the document could address this issue and advocate that assessments consider as many factors as possible. Douglas Crawford-Brown raised an issue about subpopulations and their vulnerability. He said that in addition to looking at stressors, another way of evaluating cumulative risks would be to consider the population and what makes it more vulnerable to risks.

Ken Bogen raised the issue about EPA's legal mandates and whether or not the *Framework* should reflect the role of cumulative risk assessment under particular legislation/regulatory programs. He questioned whether or not cumulative risk assessment would be applied in situations where an "increased risk" might result from a particular policy or new source. Mike Callahan answered that cumulative risk assessment is not constrained by EPA's mandates and that it is a tool that can be used to solve problems and answer questions that are much broader than those specifically addressed by legislation.

Following Mike Callahan's presentation, Ken Bogen commented on the importance of doing uncertainty analysis when doing cumulative risk assessments. He noted that aggregating upper bound risk estimates will result in answers that are overly conservative and not meaningful. Margo Schwab said that part of the problem with this discussion is the meaning of a quantitative assessment when the context of the decision being made is not known. It is important to know what problem is being addressed and what answer is needed before trying to evaluate uncertainty in a quantitative manner. She concluded by saying that it is important to define up front the issues of concern and the decisions that need to be made so that the analytical tools selected are appropriate. Once this is done, it would be appropriate to discuss the ability to evaluate risks in a qualitative manner, and the resulting uncertainties. Douglas Crawford-Brown added that this issue is not so much a question of the reliability of the risk estimates, but rather the adequacy of the safety margin. However the assessment is performed, it will be necessary to make some statement of the degree of margin of safety, and this is precluded if standard regulatory approaches to calculation of quantities such as hazard indices are combined. Ken Sexton

commented that more discussion on uncertainty was planned for the technical discussion session on the second day.

### 2.5 Introduction of Chair and Overview of Discussion Topics

Ken Sexton, from the University of Minnesota, was the chair for the peer consultation and served as facilitator. He started by introducing the three discussion categories for the two-day workshop. The goal of the peer consultation meeting was restated to emphasize that diverse, technical input was sought from each participant. 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 some ground rules and guides to keep the discussion focused on technical issues related to the draft *Framework* document. He talked about the post meeting activities to prepare a workshop report that summarizes the discussion and made the request that each participant prepare written comments after the meeting that will be appended to the workshop report.

# 3.0 DISCUSSION SESSION I - OVER-ARCHING ISSUES

Discussion on the draft *Framework* report started with over-arching issues. The experts were asked to consider the following topics:

- Comment on whether the draft *Framework* adequately captures, describes, and reasonably organizes the key issues for cumulative risk assessment.
- What additional issues, if any, should be covered?
- Comment on whether some of the topics presented in the draft *Framework* are too generic for the intended purpose.
- Comment on whether the draft *Framework* adequately conveys the state of the science with respect to cumulative risk assessment and the areas that are in need of further research and development.

Presented below are summaries of the main comments and suggestions as well as detailed dialogue from the over-arching issues discussion session. Presented first are the main points from the session (Section 3.1) followed by more detailed discussion (Section 3.2) which led up to the final suggestions.

## 3.1 Summary of Comments and Suggestions

Overall, many experts stated that the draft *Framework* represents a good start and it is expected to be a useful document that will help to promote consistency in cumulative risk assessment. Several individuals commended EPA for writing a concise document that maintains a broad perspective, and allows users flexibility in planning and implementing cumulative risk assessments. Some people thought that the document is too generic and needs to better present the essence of a "framework" and highlight the unique aspects of cumulative risk assessment, particularly tying in environmental health, vulnerability of populations, risk acceptability criteria and other topics. Several people felt that the lack of a coherent "framework" to the discussions

in the document limits its ability to serve as an organizing tool. As written, the draft document does not present a coherent way for the reader to understand the major issues, how they arise within the context of a cumulative risk assessment, and why they are important. As such, many individuals commented that the document needs editing/reorganization because the current draft is uneven and unbalanced, where some topics receive too much detail, while other issues deserve more information. For instance, several experts found Section 4 (Interpretation) to be more useful than Section 3 (Analysis), which was much longer. Revisions are needed to provide better balance and a clearer hierarchy of the information presented. One individual commented that the appendix on future research needs is very good, but that the document should introduce this issue earlier in the body of the report.

The document would benefit from additional examples and diagrams to illustrate the concepts and flow of information within the three steps: Planning and Problem Formulation, Analysis, and Interpretation. Particularly, adding a series of diagrams would help the reader to understand the relationships among the sections of the document that describe the three steps of cumulative risk assessment. Providing expanded diagrams for the problem formulation phase might also help to link disparate elements such as physical, chemical, biological, behavioral, and economic considerations. A proposed "framework" diagram was developed during the workshop (presented on page 3-6).

Comments were provided on the importance of up front scoping before any analysis begins. From this exercise, it might be clearer which elements can be analyzed quantitatively and which will have to be described in more qualitative terms. One suggestion was made to add a list of questions that might be asked within each step of the process to depict the types of decisions that need to be made within each step. Appendix F presents flow diagrams developed by Douglas Crawford-Brown as an example of key questions and decisions to be made within each step of the conceptual framework.

Other suggested changes to the document included providing a better representation of the scientific literature through citations of papers published in peer reviewed journals. Several individuals provided specific examples of papers that could be cited in the *Framework*. Also, some people felt that the document is redundant with previous reports. The *Framework* should provide a clearer perspective of the links between this document and previous documents cited, such as the EPA documents and the National Academy of Sciences/National Research Council (NAS/NRC) reports listed in the reference section of the draft *Framework*. Similarly, a comment was made that the *Framework* should acknowledge cumulative risk assessment activities in all parts of the Agency. One expert commented about the intended audience of the *Framework* and recommended that stakeholders participate in the process to finalize the *Framework*, which could help build trust in the development and implementation of cumulative risk assessments.

Changes such as these should help to bring better balance and a clearer presentation of the salient issues of cumulative risk assessment.

### 3.2 Detailed Discussion

Discussion on over-arching issues began with the chair, Ken Sexton, going around the room asking participants if they were comfortable with the plan to have each person make a short statement about their general comments on the draft *Framework* document, followed by more detailed discussion. After this initial discussion, each person provided a short summary of issues of concern, which led to more detailed discussion later in the session. Several individuals raised new issues to be added to the list of over-arching topics for discussion during the session.

Some of the early over-arching comments addressed concerns that the document did not present a clear picture of the overall framework for cumulative risk assessment and an integrated picture of the relationships among the individual steps. One participant voiced concerns about the extent of stakeholder involvement, both in the preparation of the *Framework* as well as later in the implementation of a cumulative risk assessment. As this discussion unfolded it became clearer

that stakeholder involvement (to be addressed in more detail under process issues) would be adequately addressed. Another participant voiced the concern that the document does not address immediate (acute) impacts from situations such as transportation accidents or chemical spills. He felt that the document would be more useful to the public if it explicitly addressed these types of circumstances where questions arise over siting of facilities and the need to evaluate the risks from those types of incidents.

Discussion on over-arching issues continued by having each participant provide an overview of their comments. Elizabeth Boa thought that the *Framework* is needed because of the many different approaches being used by different EPA offices. She encouraged EPA to make sure that the definition of cumulative risk assessment is consistent with other EPA programs and that the *Framework* addresses the variety of cumulative risk assessments that are being performed by the Agency, particularly those under FQPA. Jim Butler felt that the document should be as flexible as possible, however, he noted that there appeared to be inconsistencies in definitions/usage in different parts of the document. He suggested that the document be reviewed for consistency. Margo Schwab felt that there was an uneven level of detail in the document which posed a challenge in understanding how the various types of stressors (e.g., chemical, physical, political, etc.) would be integrated. She felt that the essence of cumulative risk assessment was not apparent and that the document should be more transparent with respect to the paradigm that is being used. She also noted that the *Framework* document should do a better job of integrating information from supporting documents (e.g., previous EPA reports as well as reports by the NAS/NRC).

Douglas Crawford-Brown proclaimed that the document is a good start at introducing very complex issues, but felt that "there is not a framework yet" that gives the reader a clear picture of the overall process of cumulative risk assessment. He also raised the issue that cumulative risk assessment needs to address margin of safety for multiple chemicals. Amy Kyle agreed with Elizabeth Boa's earlier comment that there seems to be a conflict between the FQPA definition of cumulative risk assessment and the one used in the draft *Framework* document. She

acknowledged the issue of scale and the need for a more global approach, such as that described in the draft *Framework* document.

Norris McDonald remarked that the document is concise and does a good job of introducing many of the science issues. He inquired about the target audience for the document and questioned whether policy issues can be separated from technical issues in practice. He also revisited and expanded on the issue of whether EPA is going beyond their statutory mandates. Ken Bogen thought that it might be useful for the document to list current legislative mandates and how and where cumulative risk assessment might be applied. Mike Callahan clarified that the *Framework* is for EPA staff, but acknowledged that people outside of EPA might use the document as a reference. He also noted that cumulative risk assessment is a tool and the *Framework* document is intended to provide information that can be used in a variety of scenarios, many of which are not explicitly part of the Agency's regulatory programs. Several participants noted that the *Framework* and cumulative risk assessment would be applicable for issues that might not traditionally be part of EPA's scope but which are increasingly the focus of attention for assessments, such as evaluating air pollution from traffic in local neighborhoods. Subsequent discussion took place on whether the *Framework* should be limited to issues that are explicitly addressed in EPA's legislative mandates, with two participants voicing the opinion that the document goes beyond EPA's authority.

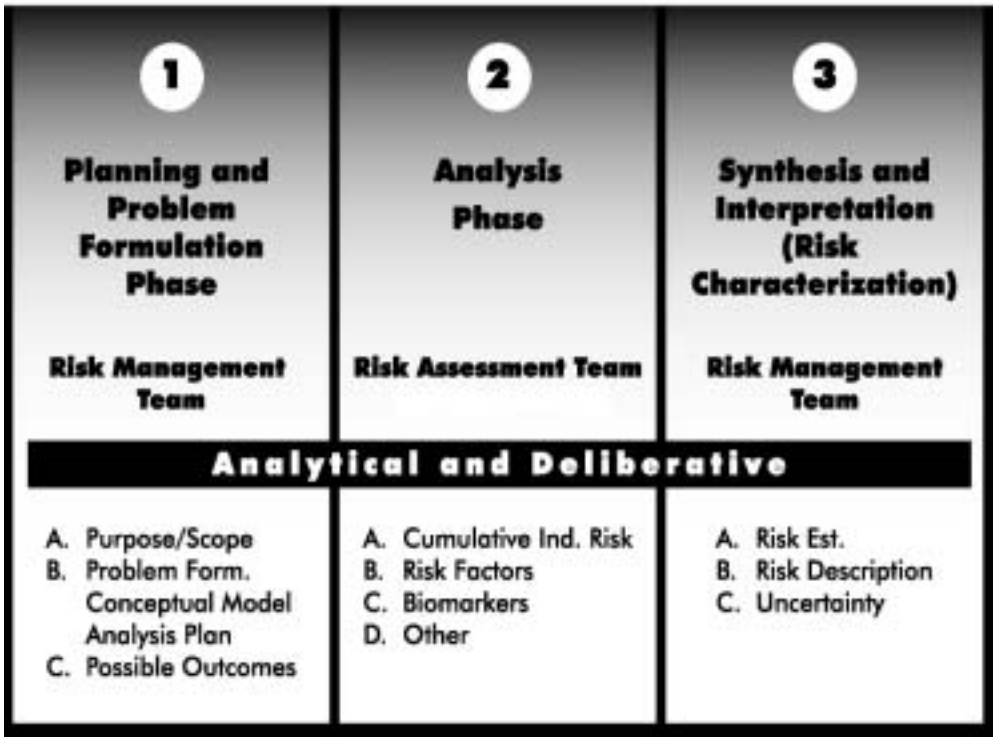
Steve Olin commented that the *Framework* is a useful and groundbreaking document, however, it needs more focus in some parts, while maintaining a broad, over-arching perspective. He also advocated adding diagrams to help illustrate the methodologies described. Jim Butler reiterated that the *Framework* is useful in providing a big picture, but commented that it may attempt to try to be too much to too many people. He contemplated that the document could be reworked to be a series of issue papers with multiple frameworks.

Discussion continued with Jennifer Sass revisiting the issue of separating policy from science when the overriding need for cumulative risk assessment is to make decisions using the best

available scientific information. Ken Bogen followed up by revisiting the earlier comments for the document to be clearer on when agency programs should/could do cumulative risk assessments. Several participants noted that this is a policy issue and beyond the scope of this meeting. Mike Callahan reiterated that the *Framework* is a technical document that describes cumulative risk assessment as a tool that is available to solve problems and answer questions. As such, it can be used at the discretion of Agency scientists in a variety of scenarios. He stated that the Science Policy Council is charged with addressing policy issues and noted that the RAF Technical Panel may be reluctant to include lists of legislative mandates that may limit the applicability of the *Framework* or make it become obsolete.

In the afternoon session, discussion on over-arching issues resumed with Ken Sexton illustrating the overall framework in a flow diagram (below). He proposed that this diagram captures the overall context and relationships among the steps of a cumulative risk assessment, the key participants in each step, the type of activity (analytical or deliberative), and the technical issues involved in each step.

Proposed "Framework" for Cumulative Risk Assessment (Sexton 8/22/01)



Margo Schwab voiced the opinion that the framework for cumulative risk assessment is a layer above Ken Sexton's diagram. She described cumulative risk assessment as the result of a function that incorporates such disparate issues as epidemiology/health statistics, chemicals, health access and many other factors. One aspect that distinguishes cumulative risk assessment from the traditional risk paradigm is the increased emphasis on the problem formulation step and the deliberative nature of conducting the assessment. Douglas Crawford-Brown commented that the framework illustrated by Ken Sexton was correct, but that it was not specific to cumulative risk assessment. Later in the meeting he distributed a flow diagram that he felt better captured the problem formulation - driven aspects of cumulative risk assessment (Appendix F).

Norris McDonald returned to the issue of target audience for the document and how stakeholders will perceive EPA's role in implementing cumulative risk assessments. Ken Sexton answered that it is difficult for the document to be targeted to anyone except EPA, but acknowledged that EPA documents such as these often become the de facto standard operating procedures used throughout the scientific community.

Ken Sexton asked again if the framework that he illustrated seemed to capture the essence of the cumulative risk assessment process. Several individuals provided comments that the diagram was helpful, but that it was still too generic and unclear how it was unique to cumulative risk assessment. Ken Sexton and Douglas Crawford-Brown also noted that none of the steps are purely analytical or deliberative, but that each step encompassed both aspects. Amy Kyle, citing the 1996 Reducing Risk Report, emphasized that analysis takes place in each step of the process and that an iterative approach should be used. Several individuals noted that issues such as uncertainty and vulnerability actually cut across all three phases and the document should reflect that these issues should not be limited to the interpretation phase. Margo Schwab again raised the issue of how cumulative risk assessment is different from the traditional four-step paradigm and contemplated whether the *Framework* tries to lay out a new approach that will be developed over the next ten years. Ken Bogen agreed that the *Framework* should be a launching pad for stimulating further developments in the science, but felt that the document does not accomplish

that goal. He thought that the document does describe ways to aggregate risks from multiple chemicals, but acknowledged that many issues related to accumulating risks were still undeveloped. Specifically, he pointed out that issues will arise related to distributions of individual risks and inequities that call for estimating risks using different approaches (such as using different potency factors) for different groups. He encouraged EPA to develop examples within the document that illustrate different scenarios, such as the kind that might be encountered with siting of facilities where one needs to consider different communities and issues of vulnerability, behavior and other inequities.

Attention turned back to Ken Sexton's diagram and whether or not it adequately captured the phases of a cumulative risk assessment. Beth Mileson revisited issues of definition and scope to question whether cumulative risk assessment is "total" risk, comparative risk, or integrative risk. She noted that it appears to be focused on "total" risk, but felt that the definition was not clear. Ken Sexton replied that when the glossary is added to the document, it might help to clarify some of the definitions and usage of terms throughout the document. Douglas Crawford-Brown added that the *Framework* is introducing a new process that is more open ended, deliberative, and inclusive. As a result, it is important that the *Framework* introduce the types of topics that can be addressed but it should not constrain the process. Mike Callahan clarified that the traditional methods of risk assessment are still useful for certain questions but that cumulative risk assessment brings a new perspective and methodology to answering new types of questions. The *Framework* document introduces some of these issues and the subsequent guideline development efforts will provide more specifics over the next few years.

Steve Olin commented that it would be helpful to include some hypothetical or actual examples to illustrate how the process might work. He also suggested that data deficiencies, variability, interactions, and the potential utility of PBPK modeling were issues that needed further discussion in the draft *Framework* document. Jim Butler again questioned the overall goal of the document and how far the *Framework* needs to go, recognizing that subsequent efforts will address some of these issues. Margo Schwab felt that cumulative risk assessment is a step

forward and a logical evolution from the traditional risk assessment paradigm. She reiterated that what distinguishes cumulative risk assessment is the problem formulation emphasis, which can hopefully incorporate epidemiology into such assessments. Jim Butler returned to the idea that the *Framework* document is intended to describe what cumulative risk assessment is, rather than how to conduct such an assessment.

Bill Rhyne posed a question about terminology and usage of the word "stressors," desiring clarification that it encompassed many factors beyond traditional chemical stressors, such as noise, physical, socioeconomic, and other threats. Ken Bogen added that the complexity of a cumulative risk assessment lies in the challenge to evaluate these different types of stressors, particularly with different susceptibilities and vulnerabilities of communities. Mike Callahan, in response to earlier comments about limiting the scope of the document to existing EPA mandates, provided a few examples on why the document needs to be as broad as possible. He noted that some air pollution issues of concern to communities may be outside of EPA's purview, but that a cumulative risk assessment will help to identify and quantify the magnitude of such problems so other types of actions can be taken. He added that stakeholders will use the information to address issues (e.g., zoning, siting, etc.) that are outside of EPA's authorities. Amy Kyle commented that it might help to think about the *Framework* as a model, where constructing it requires tying the pieces together. Douglas Crawford-Brown agreed and thought a diagram could be added to help to illustrate how the different pieces and steps relate to the questions posed. Ken Bogen noted that what is still missing is some type of risk acceptability criteria, looking at population risk and the number of cases, which he believes is the ultimate goal of cumulative risk assessment. Douglas Crawford-Brown offered that additive risk is addressed throughout the draft *Framework* but examples are needed on more complex types of risks. Ken Bogen encouraged the authors to look at the NRC report on combining risks.

# 4.0 DISCUSSION SESSION II - PROCESS ISSUES

Discussion on process issues focused on the following topics:

- Stakeholder Involvement Throughout the Process
- Using the Results of Cumulative Risk Assessment
- Cumulative Risk Assessment in the Broader Context of Environmental Analysis and Decision Making

Presented below are summaries of the main comments and suggestions as well as detailed dialogue from the process issues discussion session. Presented first are the main points from the session (Section 4.1) followed by more extended discussion (Section 4.2) which led up to the final suggestions.

## 4.1 Summary of Comments and Suggestions

Discussion on process issues focused on stakeholder issues, with some commentary on the use of cumulative risk assessment in decision making. Comments related to stakeholder involvement concentrated on (1) the level of stakeholder discussion in the document, (2) how to get stakeholders involved, and (3) the role of stakeholders in cumulative risk assessment.

### 4.1.1 Stakeholder Involvement

Comments on the document's stakeholder involvement discussion were generally positive with some suggestions on possible changes. Several participants thought that the narrative was too general and that other EPA documents referenced in the draft *Framework* present much of the same type of information on the process for (and benefits of) stakeholder involvement. Specifically, two references from the draft *Framework* document (USEPA 1999b and 2001b)

provide much of the background on stakeholder involvement and repetition in this document is not necessary. In the draft *Framework* document, the stakeholder discussion should be reduced to focus on those issues that are specific to cumulative risk assessment. Extensive comments were provided on how to promote stakeholder involvement in cumulative risk assessment projects, particularly with respect to providing a level playing field for communities and other groups that may not have technical resources available to them. Several individuals felt strongly that the document should call attention to this issue and provide guidance on how to address this situation. One specific comment on the document suggested that the list of stakeholders presented on page 17 be expanded to include "affected" industry. Some felt that this list was geared more toward community-based assessment and that it needed to acknowledge cumulative risk assessment being applied for more national issues.

With respect to the role of stakeholders, several members of the group suggested that the document provide a clearer picture of the potential role of stakeholders throughout all three phases. Stakeholders can be vital in the problem formulation phase (e.g., identifying sources and chemicals of interest), the analysis phase (in selecting the tools to be used in the assessment), and in interpreting the results. As such, the document should clarify that stakeholders may be involved in the risk management team throughout the life of an assessment, which may often require considerable time commitments. A few experts noted that while it is important to have participation from stakeholders, EPA should maintain final discretion on major decisions affecting the outcome of a cumulative risk assessment. Several individuals raised the issue of EPA developing trust with stakeholders, through up front planning and discussion of the expectations and possible outcomes from an assessment. Specifically, it is important at the beginning of a project to determine the possible end results, particularly with respect to the uncertainties and the required level of confidence in the conclusions. One participant stated that part of the front end planning should communicate if the assessment will produce a quantitative answer or if it is more likely that a ranking or comparative risk-type outcome is more feasible. With this comes the responsibility of all parties to acknowledge the difficulty in performing a cumulative risk assessment and the limitations of the results.

### 4.1.2 Use of Cumulative Risk Assessment in Decision Making

Discussion on the use of cumulative risk assessment in the larger context of decision making focused on adding narrative to the document on when to use cumulative risk assessment and how to maximize the utility of the assessment in the larger decision making process. Several individuals suggested that EPA expand the discussion to describe when cumulative risk assessment might be an appropriate tool to address a problem. Suggestions were made to present examples of the types of questions that cumulative risk assessment can and cannot answer. Furthermore, the *Framework* should also mention to the reader that a decision should be made up front to determine if cumulative risk assessment is even appropriate for the issue under consideration.

Several experts noted that this tool appears to be particularly applicable to permitting and siting issues where it can be used in a prospective manner to determine potential risks from new facilities or activities. Several individuals advocated that the *Framework* document provide clearer guidance to readers that such assessments can be most effective when done up front, possibly as a screening-level analysis, to improve decision making on proposed projects. Participants acknowledged that this type of application may be useful in determining the scope and magnitude of a problem, which can then trigger more detailed analysis that will assist decision makers in determining the potential risks from new facilities or sources. Similarly, several experts noted that because of the complexity of such assessments, it is important to keep the project manageable in size and scope. One participant added that the results of an assessment will likely be meaningless if the assessment is so complex such that no one can understand the process or results. One other point was made was to emphasize that risk estimates cannot be interpreted on an individual basis rather than, or in addition to, a population basis. This is particularly the case with epidemiological data. It is a critical misperception that risk assessment results apply to the individual. For instance, if the risk is 3/100,000 for children who have exposure X, for instance, we can only say that if 100,000 children have exposure X, we expect 3

of them to get sick. We cannot say that if a child's exposure is X then he has a 3% chance of getting sick.

### 4.2 Detailed Discussion

Ken Sexton opened the discussion by stating the importance of stakeholders in scoping the study and problem formulation phase. Bill Rhyne described two projects where stakeholder participation worked particularly well. Margo Schwab noted that stakeholders can be crucial in considering what stressors should be evaluated, which will help to ensure that the assessment will provide information on issues of interest to the stakeholders. Jim Butler added that the CCRI project had a very narrow focus (air toxics), which was decided early in the assessment because those were the issues of concern to the stakeholders. Bill Rhyne commented that one of the important roles of stakeholders is to obtain support for a project because they can reach out to other groups and bring them into the project. Steve Olin emphasized the importance of carefully identifying who the stakeholders are, noting that industry is an important stakeholder because they can provide data for use in an assessment. Also, he added that it is important to keep the stakeholders involved and engaged throughout the process, so they do not lose interest by the time the study ends and the results are produced. He also commented on the importance of agreeing up front on the issues to be addressed. Ken Bogen commented that cumulative risk assessment will be used in big decisions and that the *Framework* should emphasize that stakes are higher in cumulative risk assessment. He concluded by adding that stakeholders deserve access to resources to help them actively participate in the technical decisions that occur throughout an assessment.

Elizabeth Boa stated that several other EPA documents have addressed the issue of public participation and stakeholder involvement so the *Framework* does not need to address some of the basic issues related to this topic. In particular, EPA has a draft policy out for public comment that should be referenced here. Douglas Crawford-Brown noted that it may be important to set boundaries on the level of participation noting that cumulative risk assessments will often take

considerable time commitments and people often will not stay interested throughout the entire process. He noted that some groups will not participate at all because of a lack of trust in risk assessment and EPA in general. Similarly, it is important on the front end to define the decisions and structure for the interaction among stakeholders as part of setting ground rules. Norris McDonald added that many groups do not believe the results of risk assessments because they are often too complex. He voiced the opinion that communities will be more likely to embrace a process that focuses on a relatively limited number of parameters, particularly those closely linked to public health. Jim Butler stated that it is important for the public participation discussion in the document to be broad and flexible so that it can be tailored to site specific needs.

Douglas Crawford-Brown added that the issue of margin of safety needs to be addressed particularly because cumulative risk assessments are likely to address situations involving many types of stressors, including multiple facilities and multiple chemicals. This will naturally raise questions as to whether margins of safety are eroded by the presence of so many facilities and risk agents acting simultaneously on a community. Ken Bogen followed up on this comment by adding that it is important ro recognize how cumulative risk assessments will be used in decision making and the need for risk acceptability criteria. Ken Sexton stated that cumulative risk assessment is likely to require a dramatic increase in the time and resources that would be needed to do such an assessment, which should be discussed more in the *Framework* document. Mike Callahan acknowledged that cumulative risk assessments can be conducted at many levels, including as a screening tool, which can help to keep the scale of the study more manageable and reduce the level of effort. Douglas Crawford-Brown added that the document should also mention that the level of uncertainty may also be much greater than in a traditional risk assessment. Mike Callahan agreed that uncertainty is likely to be greater, however, decision makers need information and even uncertain information is an improvement over no information at all. Margo Schwab noted that both quantitative and qualitative analysis can be done and that up front planning will help to clarify which of the issues can be addressed quantitatively.

Douglas Crawford-Brown continued the discussion by noting that as stakeholders get involved in an assessment, basic decisions need to be made on what issues are to be addressed, whether risk assessment is the best tool for addressing the concerns, and the scope of the assessment. Norris McDonald added that this is a good opportunity to work with communities and some local groups might take the opportunity to lead projects. Jim Butler noted that the Chicago Cumulative Risk Initiative worked very well because one person was selected by the stakeholder organizations to represent all of the stakeholder groups involved in the project. He suggested that the document show examples of cases where stakeholder involvement has and has not worked.

Amy Kyle revisited the issue of a level playing field for stakeholders and acknowledged that this is a challenge. Ken Bogen stated that the idea of a level playing field is even more important in cumulative risk assessment because of the complexity involved. Stakeholder groups should have a "right to counsel" to help them participate throughout the process, otherwise their involvement will be meaningless. Amy Kyle added that the document should be explicit on what it might take to provide a level playing field for communities who may not have the same technical resources that other groups, such as industry, might have. Ken Sexton agreed with this discussion and added that the document should reflect that stakeholders have roles in all three steps of a cumulative risk assessment (the document currently only clearly reflects stakeholder involvement in the problem formulation phase). Douglas Crawford-Brown concurred, noting that stakeholders can be critical players throughout the process, for instance in selecting the models to be used in analysis. Beth Mileson agreed that stakeholder involvement can be influential in those types of decisions. Steve Olin also acknowledged the need to have better stakeholder involvement throughout all steps of the process. In the interpretation phase, all stakeholders can play a role in drawing conclusions from the analysis. He acknowledged that some community groups will know more about the local landscape which will be helpful in identifying stressors and sources during the problem formulation phase as well as in interpreting the significance of the results. Ken Sexton noted that it is often difficult to obtain community participation because of a lack of interest. He hoped that the situation would be different for cumulative risk

assessment because the stakes might be higher due to the nature of issues likely to be addressed. He encouraged EPA to review a document from Environmental Science and Technology, 1999, by Chess & Purcell, about what works and does not work with respect to community involvement.

Norris McDonald asked whether there is a difference between the target audience for the *Framework* document and stakeholders and wondered if states should be included as stakeholders. Ken Sexton mentioned that stakeholders include many types of groups and that the document discusses the importance of assembling a risk management team. He commented that the document might be expanded to address this issue. Steve Olin thought that the list on page 17 was a good starting point but that it should be expanded to include the "affected' industry. Jim Butler noted that the text states that EPA will decide if stakeholder involvement is necessary, which he felt was too vague with respect to how these types of decisions might be made. Beth Mileson added that there are so many different types of risk assessments and decisions to be made other than community-based studies that it is important to recognize other types of scenarios that call for national scale decisions. She added that she agreed with the sentiment expressed in the document that said basically "if you are not going to take the advice of stakeholders, don't invite them." Amy Kyle commented that she felt the document handled the stakeholder involvement situation quite well, particularly considering that each situation will call for specific needs.

Douglas Crawford-Brown, in response to Jim Butler's earlier comment, suggested that some text be added regarding EPA's discretionary power on when and when not to include stakeholders. Elizabeth Boa stated that it is hard to know in advance if an issue is significant enough to include stakeholders. Ken Bogen acknowledged this situation and suggested the possibility of performing a screening analysis first which might trigger the need for more study and prompting notification of the public so they can get involved. Douglas Crawford-Brown disputed this hypothesis because of the importance of the stakeholders' knowledge in the initial scoping and screening process, where significant sources or exposure routes could be missed without their

involvement. Norris McDonald stated that communities are often in front of the government in identifying problems and provided examples where local groups initiated efforts themselves. He acknowledged the difficulty in performing a cumulative risk assessment, but provided a warning that if it is "impossible to do it" then the results will not be useful or believed by the stakeholders. Margo Schwab followed up by emphasizing the importance of discussing the expected outcomes up front so it is clearer what the results will represent, particularly relative to the qualitative conclusions. This may also entail planning the type of analysis (e.g., ranking or comparison) as well as prioritizing attention on select stressors. Douglas Crawford-Brown added that this type of up-front planning goes along with EPA becoming more proactive in the process.

Beth Mileson commented that people have different ideas of what cumulative risk assessment is and what the questions to be answered should be. She also recognized the importance of focusing the assessment so it does not get overwhelming. Douglas Crawford-Brown emphasized the importance of the initial stakeholder phase and getting people to agree on the scope of a project so people do not back out at the end of the process because they do not like the results. Ken Sexton added that it may be helpful in the problem formulation phase to establish a time line on how long it may take to obtain results and to determine if that time line is consistent with the decision makers' needs. Ken Bogen thinks that the *Framework* document should point out responsibilities of parties such as state legislatures, which might play a role in setting boundaries for the assessment as well as the degree of stakeholder involvement. Douglas Crawford-Brown thought that this issue should not be addressed in the *Framework*, as it is a policy issue. Ken Sexton noted this as an area of disagreement where some people think that certain issues should be addressed in the *Framework*, while others think it is outside of the scope of this technical document.

Ken Bogen introduced the issue of when a cumulative risk assessment should be conducted. He recommended that the *Framework* advocate the use of cumulative risk assessment to identify problems before they occur. He stated that the tool is particularly useful for siting decisions, in permitting, and in other situations where risks should be evaluated before an action is taken that

may result in unacceptable risks. He lamented that too often such an assessment will be conducted after the fact when it is too late to remedy the situation. He encouraged EPA to revise the document to state that cumulative risk assessment will be most useful to decision makers if it is used as a planning tool at the beginning of the process. He emphasized that cumulative risk assessment can be particularly powerful if used in a proactive manner. Douglas Crawford-Brown acknowledged the importance of such use of cumulative risk assessment, but added that decisions on when to use cumulative risk assessment can be made by the scientific community, the policy community, and the stakeholders. Elizabeth Boa stated that it might be helpful to have language in the document on what situations might be appropriate for cumulative risk assessment to be used. Douglas Crawford-Brown suggested that alternate text could be added to the document to achieve this goal. He suggested that the document provide examples of the types of situations where cumulative risk assessment is particularly appropriate, such as addressing issues of multiple facilities and chemicals, as well as in the siting of new facilities. Ken Bogen agreed that the document should point out to the reader the types of uses and questions that can be answered by a cumulative risk assessment. He felt strongly that EPA has an obligation to use cumulative risk assessment in a manner that is most beneficial to society, which would be before decisions need to be made and actions are taken. Douglas Crawford-Brown noted that there are societal considerations that are beyond the scope of the *Framework* which are under the purview of society in general.

## 5.0 DISCUSSION SESSION III - TECHNICAL ISSUES

Ken Sexton identified the technical issues for discussion as follows:

- Approaches to Cumulative Risk Assessment
- Biomarkers of Exposure or Effect
- Uncertainty/Variability in Cumulative Risk Assessment
- Vulnerability
- Combining Chemical and Non-chemical Stressors
- Combining Different Types of Risk
- Limits on Information Provided by Cumulative Risk Assessment
- Distinguishing Between Cumulative Risks and Cumulative Impacts

Ken Sexton then asked the group if there were certain topics under the technical issue category that they felt should not be discussed or, conversely, if additional issues should be added. Margo Schwab recommended that "epidemiology" be added as a topic because she felt that epidemiological studies provide data on health impacts at the population level. She also said that it is important to make the distinction between individual health studies and population studies and that the *Framework* document is a good place to address the broad scope of epidemiological studies.

Several experts noted that the draft *Framework* document addresses quantitative risk but does not discuss qualitative risk to the same extent. For that reason, they recommended that the issue of "completeness" (including both qualitative and quantitative risk assessment) be added to the list of technical issues. Douglas Crawford-Brown stated that there are established methods for dealing with variability and uncertainty in risk assessment and wondered if these methods can be used in the same way for cumulative risk assessment. To address Douglas Crawford-Brown's comment, Ken Sexton recommended that "variability" be added to the "uncertainty" technical issue.

Following this brief discussion, the participants addressed the technical issues. The following section is organized by technical issue in the order they were discussed and includes the overall recommendations on how to address that particular issue in the *Framework* document.

## 5.1 Vulnerability

Ken Bogen stated that the *Framework* document should emphasize the importance of treating all endpoints consistently when possible with regard to vulnerability. There is a current disparity with carcinogenic and non-carcinogenic risks such that there is a means of addressing vulnerability for non-carcinogenic risks (e.g., modifying the uncertainty factor as 1, 10, 100, etc. to account for more vulnerable segments of the population) but there is no equivalent method to address vulnerability for carcinogenic risks. Ken Bogen stressed that analyses should be done as consistently as possible in cumulative risk assessment which would involve harmonization of carcinogenic and non-carcinogenic risks, possibly through the use of consistent uncertainty factors in cancer and non-cancer assessments.

Margo Schwab noted that another way to address this disparity would be to take out the information on the cancer/non-cancer dichotomy and say that the methodology is currently evolving toward having a similar, systematic approach for different endpoints. Beth Mileson commented on the complexity of the vulnerability issue and recommended that the *Framework* keep a placeholder for methodologies not yet developed so that information can easily be incorporated at a later time. Amy Kyle said that the document should address, when you are considering different types of endpoints, how you can summarize these effects. She agreed that harmonizing results should be a goal but does not think the document should endorse certain directions for harmonizing (i.e., should not try to combine chemicals' effects when they have different mechanisms of action).

Margo Schwab stated that the issue of vulnerability should come up sooner in the document and that it needs to be addressed as an overarching issue. Amy Kyle felt that the question of health

disparities as related to the issue of vulnerability needs to be addressed in the document. Norris McDonald wondered if there is enough information on environmental justice as related to vulnerability in the document. Finally, Steve Olin said that the synergy of vulnerability is missing in the current document and that it needs to be addressed when dealing with multiple stressors and vulnerability. Subsequent discussion addressed the importance of incorporating social sciences into cumulative risk assessments, particularly those that address complex non-chemical stressors.

### 5.2 Combining Chemical and Non-Chemical Stressors

There was general agreement that combining chemical and non-chemical stressors is problematic and the experts offered various suggestions as to how this issue could be addressed in the *Framework* document. Douglas Crawford-Brown said one way to address the issue would be to make the text in the document general enough so that it could apply to both chemical and non-chemical stressors (e.g. by reference to fraction of individuals with an effect, severity of effect, etc, all of which are concepts that apply to all effects regardless of cause). Ken Bogen noted that the document should say early on that it is not possible to quantify everything with current science and should not give the indication that you can. Jim Butler commented that because this is a *Framework* document it should have a broad scope and include all stressors and that it is alright that you don't know how to deal with all of them quantitatively. He added that even though the document is not focused on methodology, it might be helpful for the reader to have examples on how chemical and non-chemical stressors could be combined.

Margo Schwab indicated that one example of combining stressors would be to have a simple matrix (e.g., with toxicity high and low and exposure high and low, and then consider the high/low for other factors, like vulnerability (e.g., sensitivity of geographic areas – where one area has 95% health insurance coverage and another area has 50% health coverage). So even though you cannot discuss socioeconomic issues on the same level as chemical toxicity, you can still address it along with chemical stressors and consider it in decision making. Beth Mileson

noted that since all factors cannot be quantified to the same extent, another approach would be to consider comparative risk analysis. This would allow for the evaluation of different factors that cannot be easily combined. Amy Kyle added that it is important to try to identify all the different stressors and that even though it is problematic to compare apples and oranges there is some merit in doing it as long as you acknowledge the shortcomings. Ken Sexton noted that the draft *Framework* makes explicit the type of value judgments that may often be made and that value judgments are more important in these assessments than in traditional human health risk assessments (since multiple types of effects are being combined, and some judgment must be made as to their relative severity).

Steve Olin noted that the interactions that can occur from different types of stressors need to be considered in the *Framework* document. He gave the example of chemical exposure combined with radiation, and cited the McKone and Chen paper, as a good recent reference. Also, Ken Bogen said that the major stressors to be included in the evaluation need to be identified early on, otherwise anything could be included as a stressor at any point in the assessment and that would be problematic.

### 5.3 Combining Different Types of Risk

Some reviewers felt that the current discussion regarding combining different types of risk in the draft *Framework* document was adequate, while others thought that some changes and additional information were needed. Ken Sexton said he thought the document was appropriately ambivalent in this area, stating that combining different types of risk can be done many different ways without really advocating one particular method. Douglas Crawford-Brown was also generally comfortable with the section although he thought some text should be included which states that there are disparities in combining different types of risks, that it cannot always be done, and that failure to place all risks into a common metric does not make the assessment irrational.

Ken Bogen noted that the section left out one of the more obvious methods used to combine different types of risk. This method, used in the 1994 NRC report, is a systematic and probabilistic approach to endpoints that can be addressed in that way (for cancer, it is the occurrence of cancer, for non-cancer it is the occurrence of a particular effect). According to Ken Bogen, the risk becomes more straightforward when using the probabilistic approach, yet the document barely addresses this methodology. Jim Butler said that the section mentions GIS as a means to combine different types of risk in passing and thought that some additional text would be helpful, informing the reader that GIS can provide a visual way of developing a matrix (by allowing the viewer to overlay maps of different effects, and look for concordances).

Amy Kyle felt that the current section was not really fleshed out and that text should be added to show a way of representing risk from different types of measures. Margo Schwab added that this is an example of how epidemiology could be included in the analysis, particularly on background risks and exposures. Norris McDonald noted that cumulative risk assessment in general should focus on problem-solving when comparing different types of risk. Finally several reviewers agreed that the discussion regarding background exposure should probably be expanded in the document. They felt that the fact that cumulative risk assessment addresses background exposure is important since traditional risk assessments generally do not. Overall, people felt that the document can present the different approaches available, assess the strengths and weaknesses of each, and not recommend use of any particular one.

### 5.4 Uncertainty/Variability Issue

The experts offered several general suggestions for modifying this section. Steve Olin noted that the current discussion on uncertainty is somewhat generic and is not really specific to cumulative risk assessment. He added that text on this topic could be combined with a discussion of the importance of variability and how it should be considered in cumulative risk assessment. Ken Bogen felt that the document needs to emphasize the fact that meaningful quantitative estimates in cumulative risk assessment can only be generated if you adequately address uncertainty. The

fact that all inputs in cumulative risk assessment are likely to be typically upper-bound values underscores the need to track the level of uncertainty.

Douglas Crawford-Brown commented that people reading the document need to know why the emphasis on uncertainty analysis is important (e.g. that it is related to issues such as margin of safety). He also thought the document should say that some kinds of uncertainty analyses cannot be done quantitatively, but that this should not be an excuse to ignore them. Building on that point, Jim Butler said that the current section should be expanded to show that the limitations of the analysis include more than just statistical uncertainties. This broadens the concept of uncertainty from just quantitative uncertainty to actual confidence in the assessment. Margo Schwab said the uncertainty issue illustrates the need to determine up front what the scope and issues of the assessment are and let the reader know how certain you can be about the results and how much uncertainty will result. She added that this kind of discussion may be used to help frame the stressors to be evaluated.

In terms of specific comments, Amy Kyle said that she did not agree with the point on page 56 which states that information that is more certain should be weighted higher. She felt that it is wrong to evaluate different factors that way. Douglas Crawford-Brown noted that for the second set of bullets on page 57, the 3rd bullet on models should be combined with the second bullet. Also, Bill Rhyne recommended that an example be included in the section to show how uncertainty analysis can be helpful.

### 5.5 Approaches to Cumulative Risk Assessment

Several reviewers felt that changes were needed in this section. Douglas Crawford-Brown thought it was confusing to have the four approaches presented separately in the section, since you can use any combination (including all of them) in doing a cumulative risk assessment. Jim Butler said that the section should be expanded to include more approaches than the four currently listed, which seem to be limited to a chemical focus. He mentioned screening and

hazards analysis as examples for inclusion. The screening and hazard analysis approach involves not calculating risks but comparing ambient air concentrations (and other factors) and then using a weight-of-evidence approach and using geographic data. He concluded by encouraging EPA to consider options other than calculating risks that can give a sense of the hazards in a geographic area.

Amy Kyle commented that the section title, General Approaches to Cumulative Risk Assessment, is misleading because currently only a few random approaches are discussed. She suggested that instead of starting from the methods, it might be better to focus on how to address the scope of issues in the assessment (i.e., determine what can be evaluated quantitatively and qualitatively) and then discuss appropriate methods for these types of assessment. Douglas Crawford-Brown agreed with Amy Kyle's comment that the section appears to be a random collection of methods and sensed that too many things are jammed into this section that do not necessarily all go together.

### 5.6 Biomarkers

This part of the discussion focused more on the role of biomarkers in cumulative risk assessment rather than the specific text in the draft *Framework* document. Amy Kyle noted that biomarkers have particular value in cumulative risk assessment because they integrate exposures. Therefore, some consideration should be given as to what biomarkers could be used for. Douglas Crawford-Brown said that biomarkers can be used for ground-truthing the models' results (for models used in cumulative risk assessment) and to see how far the models are off. Margo Schwab agreed that biomarkers can give you an indication of ground-truth in cumulative risk assessment, in that it measures the total assault. She said that biomarkers will be useful, similar to other specific health indicators. You can also use other health indicators similar to the cumulative hazard approach for the Chicago study as another means to evaluate cumulative risk.

Ken Sexton noted that biomarkers have implications for biomonitoring and that the CDC is attempting to do a nationwide study using biomarkers. Jennifer Sass noted that such nationwide studies could benefit from collecting additional information. For example, she said that having information included on a person's death certificate regarding their occupation(s) and the duration of their occupation(s) could provide beneficial information. Margo Schwab made the point that even though we are collecting data that we don't know how to interpret now, we may be able to at some point, then we can go back and use the data for more analyses. She added that sometimes surveillance of certain health characteristics can be initiated based on the need for data, such as a health tracking study being conducted by the Pew Commission. Steve Olin concluded this discussion by noting that there are certain limitations to the use of biomarkers in cumulative risk assessment.

### 5.7 Distinguishing Between Cumulative Risks and Cumulative Impacts

Douglas Crawford-Brown said that 'risk' is the probability of the situation occurring, and 'impact' is the realization of the situation happening, but was not sure if that is what the authors of the document meant in developing their distinction. It also is not clear why the distinction was being drawn; i.e. what effect this would have on the conduct and interpretation of a cumulative risk assessment. He does not want the document to be over-quantitative, because sometimes you can deal with probability without the actual numbers. Ken Bogen felt that you should say what you can quantify up front to reduce the residual issues left over to deal with. Although Jim Butler thought that Ken Bogen's comment might apply in the long-term, he said that because the *Framework* is so broad, there is no way that you can quantify everything. He interpreted the section as you can have different approaches in cumulative risk assessment such as traditional (quantitative) risk assessment and more qualitative assessment such as NEPA.

Norris McDonald said he thought that the purpose of the *Framework* document and its limitations had been fairly well-defined on the last paragraph of page 58. He suggested that the text be brought forward earlier in the document so that the limitations of cumulative risk

assessment could be clearly understood. Ken Bogen agreed and thought the word 'chemicals' should be replaced with 'toxic agents.'

Beth Mileson questioned whether the document made an adequate distinction between cumulative risk and cumulative impacts. She felt that the document did sometimes, while at other times the distinction was blurred. Mike Callahan of EPA responded that the document is intentionally ambiguous so that it would increase applicability for the reader. Also, when the document says "adverse impact" it should not be interpreted as health concerns only. Amy Kyle said she thought it was good for the document to be intentionally ambiguous. Following Mike Callahan's explanation the participants agreed that it was not necessary to change the current terminology. At the close of the discussion, Ken Sexton reiterated the comments that the distinction between impact and risk is somewhat blurred in the document. He also questioned why cumulative impacts needed to be included in the discussion at all.

### 5.8 Epidemiology Studies

Margo Schwab said that there are two types of epidemiological studies; *analytical* (trying to establish cause and effect, usually involving clinical trials and cohort studies) and *descriptive* (surveillance of health statistics in an area, sometimes with individual information - the goal of these studies is to describe an area). She said that it is important to make a distinction between these two types of studies. Epidemiology studies serve as a surveillance indicator that can be used to assess past as well as present effects at the population level. As a result, these health indicators can determine the background level which can be pulled into the cumulative risk assessment and allow you to study the effect from the project(s) and site(s), of interest. Beth Mileson suggested that epidemiology studies can be used as a trigger to do a cumulative risk assessment. At the close of this discussion Ken Sexton noted that some reorganization of the epidemiology text is probably needed in the document.

## 5.9 Issue of Completeness (Quantitative/Qualitative)

This discussion was somewhat limited. There seemed to be agreement among the participants that qualitative assessment needs to have a similar level of discussion in the document as quantitative assessment. Douglas Crawford-Brown commented that the document should state that currently available methods will not necessarily drive the overall type of assessment to be done. The document should say up front how complete the analysis will be. He then noted that completeness of conception and rigor of execution are two separate concepts and they should be kept separate and given equal weight.

# 6.0 OBSERVER COMMENTS AND DISCUSSION

During the observer comment period on the first day, three people made short statements, Lowell Smith, Alec McBride, and Elizabeth Margosches.

Lowell Smith, from EPA/NCEA (but representing himself), voiced the opinion that the document should be as broad as possible. He explained that EPA's research roles extend beyond just those areas addressed in the legislative mandates (e.g., global warming) and felt that the *Framework* would be most useful to the scientific community if it provides a broad perspective on how one might approach such cumulative risk assessment. He also stated that the *Framework* needs to reflect the complexity of the types of issues that are likely to be encountered, ones that go beyond just chemical stressors and incorporate ecological, economic, cultural, and other factors that often must be considered in a decision. He provided examples of the complex issues that EPA's research program addresses and supported efforts to revise section 2 of the document to reflect the complexity of these issues.

Alec McBride, from EPA/OSWER, followed up on earlier discussion about the target audience for the *Framework* and noted again that the document is focused on EPA as the target audience, because EPA cannot require that people outside the Agency use it. He emphasized that the *Framework* will have impacts beyond just EPA because the scientific community is likely to use the document for technical information when planning and implementing cumulative risk assessments.

Elizabeth Margosches, from EPA/OPPT, suggested that possibly a modular approach could be used to reorganize the report, which might help with the unevenness in the presentation of information. Based on previous experience with risk assessment documents and guidelines, she suggested that some of the detailed discussion could be pulled out of the main body of the report and placed in appendices. This would make the *Framework* clearer to the reader.

On the second day of the meeting, brief observer comments were presented by Henry Schuver, Reggie Cheatham, Lowell Smith, and Elizabeth Margosches. Henry Schuver, from EPA's RCRA program, commented that for a risk model to be reasonable it must be calibrated with existing health effects data. Reggie Cheatham, from EPA's Office of Environmental Information, stated that it is important to recognize the role of stakeholder involvement in the analysis and interpretation phases. He noted that one aspect of this issue relates to determining how decisions to go forward with an assessment (or not to) can be influenced by stakeholder involvement. Lowell Smith felt that the stakeholder involvement discussion was good but suggested that the *Framework* include a recommendation that communities coordinate with EPA's Office of Environmental Justice during the cumulative risk assessment process. Elizabeth Margosches mentioned that areal data presentation is a strong analytical tool that can help to related disparate types of data. She mentioned the work of Lance Waller and other researchers who are using spatial data analysis tools including GIS for analysis of public health data and for making inferences from such data sets.

# APPENDIX A - LIST OF PARTICIPANTS

# Peer Consultation Workshop – Draft Framework for Cumulative Risk Assessment

## Panel Members

| Name | Affiliation |
|---|---|
| Ken Bogen | Lawrence Livermore National Laboratory (LLNL) |
| Elizabeth Boa | American Chemistry Council |
| Jim Butler | Argonne National Laboratory |
| Douglas Crawford-Brown | University of North Carolina, Department of Environmental Sciences and Engineering |
| Amy Kyle | University of California, Berkeley School of Public Health |
| Norris McDonald | Center for Environment, Commerce and Energy |
| Beth Mileson | Technology Sciences Group, Inc. |
| Stephen Olin | International Life Sciences Institute (ILSI) |
| Bill Rhyne | H&R Technical Associates, Inc. |
| Jennifer Sass | Natural Resources Defense Council (NRDC) |
| Margo Schwab | Johns Hopkins School of Public Health |
| Ken Sexton | University of Minnesota School of Public Health |

# APPENDIX B - LIST OF OBSERVERS

**Peer Consultation Workshop - Draft Framework for Cumulative Risk Assessment**

**Observers**

| Name | Affiliation | |
|---|---|---|
| Lucy Ament | Pesticide & Toxic Chemical News | (202) 887-6320/ lament@crcpress.com. |
| Jeanne Bailey | American Waterworks Association | (202) 628-8303/jbailey@awwa.org |
| Ed Bender | EPA -Office of Science Policy | (202) 564-6483 |
| Michael Callahan | EPA Region VI | (214) 665-2787 |
| Angelina Duggan | American Crop Protection Association | (202) 872-3885 |
| Steve Gibb | Risk Policy Report | (703) 416-8578/ Riskpolicy@yahoo.com |
| Loren Hall | EPA-Office of Civil Rights | (202) 564-7289 |
| Marty Halper | EPA -Office of Environmental Justice | (202) 564-2601 |
| Roger Hawks | BASF Corporation | (919) 547-2870/ hawksr@basf.com |
| Edward G. Jordan | BASF Corporation | (919) 547-2889/jordane@basf.com |
| Steve Knott | EPA-Risk Assessment Forum | (202) 564-3359 |
| Elizabeth H. Margosches | USEPA (7403M) | (202) 564-7636 |
| Alexander McBride | EPA, Office of Solid Waste | (703)-308-0466 |
| Pat Phibbs | BNA-Daily Environment Report | (202) 452-4106/pphibbs@bna.com |
| Alan Roberson | American Waterworks Association | (202) 628-8303/aroberso@awwa.org |
| Henry Schuver | USEPA-OSW-RCRA Corrective Action | (703) 308-8656/schuver.henry@epa.gov |
| Scott Schwenk | EPA-Risk Assessment Forum | (202) 564-6667 |
| Lowell Smith | EPA - NCEA | (202) 564-3389/smith.lowell@epa.gov |
| Henry Topper | EPA- Office of Pollution Prevention and Toxics | (202)-260-6750 |
| Cindy Gordon | American Petroleum Institute | (202) 682-8482/gordonc@api.org |
| Bill Wood | EPA-Risk Assessment Forum | (202)-564-3361 |
| WALK-INS | | |
| Terry Quill | Duane Morris | (202) 776-7894 |
| Martin F. Kovacs | Toxcel LLC | (703) 335-5670 |
| Margaret MacDonell | Argonne National Laboratory | (630) 252-3243 |
| Reggie Cheatham | USEPA | (202) 260-3085 |

# APPENDIX C - DISCUSSION TOPICS

# The Risk Assessment Forum
# Framework for Cumulative Risk Assessment

## Discussion Topics

August 22nd and 23rd, 2001
**Arlington, VA**



**Discussion Questions**

The following topics are provided to help guide the discussions during the peer consultation workshop. When considering these topics, keep in mind that the purpose of a framework is to identify key issues to inform a wide variety of interested and affected parties. Therefore a balance must be struck between adequately characterizing the issues and providing an excessive level of technical detail. The framework also discusses a process for gathering information and defining the problem with stakeholders. When considering the process topics, recognize that our goal is to focus the scope of the cumulative risk assessment on a parsimonious set of stressors, sources, pathways and potential adverse effects that are of interest to a particular place or community.

Overall, the RAF technical panel is seeking discussion and input on the questions and topics that follow. We are not setting policies for how to deal with the issues, but rather identifying principles and professional judgements which may lead to more specific guidance later.

Comment on whether the *Framework* adequately captures, describes, and reasonably organizes the key issues for cumulative risk assessment? Include in this discussion whether key terms have been identified and clearly defined.

What additional issues, if any, should be covered?

Keeping in mind that the *Framework* is intended to address issues that are specific or unique to cumulative risk assessment, comment on whether some of the topics presented in the draft *Framework* are too generic for the intended purpose?

The *Framework* attempts to identify where methods and data are currently lacking or are underdeveloped for application to cumulative risk assessment. Based on a suggestion during the meeting with other Federal scientists, research oriented issues have been highlighted in an appendix to the *Framework*. Comment on whether the *Framework* adequately conveys the state of the science with respect to cumulative risk assessment and the areas that are in need of further research and development.

To assist with this discussion, the following list includes a description of some of the key technical issues encountered by the Risk Assessment Forum Technical Panel during development of the draft *Framework for Cumulative Risk Assessment*. This is not a comprehensive list of cumulative risk assessment issues but could serve as a starting point for the review discussions. Where possible, the relevant sections of the *Framework* document have been referenced for each issue.

**Process Issues**

Stakeholder Involvement Throughout the Cumulative Risk Assessment Process [*Framework* Section 2; especially 2.1.3 and 2.3]

> Stakeholder involvement is recognized as an important aspect of cumulative risk assessment. The draft *Framework* highlights this involvement in the Planning and Problem Formulation Phase of the assessment. Examples of interested and affected parties are provided and the importance of defining roles and responsibilities is discussed. In addition, the importance of discussing the possible outcomes of the assessment with stakeholders is emphasized. What suggestions do you have for engaging stakeholders early? What kind of background or ground rules would be helpful? What roles and responsibilities would be most appropriate for communities and interested parties?

Using the Results of Cumulative Risk Assessment [*Framework* Section 4.5]

> The intended use of the cumulative risk assessment should be considered at each step of the process, from Planning and Problem Formulation through completion of the assessment. It is important to recognize that the cumulative risk assessment provides important information but is not the only contributor to the decision making process. How the cumulative risk assessment fits into the decision making process should be addressed when discussing possible outcomes with stakeholders during the planning phase. What kind of information could stakeholders contribute to cumulative risk assessments? Under what circumstances do you feel stakeholder participation is most effective?

Cumulative Risk Assessment in the Broader Context of Environmental Analysis and Decision Making [*Framework* Sections 1.4 and 1.5 and Section 4; especially 4.4.2 and 4.5]

An issue related to using the results of cumulative risk assessment is understanding how these assessments fit, both conceptually and practicably, into broader contexts. For example, cumulative risk assessment may be a component of assessing cumulative effects under the National Environmental Policy Act (NEPA). Further, these assessment may support Community-Based Environmental Protection efforts. What are the most appropriate situations for conducting cumulative risk assessments?

**Technical Issues**

Approaches to Cumulative Risk Assessment [*Framework* Section 3, especially introduction]

There are a number of ways to approach cumulative risk assessment, either starting with the NRC paradigm or using a different approach. Each approach may present its own challenges in methods, data, and analysis. Four example approaches are discussed in the draft *Framework for Cumulative Risk Assessment*: **combining toxicity before calculating risk**, **calculating risk factors**, **using biomarkers and biomonitoring**, and **calculating other types of probability statements**. Are important approaches missing from this list? Comment on whether there is a better way to organize this discussion on approaches to cumulative risk assessment.

Using Biomarkers of Exposure or Effect [*Framework* Section 3.1.3]

Among the approaches to cumulative risk assessment discussed in the draft *Framework*, use of biomarkers and biomonitoring information shows promise for providing an integrated measure of where an individual falls on the continuum between exposure and effect. However, existing methods are inadequate for assessing complex situations involving a large number of stressors. Further, experience using biomarkers and related information in decision-making is limited. Comment on the discussion of biomarkers of exposure and effects? Given the current state of the science, discuss the utility of this approach in the near term and in the future. Does the *Framework* include the appropriate level of discussion of this topic? How can the discussion be improved (consider, for example, whether the *Framework* discussion adequately characterizes how biomarkers can be used with more traditional risk estimates)?

Uncertainty in Cumulative Risk Assessments [*Framework* Section 4.3]

Uncertainty analysis is an important aspect of risk assessment (and policy analysis in general). However, historically, dealing with uncertainty has been a short-coming 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)?

Vulnerability [*Framework* Section 3.2.1.6]

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. 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?

Combining Chemical and non-Chemical Stressors [*Framework* Sections 3.2.1.5 and 3.2.2.5]

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?

Combining Different Types of Risk [*Framework* Section 4.1.3]

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 in this section capture the state of the science in the 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.

Limits on the Information Provided by Cumulative Risk Assessment [*Framework* Section 2.3]

There are many factors that place limits on what can be learned from a cumulative risk assessment. These include: how the problem is defined during the Planning and Problem Formulation phase, what data are available for the assessment, what models are available for the assessment, and what resources are available for the assessment (e.g., expertise, time, financial support, etc.). The adequacy of existing data may be a key factor limiting the results of a cumulative risk assessment. One outcome of the assessment may be the identification and prioritization of data gaps and research needs. This also applies to the availability of models for the assessment. Comment on the *Framework's* attempt to characterize the limits that may be encountered when using cumulative risk assessment in the decision making process. What can be added to improve this discussion?

Distinguishing between Cumulative Risk and Cumulative Impacts [*Framework* Sections 4.4 and 4.5]

The *Framework* attempts to clarify how cumulative risk assessment relates to community assessments and decisionmaking. In particular, the *Framework* emphasizes that cumulative risk assessment is only a portion of the information needed for decisions. Other factors such as employment and quality of life

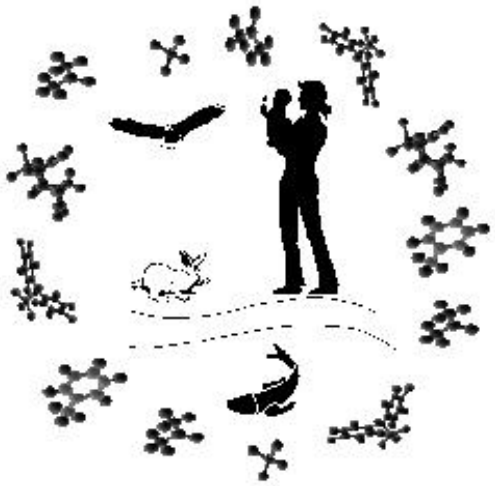
are considered for many decisions. When these other factors are brought into the assessment, the approach is often called cumulative impact assessment. Comment on how well the framework distinguishes between cumulative risks and cumulative impacts. Are the two concepts well characterized? How can the discussion be improved to clarify the role of cumulative risk assessment in the assessment of cumulative impacts?

# APPENDIX D - AGENDA

United States
Environmental Protection Agency
Risk Assessment Forum

# Peer Consultation Workshop on Technical Issues Associated with Developing a Framework for Cumulative Risk Assessment

Marriott Crystal Gateway Hotel
Arlington, VA
August 22-23, 2001



# Agenda

**Workshop Chair: Ken Sexton,**
**University of Minnesota**

## W E D N E S D A Y , A u g u s t 2 2 , 2 0 0 1

| | |
|---|---|
| 8:30AM | **Registration** |
| 9:00AM | **Welcome & Introductions** *David Bottimore, Versar, Inc.,* |
| 9:15AM | **Background** *Bill Wood, Risk Assessment Forum (RAF), U.S. Environmental Protection Agency (U.S. EPA),* |
| 9:30AM | **Presentation of the Draft Framework for Cumulative Risk Assessment** *Michael Callahan, Region VI, U.S. EPA,* |
| 10:00AM | B r e a k |
| 10:15AM | **Presentation of the Workshop Discussion Topics** *Ken Sexton, Workshop Chair* |
| 11:00AM | **Initial Discussion of Discussion Topics** |
| 12:00PM | L u n c h |

1:15PM **Discussion Session I - Over-arching Issues**

Comment on whether the *Framework* adequately captures, describes, and reasonably organizes the key issues for cumulative risk assessment.
What additional issues, if any, should be covered?
Comment on whether some of the topics presented in the draft *Framework* are too generic for the intended purpose.
Comment on whether the *Framework* adequately conveys the state of the science with respect to cumulative risk assessment and the areas that are in need of further research and development.

4:00PM **Observer Comments**

5:00PM W r a p - U p a n d A d j o u r n

## T H U R S D A Y , A u g u s t 2 3 , 2 0 0 1

| | |
|---|---|
| 8:30AM | **Discussion Session II - The Cumulative Risk Assessment Process**<br><br>Stakeholder Involvement Throughout the Process<br>Using the Results of Cumulative Risk Assessment<br>Cumulative Risk Assessment in the Broader Context of Environmental Analysis and Decision Making |
| 10:00AM | **Observer Comments** |
| 10:30AM | B r e a k |
| 11:00AM | **Discussion Session III - Technical Issues**<br><br>Approaches to Cumulative Risk Assessment<br>Using Biomarkers of Exposure or Effect<br>Uncertainty in Cumulative Risk Assessments<br>Vulnerability<br>Combining Chemical and Non-Chemical Stressors<br>Combining Different types of Risk<br>Limits on the Information Provided by Cumulative Risk Assessment<br>Distinguishing Between Cumulative Risks and Cumulative Impacts |
| 12:00PM | L u n c h |
| 1:00PM | **Discussion Session III - Continued** |
| 3:00PM | **Observer Comments** |
| 3:30PM | B r e a k |
| 3:45PM | **Wrap-Up and Next Steps** |
| 5:00PM | A d j o u r n |

# APPENDIX E - PRESENTER OVERHEADS

# Overheads From David Bottimore's Presentation

# Peer Consultation Workshop
# on the
# Draft Framework for Cumulative Risk Assessment

**August 22-23, 2001**



**David Bottimore**
**Versar, Inc.**

**Crystal Gateway Marriott**
**1700 Jefferson Davis Highway**
**Arlington, VA 22202**

# Overview of Peer Consultation Workshop

Review of Agenda

Introduction of Participants

EPA Presentations

Chair - Discussion Topics and Groundrules

Observer Comments

Post Meeting Activities – Workshop Report

# Overheads From Bill Wood's Presentation

# Risk Assessment Forum

# Framework for Cumulative Risk Assessment



William P. Wood
Executive Director
Risk Assessment Forum Staff

NCEA
National Center For Environmental Assessment

US EPA Office of Research and Development

# Risk Assessment Forum

## Risk Assessment Forum's Mission:

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

# Risk Assessment Forum

## Characteristics of Forum Projects:

- Selected because they present controversial or precedent setting scientific or science policy questions for the Agency
- Intended to guide the Agency as a whole rather than any specific program
- Designed to be regulation neutral
- Shaped and managed by the scientists in the Forum

# 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 – Phase I*



Science Policy Council (SPC)
– Guidance on Cumulative Risk Assessment.
Part 1. Planning and Scoping (July 1997)

SPC Requests that the Forum Begin Developing Cumulative Risk Assessment Guidance (FY'99)

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

# Risk Assessment Forum

## *Cumulative Risk Assessment Guidance Development – Phase I cont'd*



- Meetings with Federal and State Government Scientists (May 2001)
- Public Peer Consultation Workshop (August 2001)
- Science Advisory Board Review (Fall 2001)

***Goal:*** ***Complete the Framework for Cumulative Risk Assessment in FY'02.***

# Risk Assessment Forum

## *Cumulative Risk Assessment Guidance Development – Phase II*



- Identify/Develop Illustrative Cumulative Risk Assessment Case Studies
- Develop Technical Issue Papers on Selected Cumulative Risk Topics
- Develop Proposed Guidelines for Cumulative Risk Assessment (FY'04).

# Risk Assessment Forum

## *Cumulative Risk Assessment Technical Panel*

Michael Callahan, EPA Region VI, 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

## *The Framework*

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

1) should provide a flexible structure for cumulative risk assessment issues (capable of evolving with experience);

2) should define key terms, concepts, and basic principles to promote a common language on cumulative risk assessment;

# Risk Assessment Forum

## *The Framework cont'd*

3) will serve as a basis for the development of cumulative risk assessment guidelines;

4) will not provide substantive technical guidance.

# Overheads From Mike Callahan's Presentation

# Framework for Cumulative Risk Assessment

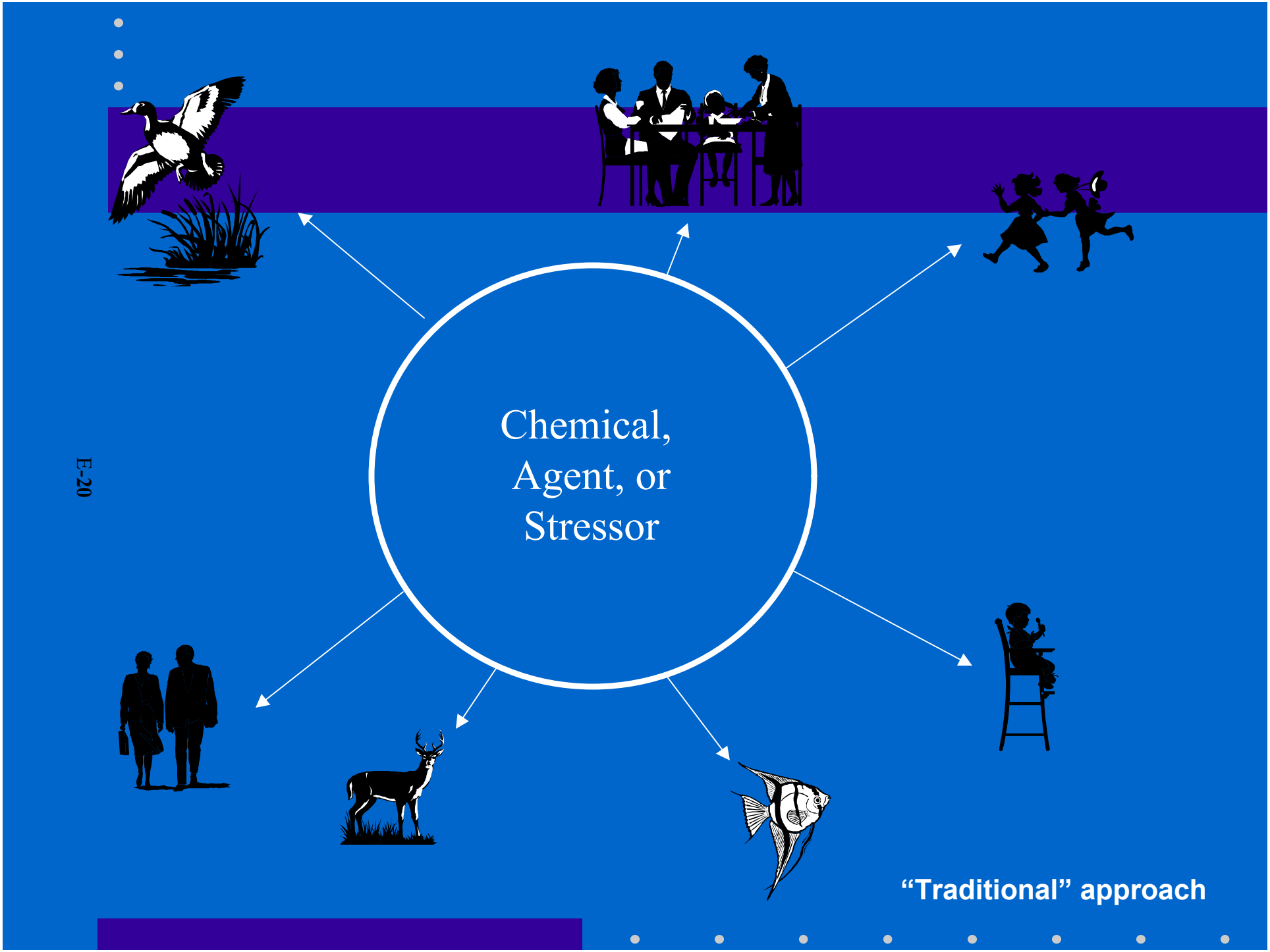


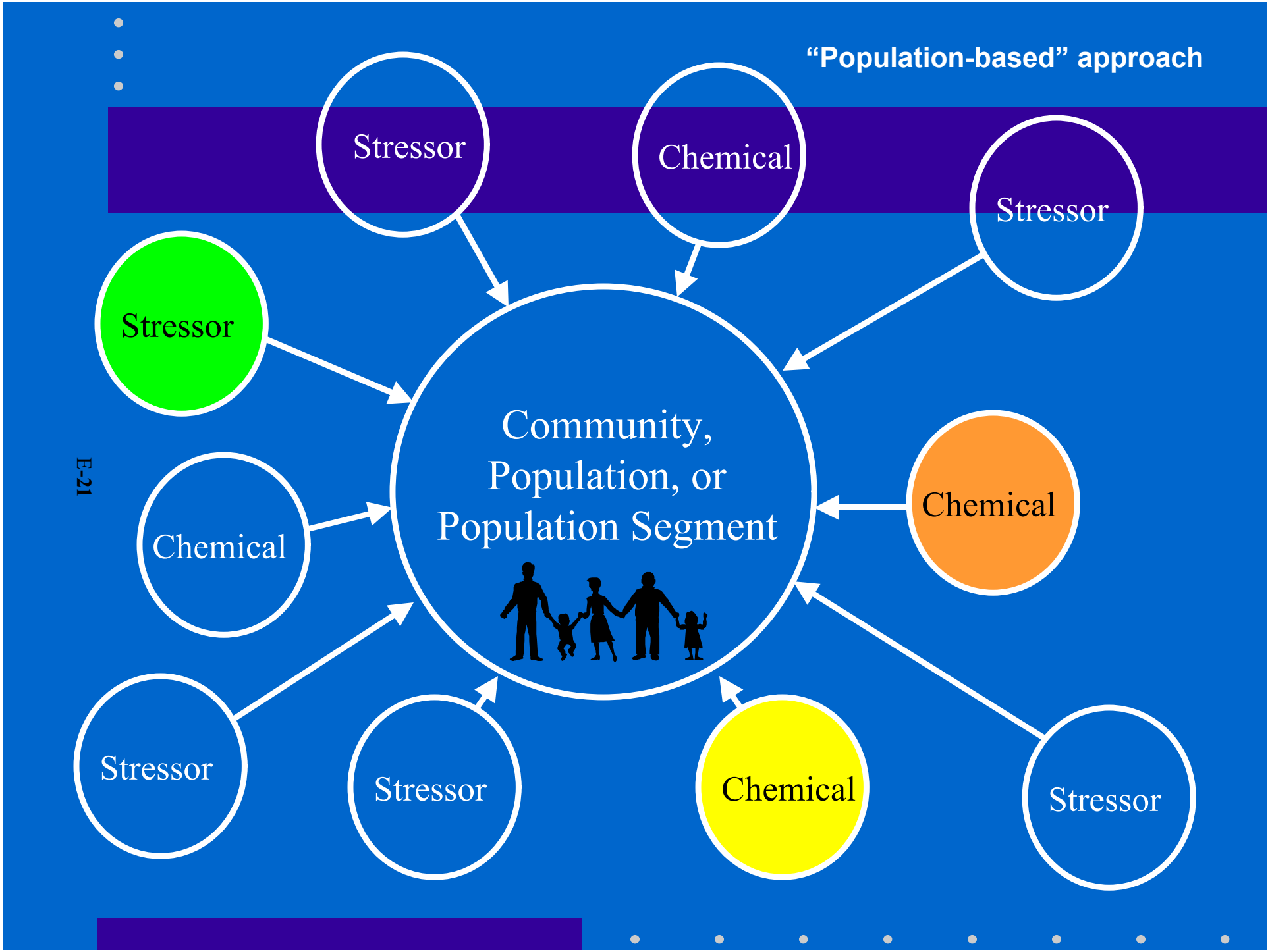
EPA Risk Assessment Forum
Technical Panel
on Cumulative Risk Assessment

# 1. Introduction

# Cumulative Risk Assessment

- "Traditional" Risk Assessment:
  - Where we've been
- Cumulative Risk Assessment (CRA):
  - Why change?
- Framework: What is CRA?
- Guidelines: How do we do CRA?
- What is today's meeting about?





# 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. (Several years away)

# Today's meeting

- Report current progress/status on the Framework for Cumulative Risk Assessment
- Report on **issues** we've encountered
- Listen to your thoughts on the subject

# Types of Issues

- Process issues: Extent of public participation, organization of Framework, etc.
- Technical/scientific issues: Feasibility of certain components, etc.
- Policy issues: Requirements, etc. (we will not discuss these today)

# 2. Issues

# Working Definition

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

# Goal of Cumulative RA

- 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.

# When do we do a CRA?

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

# Organization of Report

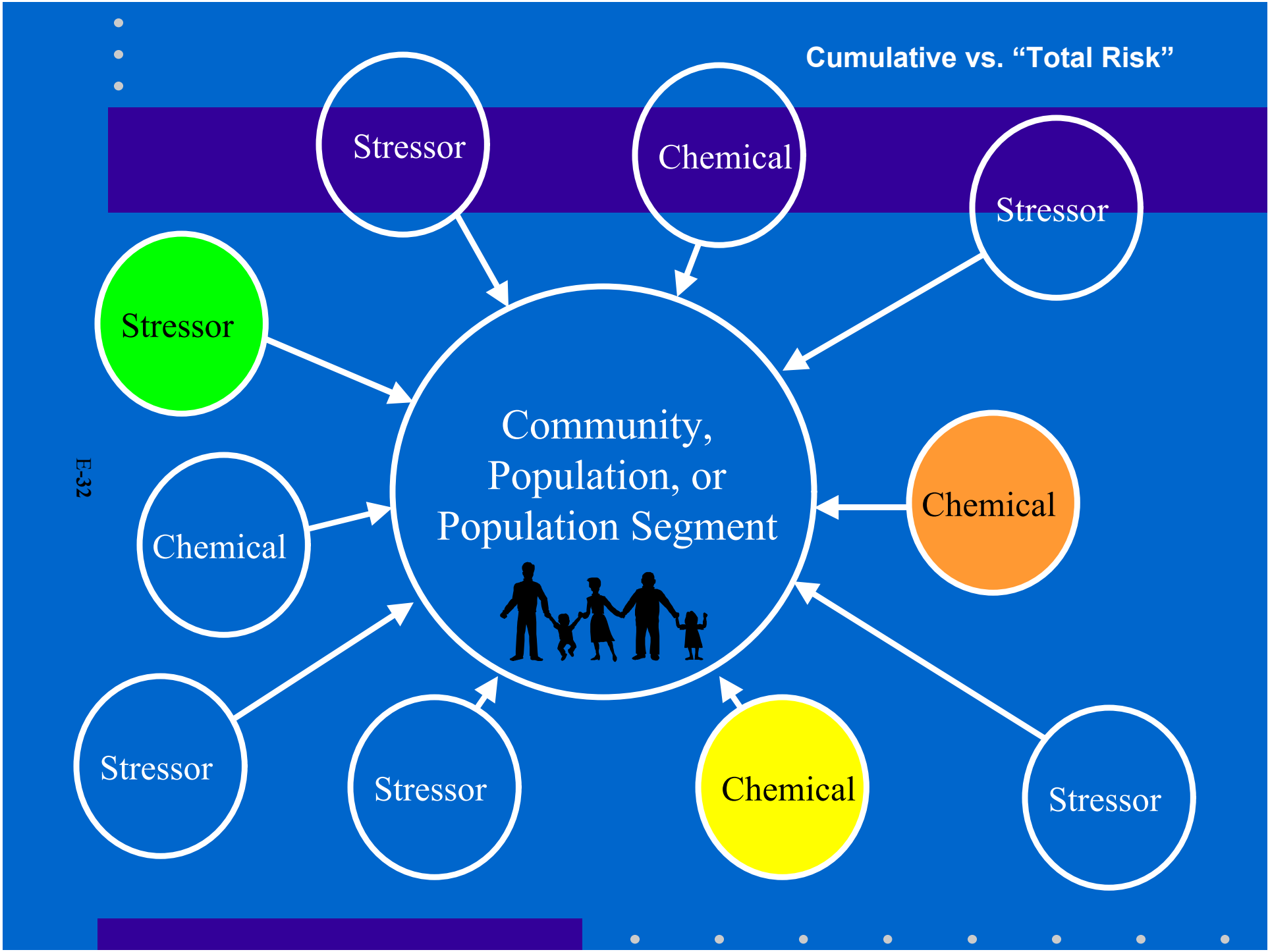
- Introduction
- Problem Formulation Phase
- Analysis Phase
- Interpretation Phase
- Glossary
- References

# Planning/Scoping, Problem Formulation

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

# Use of CRA

- How does CRA fit into the decision making process?
- How does CRA fit into broader context of various legislation, including NEPA?
- What can a CRA -- and what **can't** a CRA -- tell us?



# Stressors Acting Together

- Combination toxicology/Combining risk
- Risk factor approach
- Biomarkers or biomonitoring
- QALYs, DALYs, LLEs and other

# Combining different risks

- Can different types of risk be combined?
- Additivity vs. independence
- Interactions
- Common metric approach
- Index approach

# Vulnerability

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

- Question: How do these factors change risk?

# 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?

# 3. Summary

# Current Activity

- EPA is moving toward cumulative risk approaches in certain situations
- Methods are not completely developed, but some parts of cumulative risk assessment methodology exist now
- Guidelines are perhaps 4-6 years away

# Schedule

- Currently in technical discussion mode
- Finish SAB draft by October 1, 2001
- Peer review (incl. SAB) Fall, 2001
- Framework final early 2002
- Science Policy Council to address policy issues
- Case studies developed 2001-2002?
- Guidelines development *starts* 2002?

# Overheads From Ken Sexton's Presentation

# Peer Consultation Workshop on the Draft Framework for Cumulative Risk Assessment



**Ken Sexton - Chair**

# Chair's Opening Remarks

**Peer "Consultation" – Obtaining input on technical issues earlier in the process through a more informal dialogue with experts with diverse perspectives**

**Goals for Meeting – Provide input to EPA on technical issues related to the Framework**

**Discussion Topics – 3 sets (1) overarching issues, (2) process issues, and (3) technical issues**

**Ground Rules – process issues, do's and don'ts**

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

**Discussion Session I - Over-arching Issues**

- Comment on whether the *Framework* adequately captures, describes, and reasonably organizes the key issues for cumulative risk assessment.
- What additional issues, if any, should be covered?
- Comment on whether some of the topics presented in the draft *Framework* are too generic for the intended purpose.
- Comment on whether the *Framework* adequately conveys the state of the science with respect to cumulative risk assessment and the areas that are in need of further research and development.

**Discussion Session II - The Cumulative Risk Assessment Process**

- Stakeholder Involvement Throughout the Process
- Using the Results of Cumulative Risk Assessment
- Cumulative Risk Assessment in the Broader Context of Environmental Analysis and Decision Making

**Discussion Session III - Technical Issues**

- Approaches to Cumulative Risk Assessment
- Using Biomarkers of Exposure or Effect
- Uncertainty in Cumulative Risk Assessments
- Vulnerability
- Combining Chemical and Non-Chemical Stressors
- Combining Different types of Risk
- Limits on the Information Provided by Cumulative Risk Assessment
- Distinguishing Between Cumulative Risks and Cumulative Impacts

## Discussion Session I - Over-arching Issues

Comment on whether the *Framework* adequately captures, describes, and reasonably organizes the key issues for cumulative risk assessment? Include in this discussion whether key terms have been identified and clearly defined.

What additional issues, if any, should be covered?

Keeping in mind that the *Framework* is intended to address issues that are specific or unique to cumulative risk assessment, comment on whether some of the topics presented in the draft *Framework* are too generic for the intended purpose?

The *Framework* attempts to identify where methods and data are currently lacking or are underdeveloped for application to cumulative risk assessment. Based on a suggestion during the meeting with other Federal scientists, research oriented issues have been highlighted in an appendix to the *Framework*. Comment on whether the *Framework* adequately conveys the state of the science with respect to cumulative risk assessment and the areas that are in need of further research and development.

## Discussion Session II - The Cumulative Risk Assessment Process

- Stakeholder Involvement Throughout the Process
- Using the Results of Cumulative Risk Assessment
- Cumulative Risk Assessment in the Broader Context of Environmental Analysis and Decision Making

## Discussion Session II - The Cumulative Risk Assessment Process

Stakeholder Involvement Throughout the Cumulative Risk Assessment Process [*Framework* Section 2; especially 2.1.3 and 2.3]

Stakeholder involvement is recognized as an important aspect of cumulative risk assessment. The draft *Framework* highlights this involvement in the Planning and Problem Formulation Phase of the assessment. Examples of interested and affected parties are provided and the importance of defining roles and responsibilities is discussed. In addition, the importance of discussing the possible outcomes of the assessment with stakeholders is emphasized. **What suggestions do you have for engaging stakeholders early? What kind of background or ground rules would be helpful? What roles and responsibilities would be most appropriate for communities and interested parties?**

## Discussion Session II - The Cumulative Risk Assessment Process

Using the Results of Cumulative Risk Assessment [*Framework* Section 4.5]

The intended use of the cumulative risk assessment should be considered at each step of the process, from Planning and Problem Formulation through completion of the assessment. It is important to recognize that the cumulative risk assessment provides important information but is not the only contributor to the decision making process. **How the cumulative risk assessment fits into the decision making process should be addressed when discussing possible outcomes with stakeholders during the planning phase. What kind of information could stakeholders contribute to cumulative risk assessments? Under what circumstances do you feel stakeholder participation is most effective?**

## Discussion Session II - The Cumulative Risk Assessment Process

Cumulative Risk Assessment in the Broader Context of Environmental Analysis and Decision Making [*Framework* Sections 1.4 and 1.5 and Section 4; especially 4.4.2 and 4.5]

An issue related to using the results of cumulative risk assessment is understanding how these assessments fit, both conceptually and practicably, into broader contexts. For example, cumulative risk assessment may be a component of assessing cumulative effects under the National Environmental Policy Act (NEPA). Further, these assessment may support Community-Based Environmental Protection efforts. **What are the most appropriate situations for conducting cumulative risk assessments?**

## Discussion Session III - Technical Issues

- Approaches to Cumulative Risk Assessment
- Using Biomarkers of Exposure or Effect
- Uncertainty in Cumulative Risk Assessments
- Vulnerability
- Combining Chemical and Non-Chemical Stressors
- Combining Different types of Risk
- Limits on the Information Provided by Cumulative Risk Assessment
- Distinguishing Between Cumulative Risks and Cumulative Impacts

## Discussion Session III - Technical Issues

Approaches to Cumulative Risk Assessment [*Framework* Section 3, especially introduction]

There are a number of ways to approach cumulative risk assessment, either starting with the NRC paradigm or using a different approach. Each approach may present its own challenges in methods, data, and analysis. Four example approaches are discussed in the draft *Framework for Cumulative Risk Assessment*: combining toxicity before calculating risk, calculating risk factors, using biomarkers and biomonitoring, and calculating other types of probability statements. **Are important approaches missing from this list? Comment on whether there is a better way to organize this discussion on approaches to cumulative risk assessment.**

## Discussion Session III - Technical Issues

Using Biomarkers of Exposure or Effect [*Framework* Section 3.1.3]

Among the approaches to cumulative risk assessment discussed in the draft *Framework*, use of biomarkers and biomonitoring information shows promise for providing an integrated measure of where an individual falls on the continuum between exposure and effect. However, existing methods are inadequate for assessing complex situations involving a large number of stressors. Further, experience using biomarkers and related information in decision-making is limited. **Comment on the discussion of biomarkers of exposure and effects? Given the current state of the science, discuss the utility of this approach in the near term and in the future. Does the *Framework* include the appropriate level of discussion of this topic? How can the discussion be improved (consider, for example, whether the *Framework* discussion adequately characterizes how biomarkers can be used with more traditional risk estimates)?**

## Discussion Session III - Technical Issues

Uncertainty in Cumulative Risk Assessments [*Framework* Section 4.3]

Uncertainty analysis is an important aspect of risk assessment (and policy analysis in general). However, historically, dealing with uncertainty has been a short-coming 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)?**

## Discussion Session III - Technical Issues

Vulnerability [*Framework* Section 3.2.1.6]

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. **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?**

## Discussion Session III - Technical Issues

Combining Chemical and non-Chemical Stressors [*Framework* Sections 3.2.1.5 and 3.2.2.5]

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?**

## Discussion Session III - Technical Issues

Combining Different Types of Risk [*Framework* Section 4.1.3]

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 in this section capture the state of the science in the 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.**

## Discussion Session III - Technical Issues

Limits on the Information Provided by Cumulative Risk Assessment
[*Framework* Section 2.3]

There are many factors that place limits on what can be learned from a cumulative risk assessment. These include: how the problem is defined during the Planning and Problem Formulation phase, what data are available for the assessment, what models are available for the assessment, and what resources are available for the assessment (e.g., expertise, time, financial support, etc.). The adequacy of existing data may be a key factor limiting the results of a cumulative risk assessment. One outcome of the assessment may be the identification and prioritization of data gaps and research needs. This also applies to the availability of models for the assessment.
**Comment on the *Framework's* attempt to characterize the limits that may be encountered when using cumulative risk assessment in the decision making process. What can be added to improve this discussion?**

## Discussion Session III - Technical Issues

Distinguishing between Cumulative Risk and Cumulative Impacts
[*Framework* Sections 4.4 and 4.5]

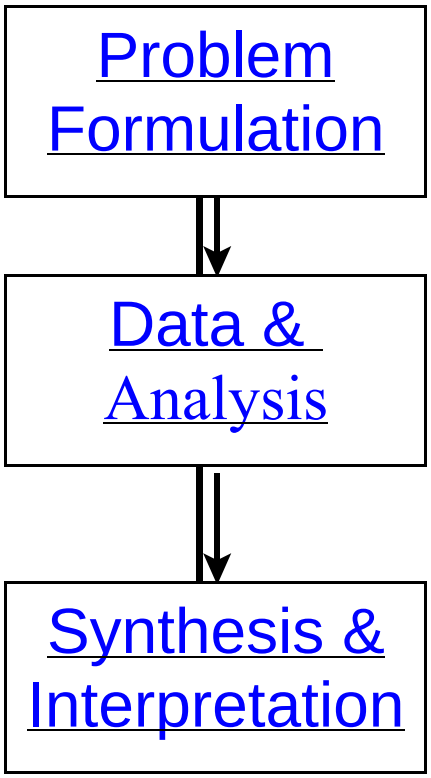
The *Framework* attempts to clarify how cumulative risk assessment relates to community assessments and decisionmaking. In particular, the *Framework* emphasizes that cumulative risk assessment is only a portion of the information needed for decisions. Other factors such as employment and quality of life are considered for many decisions. When these other factors are brought into the assessment, the approach is often called cumulative impact assessment. **Comment on how well the framework distinguishes between cumulative risks and cumulative impacts. Are the two concepts well characterized? How can the discussion be improved to clarify the role of cumulative risk assessment in the assessment of cumulative impacts?**

# APPENDIX F - FRAMEWORK CONCEPTUAL DIAGRAMS (FROM DOUGLAS CRAWFORD BROWN)

1. Historical Introduction: How did we get to this point of thinking about Cumulative Risk Assessment? What are the issues that drove the need for such a tool?

2. What is Cumulative Risk Assessment? What are some examples of its application? How does it differ from previous assessments in these examples? How does it address the limitations in traditional regulatory risk assessments that drove the issue?

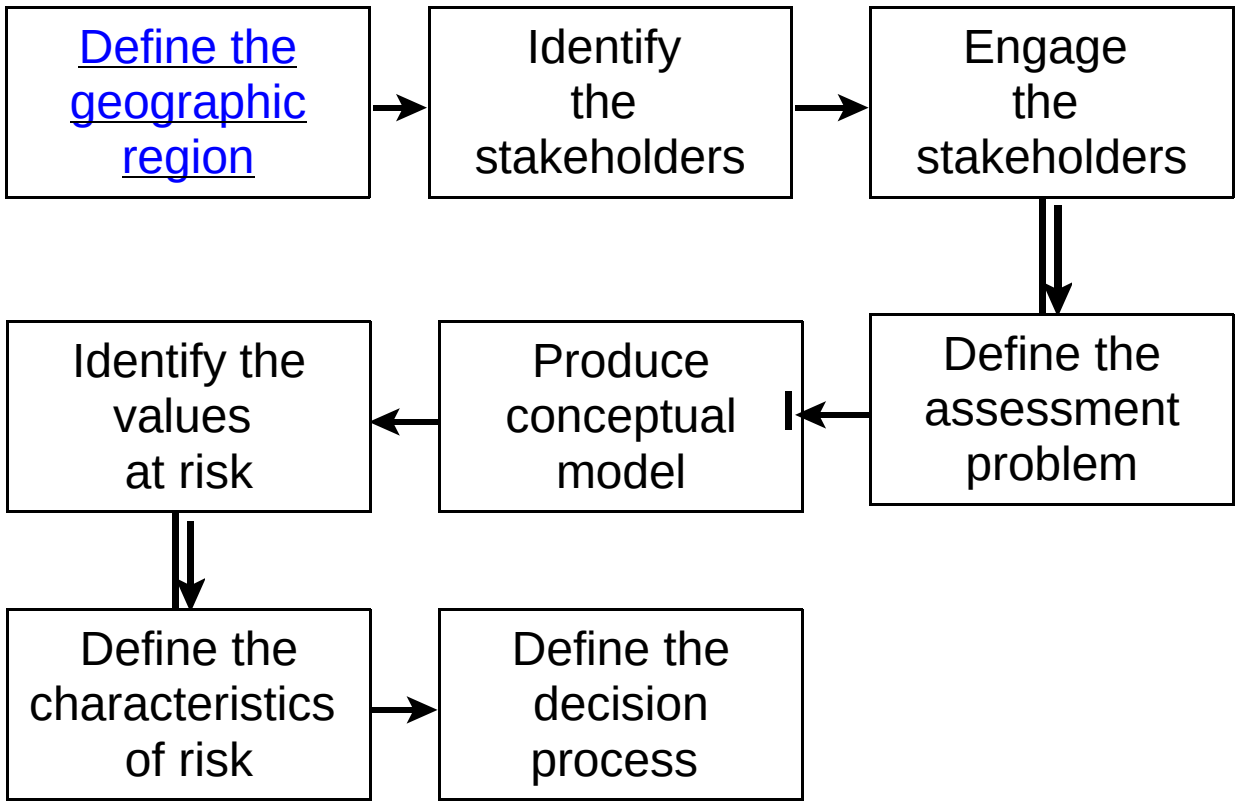
3. What are the steps of a Cumulative Risk Assessment? What is the *process* of discourse conducted in these steps? What is the *content* of discourse conducted in these steps? What are the *principles* that ensure the process and content are of the necessary quality?



# Problem Formulation

1. Purpose: *The goal of Problem Formulation is to state concisely and clearly the environmental situation under consideration, the values at risk from this situation, the parties to be included in the discourse, the categories of answers that must be generated, the risk characteristics to be included in these answers, and the role of these answers in decisions*.

2. The explicit steps of Problem Formulation are (the first step has a hyperlink to a representative second level of the framework):



# Define the geographic region

Purpose: *To be clear as to the geographic boundaries of the environmental situation and affected community, including all sources that might impact that community even if these are not contained in the boundaries where risks and impacts are being assessed*.

Questions to be addressed:

- *What are the criteria used to identify the geographic boundaries of a problem?*
- *Using these criteria, what are the boundaries for this community?*

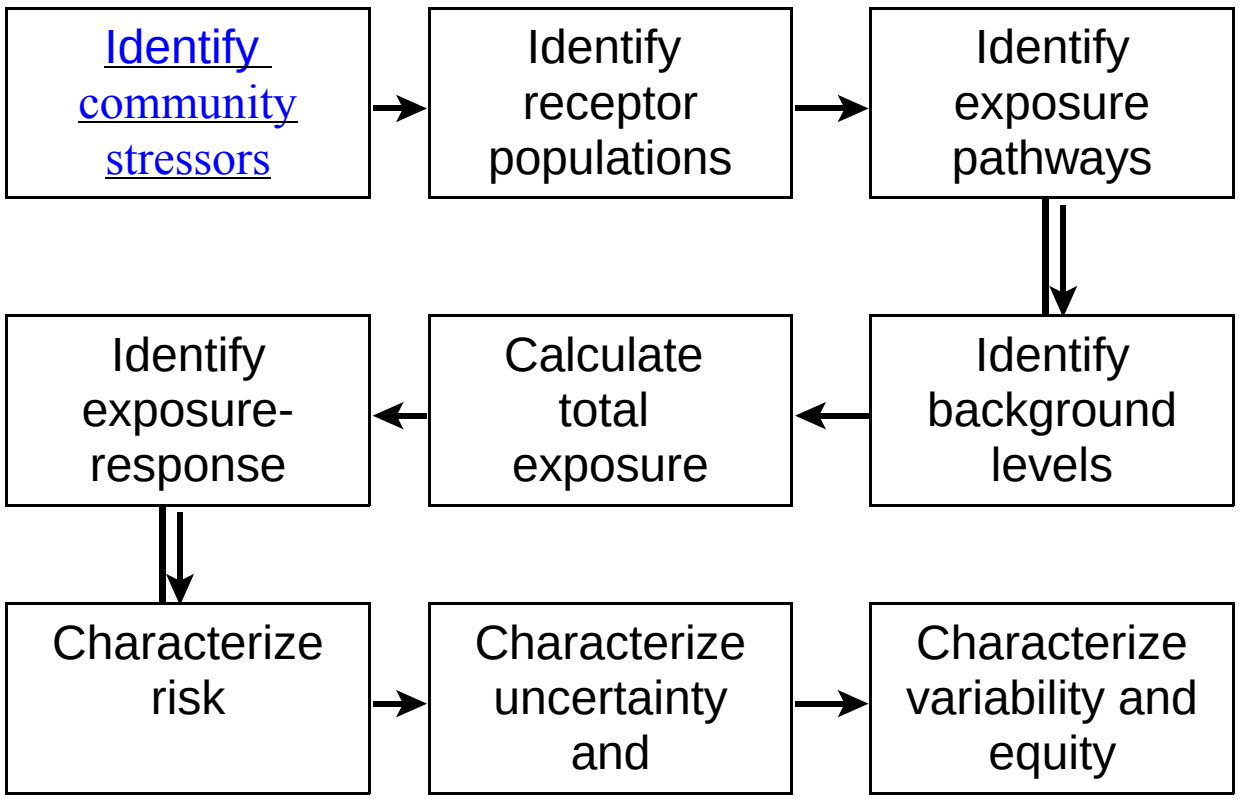
Example answers:

- *Within 50 km of the industrial complex.*
- *Orange County, NC and parts of Wake County, NC.*

# Data & Analysis

1. Purpose: *The goal of Data & Analysis is to assemble necessary data, assess the quality of those data, estimate exposures and risks to the population in the community, and summarize uncertainty and variability for these estimates*.

2. The explicit steps of Data & Analysis are (the first step has a hyperlink to a representative second level of the framework):



# Identify community stressors

Purpose: *Identify the kinds and sources of stressors in this community*.

Questions to be addressed:

- *What is meant by a stressor?*
- *Which stressors are relevant for this kind of assessment?*
- *Using these criteria, what are the relevant stressors for this community?*

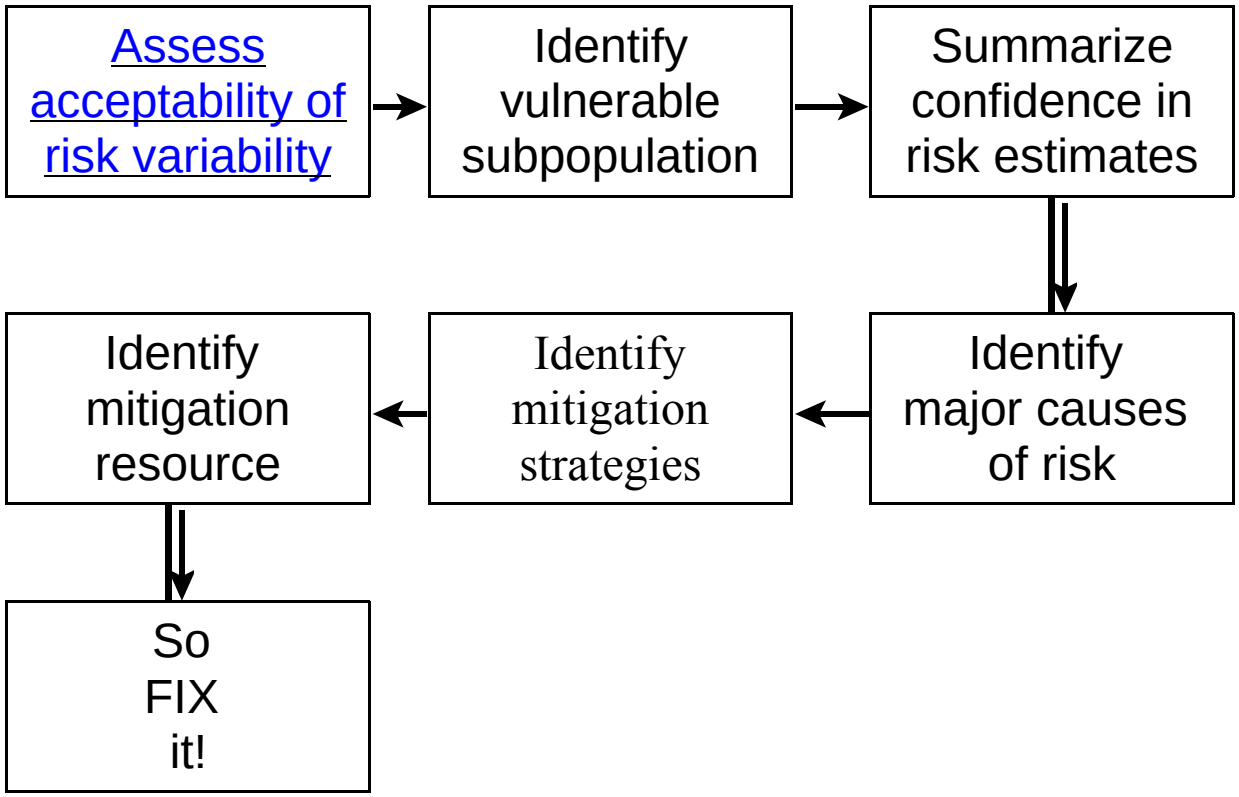
Example answers:

- *Stressors are physical, biological, chemical and social factors that increase the incidence of disease.*
- *All factors that increase the incidence of childhood leukemia.*
- *Viruses, benzene, radiation.*

# Synthesis & Interpretation

1. Purpose: *The goal of Synthesis & Interpretation is to summarize the results in ways that inform the original decision framework, are understandable to the stakeholders, and allow identification of both risks and their causes*.

2. The explicit steps of Synthesis & Interpretation are (the first step has a hyperlink to a representative second level of the framework):



Assess acceptability

Purpose: *To determine whether the variation in risk is acceptable in terms of the criteria of equity established in Problem Formulation*.

Questions to be addressed:

- *Is there an acceptable level of variability?*
- *Is the upper bound of risk acceptable?*

Example answers:

- *No, there is wide variation across the community.*
- *Yes, so while there is not equity, no individual rights are being violated.*

# APPENDIX G - POST-MEETING WRITTEN COMMENTS

**Post-Meeting Written Comments From Elizabeth Boa**

# The Risk Assessment Forum
# Draft Framework for Cumulative Risk Assessment
# Peer Consultation Comments of Elizabeth Boa

**Summary:**
I support the development of a cumulative risk assessment framework, as there is a need in to coordinate and direct the multiple, highly variable efforts within EPA. However this document is so general that I don't believe that inconsistency in conducting cumulative risk assessments can be avoided among and within program offices. It is unclear how the framework could be applied in any program. It appears to be a summary of several other EPA documents/sources and hits on concepts only superficially. There is very little science to underpin the broad cumulative risk assessment approach of multiple unrelated stressors and thus the framework is held together only by theory.

At a minimum, before the framework goes any further, e.g. to SAB review, it needs to add case studies that illustrate application of the suggested processes. It is through development and working through such case studies that the applicability of the procedures in the framework can be assessed.

Currently, different EPA program offices take different approaches to cumulative risk assessment. The variety of approaches that have proliferated, and the diverse terminology accompanying these approaches, leads to confusion among the regulated community and risk assessors about cumulative risk assessment.

The Framework needs to differentiate among these various approaches, especially as applied to risk assessments of chemicals, to prevent the misapplications of the terminology and the approach both by regulators and non-governmental organizations and other risk experts.

Cumulative risk assessments need to follow a clear, scientifically sound procedure to evaluate cumulative risks to be useful in policy making or regulating. I suggest that the Framework improve its organization by more clearly focusing on the two overall categories: approaches to cumulative risks with a chemical focus which may or may not be restricted to those with common mechanisms of action; and those including stressors beyond chemicals. My preliminary review found that there are four general approaches to cumulative risk assessments for chemical stressors and two overall approaches to cumulative risks of multiple stressors. Some approaches are very clear about the adverse endpoint or effect, naming a specific common endpoint, while other approaches are not. The cumulative risk assessment may consider a single common adverse effect or it may consider broadly defined effects such as human health or ecological effects or regional cancer risk. Each may be useful for different purposes such as screening to compare regional variations in stressors (as opposed to risks) or as a basis for regulating chemicals which cause a common adverse effect by a common mechanism.

As an illustration of the confusion around "cumulative risk," I have listed the many terms used to express the concept used within and outside the EPA:

Aggregation
Body burden
Comprehensive chemical exposure
Comprehensive risk
Cumulative effects
Cumulative environmental hazards
Cumulative hazard
Cumulative pollution
Holistic risk
Incremental impact
Integrated risk
Mixture
Multipathway exposure
Multiple chemical
Multiple exposures
Multiple risk
Overall regional risk
Risk "in context"
Synergistic effects
Total load
Total risk

As variations of cumulative risk assessment proliferate, it will become increasingly important to distinguish among the variations in meaning so analytical approaches can be distinguished. This is a role that the Framework can embrace. For example, the term "aggregate risk" has been used synonymously with the term "cumulative." However, as defined by the EPA Office of Pesticide Programs (OPP), aggregate is the term for single chemical, multiple pathway exposures causing a common effect. In the context of pesticide risk assessment at least, aggregate should not be used to describe risks from multiple chemicals.

The use of specific, precise terminology is needed to identify various approaches to risk assessment that are labeled "cumulative," so that a common lexicon for the various forms of "cumulative" risk assessments can be developed. "Cumulative risk assessment" also needs to be precisely defined especially as it applies to risk assessments of chemicals to help prevent the misapplications of the terminology and the approach both by regulators and non-governmental organizations.

> Comment on whether the *Framework* adequately captures, describes, and reasonably organizes the key issues for cumulative risk assessment?

I. The document can be improved. There is a need for a better differentiation between what has been considered cumulative risk as a regulatory term (FQPA) and this much broader presentation of cumulative risk. Chemical focused cumulative risk can be better described in this document and kept separate from the other broader "integrated" risk assessments this document also describes which include more risks than only chemicals.

II. This document is also written at different levels: some is very basic and some is highly technical. Needs to be written with a clear idea of the audience and target that audience. The target audience should be risk assessors and managers, so the document should be written at that level.

III. Considering the state of the science, the goal of this document would be better to identify the areas of research needed. Currently, attempting a cumulative risk assessment would involve a great deal of uncertainty.

IV. The document needs to focus on what we are trying to accomplish with a cumulative risk assessment: usually, this is lowering risks through regulations. This needs to be considered in the problem formulation stage when stressors are identified.

V. I agree with the working backward, population based approach generally, however, this has not been how cumulative risk assessments have been conducted under the FQPA. FQPA works "forward" from identified pesticides. How will this approach be integrated into the document? A preferable approach is to work backward from specific, identified health effects rather than from all stressors in a community to identify and evaluate the stressors that are actually a problem. Although identifying the cause(s) of a particular effect is not always possible, focusing on particular health effects and working backward is more economical and efficient than focusing on all community stressors indiscriminately.

Include in this discussion whether key terms have been identified and clearly defined.

I. Need new terminology to differentiate between the previously defined "regulatory cumulative risk" term (that is, the FQPA definition, which is highly specific and very technical) and the very much broader cumulative risk approach that is described here. To avoid confusion between the regulatory definition and the broader one, perhaps assigning the term "integrated risk" would be more accurate and less confusing. The use of specific, precise terminology is needed to identify various approaches to risk assessment that are labeled "cumulative," so that a common lexicon for the various forms of "cumulative" risk assessments can be developed.

What additional issues, if any, should be covered?

I. The document should focus on the assessments conducted or underway in EPA. There are assessments by Office of Pesticide Programs, the Office of Water, (disinfection byproducts), the National Air Toxics Assessment (NATA), which are chemical only and which may provide lessons learned and help define general principles for chemical cumulative risk assessment. Those that have been conducted on broader stressors have included ecological risk assessments which could be described here. Also, the framework should include examples of

community risk assessments: what have they shown in terms of the usefulness of their results, the techniques used, can they stand up to technical review in terms of methodology and results. Many of the community risk assessments used for environmental justice are aggregate exposure assessments as opposed to risk assessments. Examples of this type of assessment need to be described in the document, and compared with the approaches suggested in this document. Likewise, the framework should describe how multi-stressor ecological risk assessments are conducted and how this population based paradigm can be applied to human populations. This document does not include much on ecological cumulative risk assessment, and it is therefore unclear whether this framework is intended for human health risk only.

II. The Framework should be built from these experiences to develop principles for cumulative risk assessments, and describe lessons learned and best practices.
III. The document could be more useful to those doing cumulative risk assessment and facing issues such as model selection. The OPP is conducting a cumulative risk assessment on organophosphates (OPs); one of the biggest difficulties being encountered in this attempt is the identification of a dose-response model that is consistent with the data and the mode of action. The Framework could provide input to OPP and other offices facing the challenge of selecting models or data for cumulative risk assessments.

IV. The framework should also include information on how cost-benefit analysis can be included to determine alternative risk reduction strategies after risk characterization is completed.

V. The Framework needs to give more details on selecting dose versus response additivity when combining chemicals in a cumulative assessment. The framework advises selecting dose additivity as a default when for the most part response additivity is the more appropriate method. This issue is covered in the Mixtures guidance and comes up in the FQPA application of cumulative risk assessment..

> Keeping in mind that the *Framework* is intended to address issues that are specific or unique to cumulative risk assessment, comment on whether some of the topics presented in the draft *Framework* are too generic for the intended purpose?

I. The document could spend less time up front on the assessment process used for single chemicals and describe how the process applies to cumulative risk assessment specifically.

> Comment on whether the *Framework* adequately conveys the state of the science with respect to cumulative risk assessment and the areas that are in need of further research and development.

I. In places the document mentions that research and data are needed. However overall it does not capture that we don't have any experience with such assessments, that most data and methods are not available to conduct these. Any attempts to do so have been experimental and need thorough evaluation to determine how technically accurate and useful they are.

II. This document is somewhat inconsistent in describing the combination of stressors as opposed to risks, particularly when non-chemical stressors are part of the assessment, without considering the interaction of the stressors which is the key part of cumulative risk assessments. Part of the process of cumulative risk assessment is characterizing the risk posed by the stressors ACTING TOGETHER. The chemical and non-chemical stressors may not act together, they may be independent, or be additive, synergistic, or antagonistic. The framework needs to discuss how the interaction of the non-chemical stressors will be accounted for in the assessment.

To assist with this discussion, the following list includes a description of some of the key technical issues encountered by the Risk Assessment Forum Technical Panel during development of the draft *Framework for Cumulative Risk Assessment*. This is not a comprehensive list of cumulative risk assessment issues but could serve as a starting point for the review discussions. Where possible, the relevant sections of the *Framework* document have been referenced for each issue.

**Process Issues**

Stakeholder Involvement Throughout the Cumulative Risk Assessment Process [*Framework* Section 2; especially 2.1.3 and 2.3]

What suggestions do you have for engaging stakeholders early? What kind of background or ground rules would be helpful? What roles and responsibilities would be most appropriate for communities and interested parties?

I. Communities, interested parties, and stakeholders all have a role in providing input into cumulative risk assessments. As the Agency increasingly relies on science as the foundation of its decisions, the question of how best to make sure science is sufficiently represented in stakeholder processes has emerged as a vital issue. Recognizing this fact, EPA's Science Advisory Board (SAB) last year initiated an evaluation of how best to promote "a full and careful consideration of all available science" in stakeholder-based environmental decisions.

I strongly urge EPA to address in the Framework the need for assuring the use of scientific information, underscoring the fundamental place of science in EPA decision-making. As noted by the SAB in its Oct. 7, 1999, letter to then-Administrator Carol Browner, the concept of the general public interest "lies at the heart of many of our most cherished democratic institutions," and the Agency would best serve this interest when it carefully considers all available science as well as addressing stakeholder needs and interests. I second this SAB position. The Framework should clearly describe the importance of credible scientific information in Agency deliberations and provide the best guidance possible on how to ensure that such science plays an appropriate role in stakeholder involvement processes.

II. Addressing scientific uncertainty, and diligently working to reduce it through research and the use of all available data, must be a central component of Agency decision-making. Informing stakeholders as accurately as possible about what the Agency knows, does not know, and assumes in the face of limited data must be central to stakeholder involvement.

Using the Results of Cumulative Risk Assessment [*Framework* Section 4.5]
What kind of information could stakeholders contribute to cumulative risk assessments? Under what circumstances do you feel stakeholder participation is most effective?

The communities and interested parties would be valuable in highlighting concerns, values, behaviors as well as constructing a complete picture of risks to the community. The community could help identify holistically the major health or ecological effects they are facing.

Cumulative Risk Assessment in the Broader Context of Environmental Analysis and Decision Making [*Framework* Sections 1.4 and 1.5 and Section 4; especially 4.4.2 and 4.5]
What are the most appropriate situations for conducting cumulative risk assessments?

I. There are several situations: concern about exposure from a source (or sources) of multiple chemicals, a decision about where to site a facility, or concern about a specific health or ecological effect that may be caused by multiple stressors.

II. The various applications of cumulative risk assessment, which use various quality information should be used for different purposes: regulatory; screening for more research; risk ranking; or comparison among regional

risks. I agree with document (page 11) That it is very important to apply CRA in the context of the decision to be made or the problem to be solved.

III. The framework does not give guidance in the problem formulation stage for putting an analysis in context when it is required by law. For example, the OPP cumulative risk assessment is justified by the requirement of FQPA. It is not justified by identification of a particular problem being solved such as a health problem. The framework needs to give guidance to the Agency on providing a context or a reason for a cumulative risk assessment being conducted beyond a law or a regulatory requirement.

**Technical Issues**

Approaches to Cumulative Risk Assessment [*Framework* Section 3, especially introduction]

Are important approaches missing? Comment on whether there is a better way to organize this discussion on approaches to cumulative risk assessment.

I. Clearly delineate in the Framework the types of cumulative risk assessment that are used now in the agency for chemical risk assessments v. the community based risk assessments that are discussed in this document. These are different approaches with different outcomes and for different purposes. These approaches are very different in how they should be conducted and their ultimate outcome and purpose.

II. For chemical cumulative risk assessment, there are two categories that I see. A. For cumulative risk assessments of non-carcinogenic chemicals used in regulating or permitting, such as those conducted by EPA's pesticide office, it is appropriate only to link risks of chemicals that act by a common mechanism, with parallel dose-response curves, to cause a well-defined common adverse effect at a common site. This is to ensure that the regulation of chemicals acting by common mechanism will be aimed at reducing a particular risk and will not artificially reduce the risk cup by including inappropriate chemicals. The requirement of common mechanism is consistent with the EPA mixtures guidance recommendations for dose additivity. Combining multiple stressors by dose additivity needs an understanding of mechanism of action of each stressor and therefore the interaction among the stressors. For very few chemicals do we have this understanding. The document at 32 says that the prediction of how specific mixtures of toxicants will interact must be based on an understanding of the mechanisms of such interactions. This is true. The framework doesn't state that we usually don't have this knowledge. It is very complex. Under FQPA, the risk assessment is only looking at common mechanism causing common effect to assume dose additivity and yet it is a very complex determination of interaction.

B. For a "screening" cumulative risk assessment used for ranking purposes, chemicals can be grouped by common target organ, as a surrogate for common mechanism in the absence of data (that is, with mode/mechanism of action unknown). But such an assessment must assume the chemicals have parallel dose-response curves and cause a common adverse effect. The common mechanism requirement is waived in this case because that information is likely not known in a screen. A "screening level cumulative risk assessment" attempting to combine multiple risks should be only for the purpose of, for example, developing an understanding of the various regions and populations most at risk. Screening level assessments should be used only for prioritizing further data collection and research. For example, the EPA's National Air Toxics Assessment (NATA) draft report combines diverse risks rather than common adverse effects with a common mechanism of action.

III. The framework does not address chemical mixtures issues such as assumption of response additivity. It does not adequately address the fact that most chemicals do not interact but act independently, and cause different effects and/or operate through a different mechanism of action. That is where response additivity should be used not dose additivity. Examples of how independence would be handled should be included. The Framework needs to indicate that response additivity should also be used when assessing the cumulative risk of chemical exposures below individual chemical's NOAEL unless there is evidence that identical metabolic pathways detoxify the chemicals.

IV. At page 34, the document says that toxicants may interact by causing different effects at different receptor sites. I don't understand: What is the basis for that statement? Based on that information, there is no basis to assume an interaction. That implies independence of action. That provides no basis for "adding" these risks together. See III. above.

V. The Framework does not give guidance on choosing an index chemical and supporting that choice or for selecting among available dose response data sets. This guidance could help the OPP with its OP cumulative risk assessment; in that case an index chemical was chosen based on a good data base for that chemical but without supporting documentation as to why other chemicals were not chosen as the index chemical. The Framework could also help OPP with selecting the dose-response data set. Their OP cumulative risk assessment uses surrogate dose-response data for the index chemical and the other chemicals, rather than the best available data.

VI. P. 45: I don't understand the statement that using the Relative Potency Factor can be applied to all toxic endpoints for the chemical group being assessed when the similarity is justified on mechanistic grounds. Is similarity based on the mechanism of action? Or the SAR? If there is an understanding of a mechanism of action for one endpoint it doesn't mean that the same group of chemicals will

all work with the same mechanism of action for all endpoints. This needs to be determined for each endpoint.

VII. Multi-stressor assessments for ecological risk consider that an array of factors of chemical, physical, or biological origin may be active, either concurrently or sequentially, in the deterioration of natural ecosystems (Foran and Ferenc 1999). Ecological risk is not addressed to any extent in this document.

Using Biomarkers of Exposure or Effect [*Framework* Section 3.1.3]

Among the approaches to cumulative risk assessment discussed in the draft *Framework*, use of biomarkers and biomonitoring information shows promise for providing an integrated measure of where an individual falls on the continuum between exposure and effect.

This can only be done if there is a lot more information on mechanism of action of the chemical and how other stressors are affecting that mechanism.

However, existing methods are inadequate for assessing complex situations involving a large number of stressors

OR even a single chemical.

Comment on the discussion of biomarkers of exposure and effects?

This document needs to discuss the limitations of what realistic use biomarkers are at this point, and distinguish between biomarkers of "exposure" and biomarkers of "effects." Exposure will not necessarily lead to effects. Additionally, biomarkers of effects do not indicate the cause of the effects.

Given the current state of the science, discuss the utility of this approach in the near term and in the future. Does the *Framework* include the appropriate level of discussion of this topic? How can the discussion be improved (consider, for example, whether the *Framework* discussion adequately characterizes how biomarkers can be used with more traditional risk estimates)?

The Framework should give more guidance on when available biomonitoring data should be used rather than exposure modeling or as a reality check for monitoring. The OPP cumulative risk assessment of OPs relies on complex exposure modeling although biomonitoring data are available. The Framework should address when real data should be used over model outputs.

Uncertainty in Cumulative Risk Assessments [*Framework* Section 4.3]

Cumulative risk assessments present new challenges for uncertainty analysis.

In cumulative risk assessment, there is a great deal more uncertainty introduced, more than has been dealt with in single chemical assessments. It strikes me that there is uncertainty to a level never seen before. It is imperative to quantify these uncertainties so we know how close the result is to actual risk. Uncertainty AND variability need to be dealt with in the beginning of the risk assessment process and throughout.

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.

The Framework should clarify that these "soft" assumptions will introduce a great deal of uncertainty the more they do not rely on science.

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. The Framework should discuss in the risk characterization section that a range of risk (best case, worst case, average case numbers) should be included to give people an idea of uncertainty.

II. The risk characterization needs to acknowledge the data gaps and the severe limitations these result in by using defaults. Where there is no information, this fact has be carried through on the risk characterization for the decision-maker.

III. The document should also include that uncertainty models used should include "average" and "least conservative" assumptions.

Vulnerability [*Framework* Section 3.2.1.6]

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. 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?

I. Definitions issue: susceptibility and sensitivity traditionally encompass all the other aspects that are now labeled "vulnerability." Change "sensitivity and susceptibility" to "biological differences."

Combining Chemical and non-Chemical Stressors [*Framework* Sections 3.2.1.5 and 3.2.2.5]

Combining Different Types of Risk [*Framework* Section 4.1.3]

Comment on the *Framework's* discussion concerning the combining of disparate measures of risk. Do the example approaches discussed in this section capture the state of the science in the 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. I am not sure whether different stressors, which act independently, can even be added up or what it would mean even if they were. This is very different from cumulative risk of chemicals. This type of assessment is not truly assessing "cumulative" risks from a toxicological standpoint and is more appropriately labeled "number of hazards from multiple stressors." I think a comparative risk approach would be more useful than a combination approach. Isn't it more important to figure out the risk drivers than the total risk in a meaningless numerical score?

II. The addition of diverse hazards provides limited information beyond comparison, for example, of variations among number of regional hazards. The Framework should include that the assessor needs to consider what such a combination of diverse risks would mean scientifically -- and articulate a justification for assuming additivity of diverse risks -- and from a policy standpoint.

III. For assessments of cumulative risks to human health, combining multiple, unrelated chemical and non-chemical hazards, the hazards need to be assigned weights in terms of probability of risk and in terms of the relative adverse effect.

IV. The Framework needs to address how it will deal with combining in a ranking system data that are high quality with data that are highly uncertain.

V. It is not clear how the Framework would suggest the Agency integrate what may be incommensurables e.g. cancer and non-cancer effects, health and eco effects, extrapolated risks based on animal studies and actual risks based on epidemiology.

VI. Caveats need to be made with regard to the estimated hazard numbers, indicating that adding diverse hazards provides a number that has limited descriptive capabilities or meaning and gives a possibly misleading picture of the magnitude of risks to which populations are exposed. Without a clear understanding of the purpose for acquiring the information from the cumulative assessment, this information can easily be taken out of context.

Limits on the Information Provided by Cumulative Risk Assessment [*Framework* Section 2.3]

Comment on the *Framework's* attempt to characterize the limits that may be encountered when using cumulative risk assessment in the decision making process. What can be added to improve this discussion?

I. We should try to identify the data gaps and quantify how big they are. The framework should include information on what models are out there and their availability.

II. One thing that could be addressed is that cost benefit analysis should be instituted as part of the cumulative assessment.

# Post-Meeting Written Comments From Ken Bogen

Ken Bogen

# Comments of K.T. Bogen on the

# USEPA Review Draft
# *Framework for Cumulative Risk Assessment*



Comments below are organized with reference to section number of the USEPA Review Draft Framework for Cumulative Risk Assessment (NCEA-F-1098; 2001).

## General: Specific aims of the Framework are not clear

CRA is now fairly established as an acronym for Comparative Risk Assessment. Also, technical aspects of how to aggregate risks have been addressed in detail in several EPA guidelines as well as in the NRC 1994 report, Science and Judgment in Risk Assessment, that already are cited in the Framework, which apparently is neither intended to add to nor comment substantively upon these existing risk-cumulation methods. Consequently, it may be argued that the proposed "cumulative" risk assessment Framework is nothing but a generic description of risk assessment that is properly executed to consider all relevant risks associated with one or more risk sources of concern. That is, the only new problem being addressed by the word "cumulative" in the Framework appears (but is nowhere clearly stated) to be simply how best to define a set of risk sources that are (or could?, or should?) be considered relevant to a specific public-policy decision. SIN this context, some careful thought might be given to an alternative name for the Framework. The use of the word "Assessment" (rather than, say, "Analysis and Characterization") suggests a framework intended to address risk management issues that appear to be beyond the intended scope of the present Framework, because it currently presents no background or information concerning the array of different methods often used to make decisions involving uncertain risks, costs and benefits. Thus, it appears that the intended, and more restricted, focus is a framework for Cumulative Risk Analysis and Characterization (CRAC) or Risk Assessment for Multiple Endpoints and Sources (RAMES). A Framework for RAMES might be denoted "FRAMES". Nevertheless, "CRA" is used below to denote Cumulative Risk Assessment.

## Section 1. Introduction

As noted above, this section needs to define the nature and purpose of the Framework more clearly, particularly in relation to previous/parallel EPA documents such as the SAB report, *Toward Integrated Environmental Decision-Making* (EPA-SAB-EC-00-011; 2000). The latter report gives examples of regulatory mandates that require integrated environmental decisionmaking. The Framework for Cumulative Risk Assessment likewise should list and discuss how at least an illustrative set of regulatory and nonregulatory EPA mandates currently and/or potentially could require and/or benefit from CRA.

This section should spell out specific issues that are newly being addressed in the proposed Framework, and explain—and illustrate using a few simple, diagrammed examples—how these new issues differ from problems addressed by previous documents. Using these illustrative examples,

this section should state clearly (in generic terms, if necessary) some examples of why and/or under what circumstances current applications of existing approaches might be considered deficient, and thus why a new framework is needed. To the extent that existing approaches might be considered deficient, why is this so? Do such deficiencies arise from overly narrow statutory mandates, overly narrow regulatory implementation of existing statutory mandates, inappropriate/inconsistent implementation of mandated regulatory goals, or lack of appropriate procedures and a suitable/consistent methodology for undertaking CRA? For example, if the application of current RfD methods to set MCLs fails to consider background doses in exposed subpopulations, then this indicates that those methods were simply defective methods to implement appropriate regulatory toxicology, not that a whole new framework is needed. Is the new framework intended to facilitate new regulatory and/or scientific goals that involve aggregate risk, or rather to improving the achievement of previous goals that were not met because aggregate risks were not considered appropriately?

The text in current Section 4.5, para. 3 line 1 (p. 60, 2nd line from bottom) should also appear in Section 1, as a specific example of a CRA application and CRA goals.

A key potential application of CRA is for long-term/anticipatory planning, e.g., with regard to siting new sources of pollution in specific areas. Implications of using this method should be discussed. E.g., use of CRA implies that, where not already in place (give examples), new procedures need to be developed for planning for and implementing source-specific caps on the siting of new sources in regions identified through CRA to be approaching or at a maximum level of acceptable environmental health stress.

This section should end with a brief (1-paragraph) introduction to, and a corresponding schematic diagram summarizing the elements/steps that comprise, the proposed framework. Consideration might be given to renaming section 1 to refer to a substantive topic, e.g., "1. The Need for a Cumulative Risk Framework".

## Section 2. Planning and Problem Formulation

On page 16 (sec. 2.1.2, line 6), the draft now states that "The issue of background exposures should be discussed and agreements reached (see Appendix E)." This statement is very problematic, insofar as the "issue" of background risks might reasonably be considered to be a technical issue driving the "correct" prediction of source-induced risk, particularly for noncancer (e.g., threshold) endpoints, and as such ought not be subject to political interpretation/agreement. If I am currently environmentally exposed to X mg/kg-d of a toxic agent (e.g., mercury), if the accepted ADI for the agent is A mg/kg-d, and if the focus of a CRA is whether or not to accept a new source that imposes a new exposure to me of Y mg/kg-d, a relevant CRA issue must be whether or not $X + Y < A$ (or to what extent $X + Y < A$, considering uncertainties involved), and not whether $Y < A$, regardless of how participants in any CRA scoping discussion may feel about this. Accordingly, this section, and Appendix E, need to be developed with more rigor. The framework needs to discuss in generic terms how background levels of various factors like those listed in Figure 3 (conceptual model shown on page 21) might influence the different endpoints identified in the conceptual model, and how these expectations may therefore logically relate to technical requirements of CRA methods. The diagram

of this conceptual model should reflect feedback loops not currently diagrammed (e.g., loss of property value, aesthetics, etc., tend to negatively affect the socioeconomic system, which in turn tends to increase rates of crime, traffic accidents, and communicable-pathogen transmission).

In discussing the scope of conceptual models that can be considered in CRA, some expression should be given to the concept that the more overly broad the CRA scope is, the more difficult it will be to implement systematic and consistent CRA methods, and so the more difficult it will be to interpret and apply CRA output to help resolve a policy question. Conversely, CRAs with more narrowly defined scope of problems may more easily contribute substantively to public policy decisionmaking. There is text on p. 23 (section 2.3, 1st para., last 2 lines) that refers to the extent to which CRA-team "members accept" CRA conclusions. This text unrealistically implies that those members generally will and/or should themselves be free to define the scope of CRA. The Framework should point out that statutory mandates, corresponding regulations, and legal interests (e.g., property rights or other due process rights) may constrain and/or define most if not all risk acceptability criteria applicable to CRA.

On page 17 (lines 3-4 from bottom) it is stated that "it is important that community involvement be sought and encouraged," and on p. 18 provision of "the opportunity to obtain technical assistance" is listed among highlighted Guidelines for Stake holder Involvement. However, these briefly stated recommendations for supporting stakeholder involvement are totally inadequate to address the absolute requirement for substantive access to trusted technical expertise in order for any stakeholder to participate meaningfully in a CRA process in which their vital environmental health interests are at stake. Here, the Framework fails to note the unique feature of CRA that makes it more of a high-stakes process than more typical (non-CRA) risk assessments. Namely, because CRA generally will focus on integrated risk of multiple endpoints arising from multiple sources through multiple pathways, it generally will involve integrated risks substantially larger than those addressed in a conventional (non-CRA) assessment. Insofar as CRA may typically involve such high stakes, the Framework ought to propose consideration of a legal right to "environmental health defense counsel" for stakeholders participating in a CRA process, analogous to the right to legal defense counsel during criminal procedures.

Finally, it should be emphasized in this section that CRA is a potentially resource-intensive type of analysis. For this reason, the Framework should refer to the utility of identifying/developing and adopting a set of conservative-default bounding assumptions and methods (CRA-inference bridges) that would be applied to CRA-related factors in the absence of better information (analogous to defaults used for routine risk assessments). In any particular case, CRA defaults could be used (in combination with other routine defaults) to define a worst-case cumulative-risk scenario to be applied routinely prior to CRA/scoping to determine whether a more formal/rigorous CRA process is required. Reference to the need to develop such defaults, and illustrations of specific aspects of CRA for which such defaults are needed, should be emphasized throughout the Framework (Sections 1-4).

## Section 3. Cumulative Risk Analysis

The logical distinction between Sections 3 and 4 needs to be clarified, insofar as certain topics appears to be addressed de novo in each of these sections . For example, Section 3.1.1 (Combining Individual Stressor Risks) appears to duplicate concepts covered in Section 4.1.3 (Combining

Different Types of Risk). Section 3 should begin with a clear schematic diagram summarizing/illustrating the generic type of technical/logical problem posed by CRA. This diagram should be more generic than current Figure 3 (conceptual model), and should in general terms represent a simplified version of the general conceptual problem being addressed in any CRA. Some heuristic notation might be helpful in this regard. For example, it would be useful to adopt some notation for and to illustrate *m* multiple stressors or sources ($S_i$) that may individually or jointly affect any among a total of *n* different health and/or ecotoxicity endpoints ($E_j$) considered (via regulatory requirement and/or by the CRA team) to be relevant in a given CRA, where $i = 1, 2, ..., m$, and $j = 1, 2, ..., n$. The diagram should how *n* different (but not necessarily mutually exclusive) subsets of $S_i$ may each affect each of the $E_j$. For example, each member of the source set $\Sigma_1 = \{S_1, S_3, S_4\}$ might affect endpoint $E_1$, sources $\Sigma_2 = \{S_2, S_3, S_4, S_5\}$ might affect endpoint $E_2$, and so on, where $\{E_1, E_2, E_3, ..., E_n\}$ might denote {cancer, asthma, reproductive/developmental toxicity, ..., serious ecological disruption}. Cumulative or aggregate risk, $R_{cum}$, should be defined as some (yet to be defined) function of the entire set of $E_j$ conditional on $\Sigma_j$. Such an illustration would be analogous to (or could simply reprint) the corresponding figure that appears in the first section of Appendix I of *Science and Judgement in Risk Assessment* (NRC, 1994), which appendix is referred to in Chapter 11 (titled "Aggregation") of that report, which chapter and appendix specifically address the topic of calculating and characterizing aggregate measures of environmentally induced health risk.

Sections 3.1-3.2 of the Framework (General Approaches to Cumulative Risk Assessment) need to be researched better and to be rewritten accordingly, citing and referring to concepts that appear in more of the relevant literature (e.g., NRC, 1994, Chapter 11 and Appendix I). This revised discussion would benefit by explaining what specific questions or issues are being addressed in terms of the figure proposed above relating $S_{ij}$ to $E_j$. In particular, Sections 3.1 and 3.2 do not refer to a coherent description or any example of a purely probabilistic approach to CRA (e.g., like the approach described in NRC, 1994, Chapter 11 and Appendix I), and thus fail to give any indication that such an approach exists and may offer key advantages. For example, the analytical mechanics of performing CRA are simplified greatly by adopting such a purely probabilistic framework, by focusing the analysis on quantifying the cumulative/aggregate risk $R_{cum}$ defined as the risk/probability/likelihood of inducing one or more of the (insofar as feasible, independent) endpoints $E_j$ defined via regulatory requirement and/or by the CRA team to be relevant in a given CRA. As noted by NRC (1994; Chapter 11 and Appendix I), when defined in this way, $R_{cum}$ is readily calculated using de Morgan's rule as

$$R_{cum} = 1 - \prod_{j=1}^{n} \left(1 - R_j(E_j)\right) \qquad (1)$$

in the case of independent $E_j$, where $R_j(E_j) = \text{Prob}(E_j)$ = the risk or likelihood of inducing endpoint $E_j$. Recently, Bogen (2001) used this approach to quantify combined risk of cancer and noncancer endpoints induced by the chemical trichloroethylene (TCE), including quantitative characterization of associated interindividual variability and associated uncertainty (including uncertainty regarding mechanism of carcinogenic action). This general approach is readily extended to cases involving multiple sources and/or endpoints, as explained in NRC (1994, Chapter 11 and Appendix I). Technical hurdles involved in implementing this approach become those of defining the set of

relevant (preferably independent) endpoints $E_j$, and of quantifying Prob($E_j$) (the likelihood of inducing each $j^{th}$ adverse health or ecotoxic response considered unacceptable) as a function of $\Sigma_j$. As noted in NRC (1994), if it is possible to adopt endpoint-specific risk models all of the form, $R_j(E_j) = 1 - \exp[-H_j(\Sigma_j)]$ in which $H_j$ denotes a hazard-type function of a corresponding set $\Sigma_j$ of sources affecting the $j^{th}$ endpoint, then Eq. (1) reduces to

$$R_{cum} = 1 - \exp\left( - \sum_{j=1}^{n} H_j(\Sigma_j) \right) \quad . \tag{2}$$

Such a probabilistic approach would of course require explicit models of the risk of occurrence of each endpoint (including noncancer endpoints) considered. The Framework currently only refers to existing, nonprobabilistic, approaches to noncancer endpoints that are currently used or are being considered by EPA. The recent report by Bogen (2001) illustrates an alternative probabilistic approach to noncancer endpoints, in which methods used for integrated quantitative treatment of uncertainty and variability are made consistent with those used for probabilistic assessment of cancer risk. This report addresses many issues concerning the implementation of probabilistic methods for noncancer endpoints, and cites a number of related references (e.g., Lewis, 1993; Dourson et al., 1994; Slob and Pieters, 1998)—none of which issues or references are discussed in the current Framework. Reference in the Framework (in Section 4.1.3.1, p. 50-51) to an ad hoc procedure of assuming that all RfDs correspond to a given (e.g., $2 \times 10^{-4}$) risk of endpoint occurrence should be dropped and replaced by references to well-documented probabilistic approaches for noncancer endpoints (Lewis, 1993; Dourson et al., 1994; Slob and Pieters, 1998; Bogen, 2001), particularly in view of the fact that not all of the extrapolation factors now routinely used for these endpoints pertain to uncertainty (one pertains to variability).

Any approach to CRA must carefully define the set of relevant endpoints $E_j$. The Framework should emphasize that precisely how this is done has important logical and practical implications for how $R_{cum}$ may be calculated and interpreted. For example, the risk $R_j(E_j)$ on inducing endpoint $E_j$ may differ among different people in a population at risk for some $E_j$ (e.g., cancer conditional on all carcinogen exposures), but may be unaffected by interindividual variability (e.g., in exposure or susceptibility) for other $E_j$ (such as ecological or aesthetic effects). Defining the latter risks $R_j(E_j)$ in terms of individual risk *per se* will thus complicate calculating $R_{cum}$ if a probabilistic approach to CRA is used, and perhaps if other approaches are used as well. In contrast, the probabilistic approach to CRA could be facilitated by defining $R_j(E_j)$ in terms of **population risk**, i.e., in terms of the predicted number $N(E_j.)$ of cases of $E_j$. For example, if the definition $R_j(E_j) = \text{Prob}[N(E_j.) \geq 1]$ were adopted, then the probabilistic approach corresponding to Eqs. (1) or (2) would be simplified because $R_j(E_j)$ (thus defined for each interindividually variable or "heterogeneous" endpoint) would be calculated by integrating over corresponding risk values pertaining to all individuals at risk (see Bogen and Spear, 1987; NRC, 1994; Bogen, 1995), thereby yielding a variability-independent measure of cumulative risk. Risk-equity issues could still be addressed by using additional, equity-related risk-acceptability criteria—see NRC, 1994; Bogen, 1995. Alternatively (or additionally), similar simplification can be achieved for all heterogeneous endpoints $E_j$ by defining $R_j(E_j)$ only with respect to those persons in the population at risk who are reasonably maximally exposed (e.g., individuals adjacent to a proposed source), or to those persons who will incur the greatest increased

risk (e.g., children or other members of a sensitive subpopulation who might be located adjacent to a proposed source).

Although population risk is a penultimate form of cumulative risk, and would thus appear to be a natural focus of CRA, it is barely mentioned in the Framework. The quantitative relationship between jointly uncertain and variable individual risk and uncertainty in population risk, and the requirement to characterize uncertainty in population risk in order to calculate quantities such potentially CRA-related quantities as Prob[$N(E_{j.}) \geq 1$], are not mentioned at all in the Framework. These relationships were first identified by Bogen and Spear (1987), and are further discussed and illustrated in additional references (see Bogen, 1990; NRC, 1994; Bogen, 1995).

The first line from the bottom on p. 35 that reads "At the current state of the science, these factors [addressing the issues related to vulnerability, meaning differential susceptibility, sensitivity, exposure, or resilience] have not been extensively developed beyond correlations between mortality rates and several socioeconomic factors such as income" is not at all accurate. Variability with regard to susceptibility was discussed in detail in NRC (1994), and the current state of knowledge concerning epidemiologically based (e.g., oncogene-specific) risk factors provides empirical data upon which at least crude estimates of the magnitude of heterogeneity in susceptibility to toxic response can be based. Current approaches implemented (e.g., by EPA) to address risk of noncancer endpoints routinely employ a 10-fold factor to address heterogeneity in sensitivity. More quantitative probabilistic approaches that address variability in susceptibility for noncancer endpoints were mentioned above (Lewis, 1993; Dourson et al., 1994; Slob and Pieters, 1998; Bogen, 2001).

## Section 4. Interpretation (Risk Characterization)

As its title indicates, the focus of this section is not at all clear. "Interpretation" would appear to involve some aspects of risk management, whereas risk characterization refers to summarization of risk-analysis output in a form that is useful to risk managers, i.e., that is relevant to a specified or potentially relevant set of risk-acceptability criteria. Some redundancy with issues covered in Section 3 was discussed above. I would suggest that the material in Section 4.1.3. (which might be renamed, Characterizing Cumulative Risk Using a Common Metric) seems to be the central problem in risk characterization for CRA. In this Section, again, a purely probabilistic approach is not presented clearly (or really at all), as was discussed above in detail. Section 4.3 (Uncertainty Analysis) does not (but should) refer also to variability analysis, and should accordingly discuss not just Morgan and Henrion (1990), but also (or rather) relevant references that explicitly address the analysis of joint uncertainty and interindividual variability in predicted environmental risks, and the related problem of compounded uncertainty in risk analysis (e.g., Bogen and Spear, 1987; Bogen, 1990,1994,1995; NRC, 1994).

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# Post-Meeting Written Comments From Jim Butler

# COMMENTS ON THE FRAMEWORK FOR CUMULATIVE RISK ASSESSMENT

**by**

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**August 2001**

The following comments are based on my review of EPA's *Framework for Cumulative Risk Assessment* (August 2, 2001 Review Draft). My comments address issues raised in the questions that were provided to help guide discussions during the peer consultation workshop on August 22-23, 2001.

## OVERARCHING ISSUES

**Comment on whether the *Framework* adequately captures, describes, and reasonably organizes the key issues for cumulative risk assessment?**

Many of the key issues have been adequately captured and described, often with real insight into the practical implications of implementing this type of framework. The authors are to be commended for tackling such an important and technically challenging project. Because semantics are often a problem with cumulative risk assessments, the *Framework* will be particularly helpful in providing consistent definitions for risks that are referred to as cumulative, total, aggregate, incremental, holistic, integrated, etc.

With various interpretations of cumulative risks today, it is important to clearly state the goal of the *Framework* in the introduction. To put the significant changes being proposed here in context, the approach that EPA risk assessments have historically followed should also be explained (i.e., a methodology which focuses on the incremental risks of contaminants emitted from a single source). In addition, the possible uses of the results of a cumulative risk assessment (e.g., during the permitting process) should be included early in the document.

**What additional issues, if any, should be covered?**

It should be emphasized that a cumulative risk assessment can be done on a variety of scales, from looking at aggregate risks of a single pesticide (under the FQPA) to a broad screening analysis of community hazards. On a related note, the *Framework* places most of its emphasis on chemical risk assessments, especially in Section 3 on the analysis phase. Approaches for placed-based cumulative risk assessments need to be included for evaluating exposure and risk from multiple sources within a given geographic area. For example, often this type of analysis would provide stakeholders with

a more complete picture of a particular facility's emissions in relation to environmental loadings from currently operating facilities in the same community.
The National Environmental Policy Act (NEPA) approach to evaluating cumulative impacts is mentioned in the *Framework* as having parallels with cumulative risk assessment, but then is not presented as a possible model to use (especially for community-based assessments).

Finally, how does the guidance in the *Framework* "fit" with other guidelines that have recently been issued, e.g., from the Science Policy Council, Office of Pesticide Programs, OAQPS's National-Scale Air Toxics Assessment, and the Cumulative Exposure Project?

**Comment on whether some of the topics presented in the draft *Framework* are too generic for the intended purpose?**

At this point early in the development of the framework, I think the organization of the report is more important than if some topics are too generic (and in some cases, too specific). There are so many variations on the theme of cumulative risk assessment, and this report addresses only some of them. It is probably better to keep it all the different approaches and levels of analysis under the umbrella of cumulative risk assessments in this framework because of some common concepts, and also because methods and data may be transferable to situations other than what they were originally intended for.

I suggest revising the report so that the conceptual, overarching components of cumulative risk assessment are clearly explained and organized in a concise framework, including a schematic representation of the process. The more detailed technical issues and methodologies could then be presented as a series of issues papers that would be appended to the *Framework* report. The level of detail would, of course, vary depending on the topic, and may include the generic material from other guidance documents. This kind of modular approach would give EPA more flexibility in further developing the framework, while having the advantage of keeping the overall framework consistent and relatively simple. The issues papers (or white papers) should also include details on additional approaches to cumulative risk assessment that are currently being explored (including screening-level analyses, place-based assessments, comparative risk assessments, NEPA cumulative effects analyses, and hazard assessments) that may fit more easily within a flexible, streamlined framework than they would in the present framework. In addition, the issues papers could include summaries of case studies of cumulative risk projects that would extend the *Framework* from theoretical to practical approaches and applications. This approach would also address the disconnect between the rigid analysis approaches of Section 3 and the flexible interpretation methods of Section 4.

**Comment on whether the *Framework* adequately conveys the state of the science with respect to cumulative risk assessment and the areas that are in need of further research and development.**

Long-term research areas that would improve the process for evaluating cumulative risks have been identified in Appendix F. Important data gaps and information needs are also identified in the text, albeit often at a superficial level. However, future inserts may provide supplementary information

on key topics (e.g., biomarkers). The development of a series of issues papers (as described above) would also strengthen the discussion of the state-of-the-science with respect to cumulative risk assessment-related topics.

**PROCESS ISSUES**

**Stakeholder Involvement Throughout the Cumulative Risk Assessment Process**

The level of stakeholder involvement at different stages of the process is not always clear. A suggestion that I have for engaging stakeholders early is to identify a "point person." This is not to imply that stakeholders must speak with a single voice (not likely in any case), but that they have at least one person to help facilitate interactions and identify available technical resources and other sources of information. Another suggestion for engaging stakeholders early is to set up a public web site for the project. A variety of resources can be posted, including cumulative risk tools and databases, project-related news, list of experts, glossary, reports, related links, etc. An online discussion forum could also be included on the web site as a more interactive way of exchanging information with stakeholders.

In Section 2.1.3, it is stated that EPA is the decision maker and will determine if stakeholder involvement will be useful. This sounds too open-ended, with the potential to avoid the more difficult cases. What are the checks on this process issue? Also, EPA and the stakeholders should agree early in the process about timing for the public release of results during the course of the study.

**Using the Results of Cumulative Risk Assessment**

In discussions of possible outcomes with stakeholders, it is important to discuss not only outcomes, but also the limitations on the information that is generated. By this, I mean not just statistical uncertainties, but also what the overall study limitations are. For example, there could be limitations related to the inherent quality of input data, mapping (boundaries of emissions), spatial distribution resolution, inconsistent treatment of chemical classes/mixtures in various databases, etc. Know what the appropriate applications of the information are ahead of time.

There are also situations where stakeholders are focused on a specific issue, e.g., they may be interested in only permitted or regulated sources. This focus may not only rule out complete categories of stressors and pathways, it is intended to yield cumulative risk assessment results that will have specific uses, e.g., to influence the permitting process or EPA's risk management efforts.

**Cumulative Risk Assessment in the Broader Context of Environmental Analysis and Decision Making**

One of the most obvious situations for conducting cumulative risk assessments is in an environmental justice context. But I think a more immediate question is what are existing environmental analysis and decision-making approaches and tools that may be adapted for use in cumulative risk assessments? The situations that would benefit from cumulative risk assessments are (or will become) readily apparent. The problem has been how to go about evaluating cumulative

risks today, often with limited resources. For years, cumulative effects have been assessed under NEPA. Similarly, EPA's community-cased environmental protection and comparative risk assessment efforts both have some principles in common with cumulative risk assessment. These types of approaches and outcomes have not been addressed sufficiently in the *Framework*.

Another approach that may be more practical in the short-term is the use of Geographical Information Systems (GIS) as a way to present cumulative hazards and/or risks and thus inform the decision-making process. The use of GIS and related mapping techniques was mentioned as a possible approach for avoiding the common metric dilemma, but should be described in greater detail. This approach has been used for screening cumulative hazards of air toxics in the Chicago metropolitan area.

## TECHNICAL ISSUES

### Approaches to Cumulative Risk Assessment

The four approaches discussed in the *Framework* report are a good starting point, especially for single chemical/multiple sources scenarios (they seem less suited to community-based scenarios with exposures to mixtures of hundreds of chemicals). But as mentioned in some of my other comments, there are a variety of related approaches that may provide useful interim tools until a more comprehensive cumulative risk methodology can be developed. There are times when estimating risks, as a screen, may be more cost-effective or simply the level of analysis that is needed (or available) for the decisions being made. For example, hazard and risk-based screening approaches have been used in Chicago and Baltimore, respectively. Other examples include the NEPA approach for a somewhat qualitative, big picture view of cumulative impacts or possibly a weight-of-evidence approach using available EPA databases. These kinds of practical approaches should be included with case study examples or lessons learned. It would be better to not limit the framework by the available methods, but to structure the document so that additional modules can support the general framework as additional methods are developed. Another issue paper that could be appended to the *Framework* report is a discussion (and status) of EPA's efforts to harmonize cancer and noncancer assessment techniques, which is an important methodological hurdle to enable cumulative risk assessment to move forward.

### Using Biomarkers of Exposure or Effect

The *Framework* discussion does not adequately characterize how biomarkers can be used with more traditional risk estimates. However, that may be remedied in the insert planned for Section 3.4. While the use of biomarkers in cumulative risk assessments is currently limited, the potential for verifying the modeled results is promising. Biomarkers will also be important for defining background exposures and in health surveillance studies. This section of the *Framework* can be expanded as additional biomarker and biomonitoring research is conducted.

### Combining Chemical and non-Chemical Stressors

One problem with combining chemical and non-chemical stressors will be the introduction of value judgments. For example, the same psychological stressors affect people to varying degrees. The need to explicitly acknowledge these values judgments should be stressed. It may be helpful to illustrate the difficulty of combining different types of stressors by including a hypothetical example. A visual or graphical representation of different stressors could be presented, along with a discussion of the significant limitations (e.g., caveat about not implying a causal relationship). The chemical exposure and viral infection example (mentioned in the discussion question) could be further explored along these lines.

**Combining Different Types of Risk**

As discussed under Process Issues, the use of GIS is a promising approach for presenting different types of risks to stakeholders. It is one way to present integrated risk results without mathematically combining disparate measures. The approach used for air toxics screening in the Chicago Cumulative Risk Initiative involved the use of GIS and indices of toxicity, emissions, and ambient concentrations.

The *Framework* sometimes makes cumulative risk assessment sound like an all or nothing evaluation, i.e., all accumulated risks must be accounted for and then integrated. That's an ideal endpoint, but useful information can still be provided before having all the methods available to do this. Instead of a total of all risks, sometimes we just need to identify the stressors or sources that contribute the most to a population's risk. A relative assessment of cumulative risks (or hazards or exposures) may satisfy the project's original objectives, yet technically not be an integrated assessment of all accumulated risks.

**Limits on the Information Provided by Cumulative Risk Assessment**

If it is known that the results of a particular cumulative risk assessment will be severely limited because of a lack of data or available methods, it may be advisable to start with a screening analysis to set priorities for a subsequent more detailed, focused study.

Appendix C mentions data quality issues, including the problem of combining data of different quality in a single assessment. Other related problems include combining data from different sources and/or different originally intended uses (like many of EPA's databases).

**Distinguishing between Cumulative Risk and Cumulative Impacts**

The *Framework* mentions cumulative impacts in the context of NEPA, but does not provide enough information for the reader to understand the process and potential applicability to cumulative risk assessments. The advantages of highlighting this methodology as a possible starting point for certain cumulative assessments was discussed above. A thorough analysis of the pros and cons of this type of cumulative impacts assessment should be appended to the report.

**Completeness (Quantitative vs. Qualitative)**

Jim Butler

The *Framework* report is geared toward the quantitative assessment of cumulative risks. While ultimately preferable, this often is not possible with existing methods. Plus, there is the issue of available resources; even a screening-level analysis can be labor and cost-intensive. Cumulative risk assessment should be considered a tool that can be used at different levels, as long as there is also a clear understanding of the different levels of uncertainties. Screening analyses often employ semi-quantitative or qualitative approaches, e.g., an impacts matrix, that would enable at least a broad assessment of risks to go forward. I think the approach section should be inclusive and not rule out other types of more qualitative cumulative assessments, including screening approaches, hazard analyses, impacts assessments, comparative assessments, etc.

# Post-Meeting Written Comments From Douglas Crawford-Brown

***Review of Framework for Cumulative Risk Assessment***
Douglas Crawford-Brown, University of North Carolina at Chapel Hill

**General Comments**
The document is a good start, and the Agency is to be commended for beginning a review process before a draft is fully ready. The history, methods and use of cumulative risk assessment is a new and rapidly expanding field, and a difficult one to summarize succinctly. Given this complexity, it would be surprising if the first drafts were able to capture the issues and distill a coherent framework.

At the same time, it is especially important that any Framework document establish at least a partial structure to what can be an overwhelming array of issues. The present document begins in that direction, and then falters as the details begin to pour in. While it represents a good start, and offers some insights into what a framework might look like, it does not in the end produce an explicit framework. The resulting discussion does not present a methodological framework. It might be argued that such a framework would be too technical and should be the domain of a later guidance document. That seems a fair enough argument. But the document should provide at least a conceptual framework, a systematic exploration of the issues that will arise, the order in which they are likely to arise, the kinds of answers that might be produced, and how these answers fit into the overall framework of analysis. I don't think it does that at present, but could with some improvements to both content and organization.

As an example, and only an example, I append a sample framework of questions that might be asked (see the files cra1.doc through cra7.doc). These are organized into a stage on Problem Formulation, a stage on Data and Analysis, and a stage on Synthesis and Interpretation. For each of these stages, I have provided a representative flow of issues that might be raised. For each issue, I then have provided some representative questions that might be asked, and some representative answers.

My sense of a framework document is that it does not provide detailed answers to specific questions. It does not lay down hard and fast rules for how the cumulative risk assessment must proceed. It is based on recognition that any assessment, and even a guidance document, will result from a dialogue between several parties. The goal of the framework then is to bring structure to that dialogue, to provide some guidelines as to the issues that will be discussed, why these issues are important in the flow of assessment, the range of possible approaches to addressing these issues, etc. It provides a map, and in a sense a checklist, through which the parties may proceed somewhat systematically to be sure they have raised all of the important issues.

Again, I don't think the current draft does that. It has a focus and order at times, but this evaporates periodically and the reader is left with a series of discussions that probably are important in some sense, but are not articulated clearly. It is not clear how each issue

relates to larger issues, and how all of these issues fit into a systematic framework of assessment stages. I believe this is a natural state of affairs in first documents, particularly when the issue is as conceptually complex as the one surrounding cumulative risk assessment. But there is still a need for great improvement, with some framework superimposed on the discussion. It should be possible to summarize this framework both verbally and graphically on a single page, and to use that organization throughout the document. I won't pretend that the example I provide in the attachments is the ideal example, but it does give the flavor of my thoughts.

**Answers to specific questions**
The following responses apply to specific questions addressed in the three sessions of Peer Consultation.

***Over-arching Issues***:

*1. Does the framework adequately capture, describe and organize the key issues for cumulative risk assessment? I believe my answer is contained in the general section above. The document does raise many important issues, but these are not organized into a coherent framework, or at least one I could follow. And there are issues barely mentioned but significant (discussed below).*

*2. What additional issues, if any, should be considered? There must be a better discussion of how the need to include all important factors will be balanced against a desire to be as rigorous (mathematically) as possible. There must be a better discussion of the spectrum of results from fully qualitative to fully quantitative and probabilistic (and everything in between), allowing the reader to understand why one or the other part of the spectrum might be desirable or feasible at any moment. There should be a discussion of the kinds of questions that can be legitimately answered by cumulative risk assessment and the kinds that cannot. I think the authors can give insight into that issue without wandering into the domain of policy; i.e. specify legitimate uses of the tool without specifying the kinds of policy options which must be considered. There should be some discussion of the aspects of a particular community circumstance that are on the table, and which aspects are not. For example, can the discussion include whether the EPA is to the appropriate body to address community concerns? Can it include whether risk assessment is the appropriate tool? Etc.*

*3. Are some topics discussed too generically for the intended purpose? I believe this may the case at many places in the document. I will comment on this more fully in the last section. Perhaps the problem is not that the discussions are too generic, but rather that they don't take place in a flow of reasoning that ultimately will give them meaning. As a result, the reader encounters the issues without having had the stage set clearly so they know why each issue is important in the overall flow of the assessment.*

*4. Does the framework adequately convey the state of the science with respect to cumulative risk assessment, and the areas needing further research and development? To a degree, although more on the former than the latter. With respect to the former, I do think the document lacks a good discussion of probabilistic approaches to risk assessment, which allows one to move away from simply summing already conservative quantities such as HQs. There are new methods to allow this, and the document only presents the routine regulatory risk assessment approaches. I think this will cause a real problem if conservatism is compounded improperly.*

***Process Issues**:*

*1. Is stakeholder involvement throughout the process described? Yes, the authors have done a pretty good job at this. There might be slightly more detail provided as to why stakeholders are being brought in. What role do they play in defining values, in defining the assessment problem, in selecting methodologies, in interpreting results, etc?*

*2. Is the use of results from the assessment discussed? That part needs to be improved. The reader should have some guidance as to the kinds of questions that can be answered by a cumulative risk assessment, and the kinds of questions that cannot. I wouldn't want the document to prescribe the kinds of policy choices that can be made (and the document avoids this), but it does need to provide insight into legitimate and illegitimate uses of the tool as these pertain to the scientific basis of the tool.*

*3. Is the broader context of cumulative risk assessment within environmental analysis and decision making discussed? On the first issue, the answer is a qualified yes. It is discussed at probably the correct level of detail, perhaps with the need for an explanation of how cumulative risk assessment relates to other assessment tools (such as air monitoring). I think there is a need to specify in a bit more detail the decision structure. The reader does not receive any insight into the kinds of decisions to which the tool will be applied. I understand the need to stay away from policy issues here, but a decision framework focused only on risk characterization would contain issues of decision principles as to the kinds of risk summaries needed as input into any decision, and would still be useful even if it does not extend into risk management.*

***Technical Issues**:*

*1. Comments on the discussion of approaches to cumulative risk assessment. I think this section is deficient. The document should drop back to the issue of protection of a reasonable fraction of the population against unreasonable (unacceptable, etc) risk, and with some kind of margin of safety, and present a coherent framework in which different approaches might be compared against these decision goals. I*

*disagree that the approaches mentioned are competitors. I think they feed information into a more robust assessment, and should be treated more as weight of evidence considerations than as competitors.*

*2. Comments on the discussion of use of biomarkers of exposure or effect. I think it is good to include this issue, but more detail could be given as to the uses of biomarkers. They might be used to assign exposures, but they also might be used to test models, to provide surveillance, etc. I also think the framework should draw attention to a careful consideration of the strengths and weaknesses of using biomarkers, and why these strengths might be more (or less, although I personally think more) relevant in cumulative risk assessment than in past risk assessments.*

*3. Comments on the discussion of uncertainty analysis. I think this section is somewhat deficient, but a good start. It does a good job of specifying types of uncertainty, although it at times confuses variability and uncertainty, which should always be kept distinct. The bulleted items on page 57 in the middle of the page are not always so distinct. In fact, bullets 2 and 3 are really the same- just two causes of uncertainty about model form. There should be some discussion as to why uncertainty is considered; i.e. how it relates to concepts such as reasonable confidence in protection, ample margin of safety, etc.*

*4. Comments on the discussion of vulnerability. This seems a good discussion, and a necessary one. It is not clear how some of the causes of vulnerability ultimately relate to the EPA mission, but I have no problem with that in a broad framework.*

*5. Comments on the discussion of combining chemical and non-chemical stressors. This is not so well developed. There are many existing models for combining such exposures, and none of these are mentioned. Perhaps it is OK to avoid discussion of specific models in this document, but there should be some mention of classes of models such as biologically-based pharmacokinetic and dose-response models that have the potential to include mixtures of exposures in moving organisms between distinct states or stages of health (e.g. the Moolgavkar cancer model, or some developed by Ken Bogen, or some developed by myself). The document should alert the reader better to scientific advances in this area over the past 10 years. It should describe clearly how default assumptions might be introduced, and why.*

*6. Comments on the discussion of combining different types of risk. This is probably all that can be said on this issue at present. As with many of my comments above, the need in the document is simply to better motivate the issue in the mind of the reader. The document does a good job of pointing out difficulties, suggesting some methods, and even calling up the possibility that effects should be left in a matrix rather than combined into a single measure.*

*7. Comments on the discussion of limits of information provided by cumulative risk assessment. I think this should be supplemented by a formal discussion of the specific questions that can be answered by such an assessment, and the questions that cannot, and why. The term "limits of information" generally refers to limits that affect the ability to reach specific decisions. Some decisions can still be made under limited information (e.g. ad campaigns rather than command-and-control decisions). Providing a more formal framework of discussion may help in making the decisions clearer in the document.*

*8. Comments on the discussion of distinguishing cumulative risk and cumulative impact. I never really understood this distinction in the document. I can see why it might be important, but the document didn't explain the difference clearly, or why the difference is significant for decisions. There needs to be an improvement in that part of the document- not with respect to what it says but with respect to framing the issue so the reader knows why the difference is being considered.*

*9. Comments on the issue of completeness of conception versus rigor of execution. The document does not approach this issue at all. Cumulative risk assessment involves a wide range of stressors, receptor populations, kinds of information that might contribute to the assessment, etc. The framework should help the reader understand the full range of these issues, which can be treated quantitatively and which must be treated qualitatively, how this treatment affects the ability to perform specific tasks such as developing a single summary measure of risk (if that is desired), and the conditions under which it is desirable or undesirable to leave out a factor because it cannot be assessed or phrased in a way that is commensurate with other factors. I would not want to see a factor left out simply because it cannot be treated with the quantitative rigor of another factor, but we also don't want the assessment compromised too much by poorly characterized factors. At times, it will be necessary to give a little on the criterion of trying to be as quantitative as possible, so as to avoid the loss of some key factors and, hence, a complete conception of the problem in a community.*

*10. Comments on the issue of qualitative versus quantitative assessments. The document mentions this several times, which is a strength. There should be an explicit point in the framework where the reader confronts this issue and determines whether quantification always is needed, when qualitative results might be OK, and how these two kinds of results should be combined. Some examples could be given. For example, the quantitative results might eventually be reduced to a more qualitative scale (High, Medium or Low). Or the qualitative results could provide "comments" tacked to the quantitative results. Or the assessment might simply raise "red flags" associated with specific issues (e.g. density of emitters in a community; presence of minority populations; special exposure pathways; etc); a high number of such flags would indicate unacceptable cumulative risk, even if this isn't quantified.*

*And so on. But this seems an important issue, especially since stakeholders are likely to prefer more qualitative approaches. The experience of the EU in using qualitative methods might be discussed, to show that "qualitative" is not "irrational."*

***Further Specific Comments**:*
*These comments apply either to points not discussed above, or to specific statements in the document. In the latter case, page citations are given.*

*1. New science policy default procedures may be needed for cumulative risk assessment (I would argue that they ARE needed). This should be mentioned.*

*2. There should be harmonization of cancer and non-cancer approaches. Given probabilistic methods, this is now possible. It will not be feasible to combine these two classes of effects under the existing approaches.*

*3. The document should emphasize the need for communities to have access to the necessary scientific expertise, and not simply travel to meetings. This may include access to models, data sets, etc. The OTAG process mgt be an example.*

*4. Page 17 should mention the role of discretionary power of the Agency. While stakeholder participation is good and necessary, the Agency must eventually decide what to do.*

*5. There should be some mention of the fact that such assessments may be done retrospectively (to determine existing risks), prospectively (to assess the risks of proposed facilities), or even creatively (to design a development plan for a community).*

*6. Page 22, last paragraph. It is not clear why "hypotheses" are referred to here. I don't see any sense in which scientific hypotheses appear, unless the author means something like "possible contributors". The writing should be clearer on this point.*

*7. Page 25. At some point in this discussion, the issue of differences in severity of effects should be raised. This might be related under the discussion of QALYs, but it seems reasonable to also raise the issue elsewhere (is this what is intended by the discussion of categorical regression?).*

*8. Page 25. Risk factors are not so different from slope factors, UREs, etc, at least conceptually. This issue should be raised in the context of weight of evidence, where a framework is mentioned to combine information from different approaches.*

*9. Page 26. One problem with use of biomarkers is that the decision problem often requires separation of contributions from exposure pathways so effective policies*

*can be located.*

*10. Page 28. My understanding of point of departure is that it does not refer to the entire range of observed doses, but rather to the lower end of that range (from which extrapolation may proceed if needed). But I could be wrong.*

*11. Page 29 and 30. RfDs and RfCs are not characterized by two-tailed confidence intervals. There is significantly more confidence that the RfD is protective than that it is non-protective. The document seems to suggest the threshold might lay anywhere within a factor of 10 in either direction of the RfD. This is why it is important to not simply add HQs in a cumulative risk assessment.*

*12. Page 32. Dose-rate effects are not mentioned, but they are important. It is mentioned back on page 39, however. There probably should be a distinct section on dose-rate and timing issues, and how they might complicate cumulative risk assessment.*

*13. On a more general note, there might need to be a section talking about special problems that arise in cumulative risk assessment, or perhaps problems that are made worse under cumulative assessments. I am thinking of issues related to the overall confidence in an assessment; resource needs; understanding of the margin of safety that applies; etc. While cumulative risk assessment is not so different in character from common methods used today, it does differ in terms of the level of comfort with the results and their interpretation.*

*14. Section 4.1. I think the methods discussed in this section all contain, at least implicitly, an assumption of additivity. This should be mentioned (if I am correct) and some mention given of methods that do not require additivity. That would balance the discussion, which seems to me too heavily focused on existing regulatory default procedures rather than possible advances.*

*15. At several points (e.g. on Page 51), there is too large of a distinction drawn between analytic and deliberative steps. All steps involve both aspects, even those classically assumed to be scientific. Science involves both analysis and deliberation (that is why we have scientific bodes and not individual scientists speaking for the field). And policy/management involves both analysis (the meaning of concepts such as acceptable risk) and deliberation.*

*16. Page 57. A point-by-point sensitivity analysis can be misleading. A better approach is one where uncertainty is factored into the analysis, rather than simply adjusting each parameter one at a time across the range. The approach is based on contribution to variance.*

# Post-Meeting Written Comments From Amy Kyle

**Peer Consultation Panel**

**Cumulative Risk Framework Document**

**August, 2001 - Comments of Amy D. Kyle**

**Overall comments**

Developing methods and approaches that allow for the consideration of cumulative exposures and risks is important. Such approaches can better reflect human experience with pollutants and contaminants, as well as other stressors, than can approaches that focus on single pollutants and incremental risks. As has been widely documented, and is noted in the foreword at page vi, standard risk assessments typically consider single pollutants and new releases or exposures, but not the accumulation of exposures over time and the likelihood of an accumulation of effects.

The limitation of current risk assessment methods is very apparent to people from communities that are, in a sense, at the receiving end of assessments. Estimates of risk levels that are quantified through rigorous methods but exclude obviously relevant accumulations of exposures and effects have limited credibility. Changes, either large or small, to reflect more of the actual burden of exposures and effects that people are experiencing will improve the scientific validity and credibility of risk assessments.

The document, Review Draft, Framework for Cumulative Risk Assessment, August 2, 2001, represents an impressive attempt to pull together, from varied sources, information that would contribute to a framework for cumulative risk assessment. The document presents well-developed and nuanced descriptions of many of these issues. The US EPA is to be commended for this important step.

***The purpose of a framework is to identify key issues to inform a wide variety of interested and affected parties. Therefore a balance must be struck between adequately characterizing the issues and providing an excessive level of technical detail. The framework also discusses a process for gathering information and defining the problem with stakeholder input.***

***When considering the process topics, recognize that our goal is to focus the scope of the cumulative risk assessment on a parsimonious use of stressors, sources, pathways, and potential adverse effects that are of interest to a particular place or community.***

***Overall, the RAF technical panel is seeking discussion and input on the questions and topics that follow. We are not setting policies for how to deal with the issues, but rather identifying principles and professional judgements which may lead to more specific guidance later.***

One way to look at this is to think first about what is most fundamental. What would one always want to do when considering cumulative risks? Trying to identify the essence of the framework would be helpful.

The process for involvement of stakeholders and integration of technical and policy concerns, described in detail in the National Research Council's 1996 book entitled **Understanding Risk,** is not unique to cumulative risk assessment but would be equally relevant for other kinds of risk assessment exercises.

I do not agree that focusing on cumulative risk assessments for a particular place or community is always the appropriate focus. Principles of cumulative risk assessment may be just as integral to assessments that do not focus on a particular place or community.

1. ***Comment on whether the Framework adequately captures, describe, and reasonably organizes the key issues for cumulative risk assessment. Include in this discussion whether key terms have been identified and clearly defined.***

The document describes many of the key issues for cumulative risk assessment. The narrative sections of the document are generally clear and informative and have about the right level of detail for a document such as this.

The document provides useful narrative but lacks a true framework. The document would benefit by the addition of a section that describes how the pieces fit together, perhaps in the form of a schematic or flow chart. A framework would provide an organized way of looking at the topic and thinking through the steps. I would not agree that it would be better to develop the document solely as an issue paper without working to more clearly define the essence of the framework.

Such a framework could begin by selecting a scale for an assessment and proposing what, among possible exposures, stressors, and effects, would be considered and over what term. The steps in the analytic-deliberative process laid out in section 2, beginning with a full scoping step, followed by analysis, and concluding with characterization, are appropriate. The explanation would be improved by acknowledging that the steps may be iterative and that results from one step may influence another.

It might be useful to start with principles that should always be considered, and then work through more complex points that might apply in some cases.

More linking of how the various kinds of analyses described in the document might apply to these steps could be helpful.

It is important to recognize that the scope of cumulative risk assessments will vary considerably, as some may involve one contaminant, simply considered in terms of its cumulative exposures and effects, while, at the other extreme, “place-based” assessments may attempt to capture a multitude of contaminants and stressors and consider the cumulative result. The document provides, at page 19, three cases that could be used to explain the differences in approach and issues to be considered at different scales. For each case it would be valuable to develop a model or schematic for the steps that would be involved, who would be in charge of each step, what would be decided, and what types of methods or

considerations would be relevant. Such as schematic or model could then refer to other portions of the report for narrative explanations.

The document may give too much emphasis to the most difficult case for cumulative risk assessment, illustrated at page 7, as a complete analysis of contaminants and other stressors as they interact and affect a population. This case may be informative in terms of explaining the ultimate scale and reach of a cumulative risk assessment. However, it may be unwise to set such an intensive analysis as the ideal case for the process. It may be a more productive to incorporate more of the accumulation of exposures and effects in more modest assessments. More attention is needed to the implications of cumulative risk assessment on the basic methods now used for risk assessment.

The document needs to be cognizant of the need for EPA to retain the ability to carry out its responsibility to protect public health and the environment while also including stakeholders in a process like this. It would likely be necessary and appropriate for the agency to develop an initial concept for an application of cumulative risk assessment methods, perhaps in a case where existing methods are identified as likely not resulting in sufficient protection for the public. The EPA could identify the scope and level of detail for such an assessment, identify appropriate stakeholders, and initiate a discussion of how to frame the problem, altering its initial conception as appropriate through discussions with stakeholders. However, as noted in the document, the EPA would need to be able to set some reasonable boundaries around such a process to ensure that progress is made in a timely fashion.

The term "risk management" team, as used at page 13 may not be appropriate, as some solutions may involve actions other than risk management and because, in some cases, who would need to be involved in solutions may not be apparent until the analysis is complete.

The discussion of combining risks, in some places, implies that it is essential to the framework that risks be combined. While it is valuable to combine risks, this may not be possible or desirable in all cases. First, all stressors and effects may not best be expressed in the form of "risks." Second, it may be better to consider different categories separately. Methods required to convert everything into a common metric (such as DALYs) may have more disadvantages than advantages. Moreover, the document should not assume that all "risks" would necessarily be quantified. The presentation at the meeting said that the goal was to define the probability of harm from multiple stressors. This may or may not be the most appropriate goal. As was discussed at the consultation meeting, use of weightings such as high, medium, and low or percentiles may allow the comparison and summing across a variety of disparate outcome measures without trying to convert everything into one common form. Alternatively, an index approach to scoring may be useful in some cases. Methods that show both the original scores and a combined score are most informative and allow participants to see clearly the implications of methods used. The discussion of this topic should be reviewed and clarified throughout the document.

***1. What additional issues, if any, should be covered?***

***a. <u>Completeness</u>***

The importance of considering the completeness of a cumulative risk analysis, given its purposes and scope, should be added to the discussion. The analyses used should be selected in order to address the problem that is identified. In other words, the problem should drive the method. (The method should

not drive the problem). We need to be able to consider, what are we leaving out? And, when we notice that we are leaving things out, we need to be able to use the best available approaches to integrate them. Bounding estimates that incorporate different assumptions can be useful here, but the principle should be to integrate everything that is important.

To look at this clearly, during the analytic-deliberative process, the team should consider how much of the problem they are trying to address has been captured by the methods that they have decided to use. This then allows for course correction if need be to address topics that are important but that have not been well captured by the methods used. There is often a tension between doing an analysis that is more complete but that uses methods that have more uncertainty or are less familiar and doing an analysis that is narrower but can rely upon well-understood and familiar methods. The document should acknowledge that it is not scientifically sound to leave out consideration of factors or issues that can be reasonably anticipated to be important to the scope of an analysis. It is more scientifically sound to use an imperfect model that addresses all of the factors of concern than a perfect model that clearly ignores many of them. This is the crux of much of the interest in cumulative risk assessment – we can no longer justify acting as if people are exposed to a single chemical *de novo* in every assessment.

***b. Intermediate level of analysis***

The concept of the difference in approach in looking at the population level and the release level is useful though it leaves out the intermediate level of looking at cumulative risks from ambient exposures, which can be quite useful and informative. It would obviously be most desirable to model exposures and risks at the individual level. It is not, however, parsimonious. Useful ranges can be placed on exposures and risks at a higher level of abstraction that can be very useful for policy decisions and much less intensive of knowledge and processing.

***c. Support to community stakeholders: level playing field***

Providing sufficient support for successful participation by stakeholders, particularly those representing non-governmental and community organizations, is a challenge for a cumulative risk assessment process as it is for other agency processes. The document says, at page 18, that it may be necessary to provide certain limited forms of tangible support or to provide incentives for participation. These may well be appropriate. However, to truly create a level playing field will, in some cases, require greater efforts, as community stakeholder groups may need access to adequate technical analysis and resources to be able to fully participate in the process.

***d. Vulnerability***

With regard to vulnerability, it may be appropriate and useful to consider whether there is any synergy of vulnerability. If both vulnerabilities and exposures accrue to particular segments of the population, then cumulative risks may be significantly higher for some, and this should be pointed out. It may also be useful to link the discussion of vulnerability to the national discussion of eliminating health disparities. Cumulative risk assessment will be important to eliminating disparities in the field of environmental health, and this should be recognized in the document.

***e. Clarify that cumulative risk assessment means considering all exposures***

The document should clarify that cumulative risk assessment, even for a single chemical, considers all exposures. This means both those earlier in time and those from all sources. It also considers the implications for both background and multiple sources when assessing dose and response. New exposures should be considered in terms of where they fall on a dose-response curve after adjustment for previous exposures, accumulated exposures, and other sources. The discussion of background exposures now in Appendix E should be integral to the document.

***f. Incorporate consideration of actual exposure when discussing thresholds***

The document should note that it will be important to review assumptions about thresholds for effects in light of cumulative exposures, cumulative risks, and the variability of human responses. Exposures should not be represented as being above a threshold unless it remains above a threshold when these factors are taken into account. Thresholds for risk should not be assumed when the data do not support this. (See RfD document for methylmercury as an example.)

***g. Children***

It would be appropriate and helpful to include a section that discusses issues for assessment of cumulative risk with regard to children. How to think about time patterns of exposure and of susceptibility (the former is mentioned at page 7 but not described in any detail) could be covered.

***h. Environmental justice***

It would be appropriate to add a greater discussion of how cumulative risk assessment (and management) is related to environmental justice. This is discussed from an historic perspective, but not with an operational perspective.

***1. Keeping in mind that the Framework is intended to address issues that are specific or unique to cumulative risk assessment, comment on whether some of the topics presented in the draft Framework are too generic for the intended purpose.***

The discussion of current risk assessment methods seems to be excessive. Perhaps other sources could be referenced.

The section on biomarkers is far more generic than it needs to be and does not seem to be related to the essential purpose of the document. Biomarkers could be particularly relevant for cumulative risk assessment. Biomarkers of exposure would ideally integrate all sources of exposure at the level of the individual. Biomarkers of effect could analogously integrate all sources of effect at the level of the individual. Obviously, biomarkers would need to be carefully considered and chosen to actually have such capacities. It might be worthwhile in this section to at least identify leading candidates for biomarkers that could contribute to this effort. For biomarkers of exposure, hair level of mercury and blood levels of dioxin come to mind as potentially useful, in part because the body burden metrics have been related to adverse health outcomes in recent assessment documents. In addition, there may be, perhaps in the future, some application of the field of proteomics to this area.

There has been some discussion of providing a better statement of how cumulative risk assessment could be used, in specific cases. There may be some benefit in doing this. I would not think it would be helpful, however, to tie these to specific legislative mandates, as the overall approach is not linked to any specific statute and could probably be relevant to all.

1. ***The framework attempts to identify where methods and data are currently lacking or are underdeveloped for application to cumulative risk assessment. Based on a suggestion during the meeting with other Federal scientists, research oriented issues have been highlighted in an appendix to the Framework. Comment on whether the Framework adequately conveys the state of the science with respect to cumulative risk assessment and the areas that are in need of further research and development.***

To fully describe the "state of the science" with regard to cumulative risk assessment would be a considerable undertaking that would need to incorporate the state of the science for each of the methods and approaches that could be used. This seems to be rather beyond the scope of a framework document of this type. Perhaps the most useful approach would be to summarize the state of the science with regard to the reasons to conduct cumulative risk assessment.

One critical management need is to expand the number of chemicals that have toxicity values in IRIS. This database has become increasingly outdated.

How to address other stressors is obviously a critical area of research that would apply to cumulative risk assessment and to any other form of risk assessment as well.

**Other comments**

The introduction to the document seems to include a number of questionable statements. Considering cumulative risk is not in conflict with approaches that seek to reduce or eliminate releases of contaminants. It is just as valid to limit releases of contaminants because the cumulative risk is too high as because the risk of a single chemical, considered apart from everything else, is too high. The effect may be measured in the population, but the control may still need to be at the source and could come about as a result of either "command and control" or incentive-based approaches. (It appears to me that much more has been claimed for incentive based approaches than has been achieved by them.)

The discussion of regulatory history at page 1 is somewhat odd. The "command and control" approach is usually contrasted to incentive-based approaches, not to those that consider population-based risks. It is not particularly clear to me that this has reached the point of diminishing returns. Consider the regulation of air pollution from power plants or SUVS, for example. Some things are well controlled and others are not. There is no great uniformity of approach.

The leading reason that I believe that people are concerned about current risk assessment methods is because they clearly leave out things that are important. When the risks of single chemicals are assessed, exposures that occur before today (background exposures) are usually ignored. This means that the actual risk is almost always under-predicted, as people very often have other, pre-existing exposures that affect where they are on a dose-response curve. Moreover, exposures to other things are also usually ignored. This means that people are almost always facing a higher, and often a very significantly higher,

risk than what is shown in any single chemical, *de novo* assessment. Consequently, regardless of the strategy chosen to manage the risk, there is widespread support for an approach that better reflects what people actually experience.

Use of the notion of "margin of exposure" should be excluded from this document. This approach has been used most extensively in conjunction with an attempt to convert the starting point for non-cancer risk assessment from a no-effect level to a 10% effect level. Consequently, the term is somewhat tainted for other purposes.

Page vii - In the third paragraph, the assertion that a key role of science at EPA is to reduce uncertainties in decision-making seems to be a rather odd way to sum up the role of science. I would think that, more fundamentally, the role of science would be to provide the best available information for decisions to protect public health and the environment, the mission of the agency.

The contrast between methods that focus on a chemical and those that focus on a population is drawn too sharply. As noted elsewhere, it would be possible and advisable to consider cumulative risk for a single chemical and would require a change to existing methods.

Page 1 -- In the first paragraph, use of the phrase "so-called sources" implies that you don't think that the elements listed are actual sources of pollution.

Page 3 -- In the fist full paragraph, I would advise acknowledging that there was much more to the evolution of the environmental justice movement than what is described here. The discussion of NEPA is very interesting.

Page 7, point 2 -- The notion of presenting an integrated picture of risk, as presented here, is a good one. However, as noted elsewhere, trying to combine disparate types of risk into a single measure raises issues in itself. I don't think it is wise to exclude the possibility of presenting different kinds of risks in a table as a positive outcome of an assessment.

Page 7, point 3 -- This area seems to be one for which considerable additional research will be needed.

Page 8 -- In the definition, the areas in which exposures can be accumulated should all be spelled out (and the phrase etc. should then be deleted.)

Section 1.4 -- I would add the diagram of the analytic-deliberative process given in the NRC report referenced.

Page 10, Section 1.5 -- It is a good idea to introduce some of the key conceptual differences between a decision analysis approach such as that in Clemen's book and the largely biomedical model reflected in current risk assessment methods. I am not sure that this belongs in this section, however. It also probably needs a more thorough explanation.

Page 13 -- I would recommend using the term "analysts" rather than "risk assessors" to reflect the point made elsewhere that a variety of kinds of analysis may be needed.

Page 16 -- Background exposures should be addressed in cumulative risk assessments, not just discussed as stated here.

Page 21 -- Conceptual models should be included in this document for assessments of varying scope, including examples that are simpler than this one. It is not a trivial task to distinguish between what is "known or determined" and what is "assumed." I am doubtful that it will always be helpful or appropriate to insist on agreement on a single conceptual model. The first full paragraph on page 22 seems quite naïve. It also seems to be in conflict with other portions of the document that better reflect the "deliberative" elements of the section of stressors, sources, receptors, and so on.

Page 22, Section 2.2.3. What does the following sentence mean? "Those hypotheses considered more likely to contribute to risk are given priority." As far as I know, hypotheses don't contribute to risk. The earlier discussion about the need for methods, including elements of decision analysis, that address the problem identified should be reflected here.

Section 3.1 -- This section is rather incoherent and needs to be re-thought. It now includes a somewhat random collection of methods that could contribute to a cumulative risk assessment. They are not mutually exclusive.

Page 27 -- Using "mode of action" as a way to combine risk for chemicals is problematic since the true mechanism of action of most chemicals is unknown and many chemicals have more than one.

Section 3.2.1. -- This section should acknowledge that there is not always a threshold for non-cancer effects of chemicals (see recent EPA assessments for dioxin and methyl mercury for example.)

Page 31 -- The notion of a "mode of action" as proposed in the 1996 draft cancer guidelines is based on a rather selective application of science and seems to be technically dubious. The fragmentary information that has been accepted as a basis for a hypothesized mode of action to date seems to reflect a policy goal of the agency rather than a truly scientific approach.

Page 39 -- Even though a linear model has been used for carcinogens, there may be cases when the average lifetime dose may not be the appropriate exposure metric. It could be that the averaging period is too long or that earlier exposures, particularly in children, may have a greater risk.

It seems highly unlikely that it will be possible in most cases to characterize chemical exposures "in terms of which other chemicals are present, and when."

Page 49 -- The "margin of exposure" terminology does not reflect risk. This terminology is currently being applied to represent a ratio between an exposure level and a very high effect level (ED10), not a no-effect level. The explanation of how this term is being used in the document is not correct. The phrase should be deleted to avoid this confusion.

Page 56 -- The second bullet point is not correct in this context.

## Post-Meeting Written Comments From Norris McDonald

# Center for Environment, Commerce & Energy

## PEER CONSULTATION

Provided By

**Norris McDonald**

President

**Center for Environment, Commerce & Energy**

For The

## Review Draft

# Framework for Cumulative Risk Assessment

Submitted To The

United States Environmental Protection Agency

August 2001

# Center for Environment, Commerce & Energy

## Introduction

Risk Assessment is a complicated undertaking. Cumulative Risk Assessment can become unmanageable if limitations are not placed on the input parameters. It becomes a case of "too much information in, nothing useful can come out." Paradoxically, cumulative risk assessment becomes useless if enough inputs are not included.

Legislation, such as the Food Quality Protection Act of 1996, is forcing the Environmental Protection Agency (EPA) to consider the cumulative effects of multiple chemical exposures occurring simultaneously and over time. Various entities at EPA are examining the feasibility of formulating cumulative risk assessment models. The EPA Science Policy Council [via the Risk Assessment Forum (RAF)], EPA Office of Pesticide Programs, and the Office of Air Quality Planning and Standards are examining various models. The framework is being reviewed by Federal and State scientists, peer reviewers, EPA's Science Advisory Board and will require approval from EPA's Science Policy Council.

My comments will address the RAF's request for input in the following areas: organization of the framework, additional issues, issue of generic versus specific content, effectiveness of the methods and data, adequacy of state of the science, and the need for more research and development. My comments will also address process and technical issues.

Finally, I commend the participants in the Peer Consultation Workshop held in August 2001 for their insightful comments and contributions to my thinking about the framework: **Ken Bogen**, Lawrence Livermore National Laboratory, **Elizabeth Boa**, American Chemistry Council**, Jim Butler**, Argonne National Laboratory, **Douglas Crawford-Brown**, Dept of Environmental Sciences & Engineering, Univ of North Carolina, **Amy Kyle**, School of Public Health, Univ of California-Berkeley, **Beth Mileson**, Technology Sciences Group, Inc**., Stephen Olin**, International Life Sciences Institute, **Bill Rhyne**, H&R Technical Associates**, Jeniffer Sass**, Natural Resources Defense Council, **Margo, Schwab**, Johns Hopkins School of Public Health, and **David Bottimore**, Versar. The workshop provided an informative platform for analyzing the

technical issues associated with developing a framework for cumulative risk assessment. It also provided a good forum for comparing our views with the views of a wide variety of independent scientists.

**Organization of the Framework**

The framework is very concise for an EPA document—under 100 pages. I understand that there was a directive to keep it under this number. Unfortunately, brevity was accomplished at the expense of including numerous references in the framework to other documents. I found this to be distracting and intimidating. It gives one the feeling that unless you have reviewed a large volume of background, historical documents, legislation and regulations, you could not reliably render an evaluation on the topic at hand. These references take up 13 single-spaced pages in the back of the document. Maybe the references could be included in a separate reference and appendix document. The elimination of all of these references and the massive listing in the back of the document would provide a more readable and user-friendly framework. The framework is breaking new ground and the technical concepts need to be clearly identifiable. The additional space would also provide more room for informative charts and figures.

The Conceptual Model on page 21 is a good generic description. It should be enlarged in order to provide a better view of the technical linkages and elements.

The final 38 pages of the document contain only 5 figures and no charts. It appears as though this valuable tool is utilized in the front of the document and only given token use in the remainder of the document. These 5 charts do not contain informative concepts or descriptive scientific diagrams. They are basically definitions. The policy analysis list on page 56 appears to be out of place in this scientific framework.

Conceptual Model. The framework provides a good, short description for developing the conceptual model. The framework acknowledges the importance of the conceptual model as a risk communication tool both at EPA and in interactions with the public. The chart on page 22 (Desired Outputs for Problem Formulation) is very informative but is

presented in a dull, single-spaced format. It should be more fully developed and presented in a design similar to the one on page 21 (Conceptual Model).

The chart on page 40 should be included as an appendix.

**Additional Issues/Issue of Generic Versus Specific Content**

Analysis Phase. Although the framework is considered to be a technical document, very little guidance is given to addressing data gaps in toxicity mixtures related to health effects. This is really the heart and soul of cumulative risk assessment. Can we put all of the chemicals in a particular situation along with potential health effects in a computer and get predictable results? Our current institutions are territorially separated in addressing the science. EPA is treading in Center for Disease Control (CDC) and Agency for Toxic Substances and Disease Registry (ATSDR) territory. From a strictly scientific approach, these agencies need to work together as a seamless unit, or maybe they should be combined in an Executive Branch, Cabinet-level Department - - **Department of Environmental Disease** (DED). Cumulative risk assessment modeling could provide the science to drive the policy. Then the policy could effectively drive the scientific implementation. The framework should at least consider a new scientific paradigm.

Figures. The figures provide easy-to-understand explanations of the risk assessment concepts. Again, these figures should be enlarged to make the information more accessible. The simple listing of EPA's Risk Assessment Guidelines and Selected Policy and Guidance Documents was particularly helpful. The short listing of documents was not overwhelming and the guidelines were comprehensive and diverse, but not exhaustive. More information could be provided in figure and chart form. Many National Environmental Policy Act (NEPA) documents utilize this approach very effectively.

"Corporations" should be added to the chart on page 17 and it should be moved to page 6 under intended audience. Of course, this relates to my biggest criticism of the document: making EPA the only intended audience. I recommended in the workshop and I

recommend now, that stakeholders should also be included as the intended audience. The interested and affected parties included on page 17 have as great a stake in the success of cumulative risk assessment issues as EPA risk assessors and managers. I will address this issue in more detail later in my comments.

Environmental Justice. The mention of environmental justice in the introduction is woefully inadequate. It lists a rudimentary three-line history of the movement. Note: **Benjamin Goldman** should be added to the 1987 Lee item. Goldman was the principal author along with Lee (page 3). The environmental justice paragraph should at least mention that the Executive Order addresses disproportionate impacts on minorities due to racism in addition to the quote about "Environmental human health analyses, whenever practicable and appropriate, shall identify multiple and cumulative exposures." In fact, an additional paragraph should be included which describes the complexity of race relations in the context of cumulative risk assessment. It provides an excellent example for illustrating the scientific complexities involved in integrating an abstract confounding variable into a cumulative risk model. Some mention should also be made about researcher bias. EPA is struggling with internal discrimination cases. How can they be trusted with environmental justice cumulative risk assessments when EPA managers are unwilling to quantify the weaknesses of many of their scientists, researchers and other staff? These weaknesses translate into bad science, bad policy implementation and bad service delivery. The Marsha Coleman-Adebayo Case ($600,000 discrimination judgment against EPA) is a good example of this weakness.

Intended Audience. I disagree with the framework's targeting EPA as the intended audience and final arbiter of cumulative risk assessment for America. Although it is commendable that EPA is taking the lead in framing a scientific foundation for cumulative risk assessment, excluding stakeholders as principle decision-makers and targeted audience are major flaws in the methodology of the framework. Section 2.1.3 Agreeing on Participants, Roles and Responsibilities, should be incorporated into Section 1.2. Intended Audience. Because the development of a cumulative risk assessment is in its infancy, stakeholders will be secure in their positions as formulators and respected decision makers in achieving a broad scientific consensus. Stakeholders should be

incorporated into the risk assessment planning team as decision makers with equal decision-making authority. In considering placed-based versus chemical-based assessments, stakeholders outside of the EPA oftentimes have different, and more insightful scientific perspectives. Moreover, EPA should not have the sole authority to decide whether stakeholder involvement is warranted, as proposed in the framework. Sometimes EPA is culpable in scientific oversights related to informing and protecting the public from pollutants. Some science is very simple but is made complex by EPA scientists and policymakers. For instance, if you can see the air during a hot, summer day, it is not healthy to breathe. That is an indisputable scientific observation. This conceptual model would work just as well as, if not better than, parts per million quantification. Scientific observation as it relates to policy decision-making should ultimately be tied to improving human health. We can still see the air in our major cities after 31 years of having a Clean Air Act. And the metric for enforcing compliance is basically ignored. This model continues as asthma deaths are rising exponentially. How will cumulative risk assessment address this scientific issue? It should mix the complex scientific assessment with simple indices.

**Adequacy of State-of-the-Science/Need for More Research and Development**

The framework seems to surrender to the potential complexity of the cumulative risk assessment model. The framework shouldn't surrender. Most real-world environmental threats have finite, though complex, inputs. There should be more analyses of the interaction of a variety of chemicals, in a real world model, with epidemiological inputs. The stroke example on page 25 is good, but a few more pages of this type of inquiry would be very helpful. This epidemiological and toxicological data could be illustrated in a form similar to the conceptual model on page 21.

The loss of life expectancy section is very helpful and informative.

The Vulnerability section would be a good place to expand on the environmental justice components. The specific items could provide additional insights into differential exposure, differential preparedness and differential ability to recover. The EPA Office of

Environmental Justice should provide additional information in this section. The Center for Environment, Commerce and Energy will, in addition to addressing chemical and biological stressors, examine hazards other than chemical and biological stressors in its alternative Framework for Cumulative Risk Assessment. For instance, racism and black-on-black-murder and assaults are huge stressors in the black community. Our multi-hazard risk assessment will include these non-chemical, non-biological stressors in a framework.

Section 3.2.1.5 (Hazards Other than Chemical Hazards) on page 34 could be combined with Section 3.2.2.5 (Exposures to Non-chemical Stressors). Section 3.2.2.4 (Subpopulations with Special Exposures) could be combined with a new Environmental Justice/Vulnerability section. I would consider dropping the subpopulation designation. It diminishes the importance of these groups. They aren't subs. They are populations. Although examples of runners, children, the elderly and others are used, these populations would be better served in the framework under a different heading. In the context of cumulative risk assessment, these populations are just another variable.

The examples for addressing a common metric or index are informative.

The Risk Description 4.2 should be moved closer to the front of the document. The paragraph at the bottom of page 58 should be move to the front of the document. It succinctly describes the purpose of the framework. The italics should be removed (Margo Schwab recommendation to remove italics).

**Effectiveness of the Methods and Data/Process and Technical**

The generic framework provides an acceptable starting document for developing a cumulative risk assessment model. This framework provides an excellent roadmap for future formulations. I did not find the Appendices to be very helpful in the current form. The information in the appendices on methods, data, and R&D should be incorporated into the body of the document. The resources and contacts could remain in an appendix.

## Conclusion

The peer consultation process is a very important part of developing the *Framework for Cumulative Risk Assessment*. It would be great if the final document would be titled *EPA & Stakeholder Framework for Cumulative Risk Assessment* instead of *EPA Framework for Cumulative Risk Assessment*. Although the process to date has been effective, scientific consensus will probably suffer when preliminary and final decisions are made. This could hinder the acceptance of the any final methodology at the policy level. The framework states "Assessment of cumulative risk through complex exposures is one of the high priorities of the Agency." It also states that, "The issue of cumulative risk is also an important issue with the general public." Although scientists will ultimately conduct epidemiological and toxicological research, the framework for establishing the methodology for cumulative risk assessment should be an equal partnership and collaborative effort with stakeholders.

# Post-Meeting Written Comments From Beth Mileson

**Peer Consultation Comments on the EPA Framework for Cumulative Risk Assessment**

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**General Comments**

The goal of the Framework and the charge to the RAF working group that developed the document are not entirely clear in the draft document. One of the goals mentioned is to present the scientific and technical aspects of cumulative risk assessment in the context of EPA activities without ignoring the real world of total cumulative risks that people and the environment are subject to. Thus the Framework defines cumulative risk assessment in the broadest sense possible, generally equating cumulative risk with "total risk" to an individual or population due to chemical, physical, biologic, and socioeconomic stressors. Included in the consideration of cumulative risk assessment are risk assessment of mixtures, integrated risk assessment as described by the SAB, combined effects of chemical and physical agents, comparative risk assessment, and population-based risk assessment. This all-inclusive concept of cumulative risk makes developing focus for a cumulative risk assessment a daunting task that is not necessarily clarified in the Framework draft.

A second goal of the framework is to help foster a consistent EPA approach for conducting and evaluating cumulative risk assessments, providing operational definitions for terms used in cumulative risk assessments and setting out basic principles. Unfortunately, this document was not developed before a number of EPA Offices were required to consider cumulative risk and developed their own definitions, principles and methods for cumulative risk assessment. Thus the authors are in the awkward position of developing a framework to fit around existing methods, rather than identifying unifying principles for each Office to use as they develop methods for cumulative risk assessment to suit their needs.

The framework might be more useful if the definition of cumulative risk assessment was narrowed to focus on issues related to the EPA activities. Alternatively the broad picture of cumulative risk assessment could be presented in the introduction and the risks unrelated to EPA activities (e.g., traffic accidents, earthquakes) could be set aside for consideration when appropriate, or by an agency other than EPA. In this way, the broad concept of cumulative risk assessment could be presented and structured using a modular approach, as discussed at the peer consultation. In either case, the document should focus on practical guidance for cumulative risk assessment of factors relevant to the EPA purview. The document does emphasize risk assessment of exposures to chemicals, but periodically brings up unrelated hazards (e.g., pgs. 34-35).

**Key Issues, Terms, and Framework Organization**

The discussion of the definition of cumulative risk assessment lends more murkiness than clarity to the concept, and could be simplified. A short simple definition of the word "cumulative" would serve as a good start (i.e., increasing or enlarging by successive addition), followed by adoption of the definition of cumulative risk assessment used by the Council Cumulative Risk Subcommittee (presented on page 9 of the draft).

Sections of the document are too generic to be useful in conducting a cumulative risk assessment and might be modified to account for the unique circumstances of a cumulative risk assessment. For example the section on stakeholder involvement is largely composed of excerpts of other EPA documents and could be modified to capture some of the unique types of input stakeholders may provide for cumulative risk assessment. Other sections that merely review existing methods used by EPA are sections on development of Reference Doses, Reference Concentrations and single chemical carcinogen risk assessment (pages 28-31).

A number of EPA Offices have developed methods for cumulative risk assessment that meet the regulatory or programmatic needs of the Office. Thus in some areas, the state of the science in cumulative risk assessment is well developed, while in other areas, there is little to go on. This is reflected in the draft document in an uneven level of detail, and in Appendix F, on research and development needs. The treatment of R&D needs is simplistic. To be useful the level of detail should be increased or references should be included to provide details.

**Stakeholder Involvement**

Population- or community- based cumulative risk assessment will benefit from stakeholder involvement throughout the process, as discussed in the document and at the peer consultation. Some precautions might be included to make certain that this process does not delay the assessment significantly. Section 2.3 seems to indicate that all participants should agree on the assessment plan before proceeding, but in reality it is not likely that everyone will agree.

**Approaches to Cumulative Risk Assessment**

The Framework includes sections described as general approaches to cumulative risk assessment, though in reality the topics covered are tools that can be used as needed for a given cumulative risk assessment. This was discussed at the peer consultation.

**Uncertainty and Variability**

Uncertainty and variability should be characterized and considered separately throughout the process of a cumulative risk assessment.

**Combining Chemical and Non-chemical Stressors**

Sections 3.2.1.5 and 3.2.2.5 deal in part with the combined effects of stressors that may interact to produce an adverse effect (such as the cumulative effects of inhalation of radon gas and tobacco smoke) and in part with disparate stressors. It might be useful to separate the concepts more clearly in the text.

**Combining Different Types of Risk**

It is appropriate to include a discussion of DALYs and QALYs, and these may be useful in comparative risk assessment, but the utility of these methods in cumulative risk assessment is questionable. Conversion of adverse effects to a common metric is important in evaluating cumulative risks due to multiple chemical exposures, but combining disparate risks is not likely to provide a risk manager with sufficient information to make decisions. The population's health and well-being are clearly at risk due to such diverse adverse events as floods, traffic accidents, and exposure to toxic chemicals, but a single estimate of risk to a population from all these adverse effects combined does not provide a basis for decision-making unless a sensitivity analysis is used to attribute risk to each stressor or groups of stressors (as in a comparative risk assessment).

# Post-Meeting Written Comments From Stephen Olin

Stephen S. Olin, Ph.D.
August 31, 2001

COMMENTS ON THE DRAFT FRAMEWORK FOR
CUMULATIVE RISK ASSESSMENT
EPA Risk Assessment Forum
Review Draft NCEA-F-1098

Overall, the Cumulative Risk Assessment Technical Panel of the Risk Assessment Forum is to be congratulated on the major step forward that this document represents. When the Food Quality Protection Act (FQPA) was enacted in late summer of 1996, some of us in the risk science field were more than skeptical about the near-term feasibility of doing credible, data-driven, science-based cumulative risk assessments as called for in the Act, even given its fairly narrow definition (common mechanism of toxicity) and focus (mainly pesticides). As expected, it has indeed proven to be a daunting task – but progress has been made, data are being generated, methodologies are being developed and debated, and cumulative risk assessments for selected classes of pesticides are moving forward.

The cumulative risk assessments envisioned in the Risk Assessment Forum's draft Framework could be a quantum leap beyond those being done under FQPA. The scope and complexity of the issues that fall within this broader concept of cumulative risk assessment are enormous and, in many instances, unexplored. Yet it is time to begin to think about these issues, to ask these complex questions, and to lay out a course that will encourage and facilitate the dialogue, the research, and the testing of approaches necessary to move this field forward. The need to understand the cumulative impact of multiple stressors on public health and the environment demands it. This draft Framework is a good start.

General Issues

The definition of cumulative risk assessment (p.8) in the draft Framework probably needs some further discussion and fine-tuning. Actually, the definitions proposed by the Science Policy Council for cumulative risk and cumulative risk assessment (footnote, p. 9) capture my view of the appropriate scope and intent of these terms very succinctly. Of course, there are terms imbedded in the Science Policy Council definitions that also need to be defined in the Framework glossary (e.g., aggregate exposures), but there is a distinct advantage in keeping the definitions simple to avoid limiting the scope of cumulative risk assessment unnecessarily and perhaps inappropriately at this early stage its development.

However, having said that, I have one "limiting" proposal to offer that I think would help. I suggest that multi-media risk assessments that involve only a single

chemical or stressor be excluded from the term "cumulative risk assessment". Cumulative risk assessment should imply the consideration of the combined exposures to and effects of multiple stressors/agents/chemicals. Multi-media risk assessments on individual chemicals/stressors can be referred to as such, or another term could be adopted. FQPA-driven risk assessments are referring to single chemical, multi-source/pathway/route exposures as aggregate exposures (see SPC definitions above) and to the associated risks as aggregate risks. The advantage to excluding single chemical/stressor assessments from the term "cumulative" is that it will focus the discussion of cumulative risks on the important, larger issues that need to be addressed, such as interactions of chemical/stressor effects, characterization of multi-stressor effects and risks, and the public health context and implications. Methodologies for conducting single chemical, multi-media risk assessments are much further along than for multi-stressor assessments, and it would be beneficial not to give the mistaken impression that the latter is merely a simple extension of the former by calling them by the same name.

Another smaller point on definitions: the draft document suggests in several places that cumulative risk assessment must be "population-based" or "place-based". While these are undoubtedly the broadest categories for application of cumulative risk assessment approaches, cumulative risk assessments can also be built around a group or class of chemicals. The current work on pesticides under FQPA is the obvious and important example.

The draft Framework at least touches on many of the key issues for cumulative risk assessment. The level of detail in the presentation and discussion of issues is somewhat uneven; there were a number of specific comments on this during the peer consultation, and it is recognized that this is still an early draft. It dwells mainly on chemicals as stressors, which is understandable, but it would be well to expand the scope to recognize the work that is being done in ecological risk assessment and radiation risk assessment and microbial risk assessment and the different issues that arise in considering these risks. These approaches have proceeded along parallel and somewhat independent paths from the work on chemical cumulative risk assessment and have much to offer to the discussion. They may not need to be treated in detail in this Framework but, as examples of other significant classes of stressors and receptors in cumulative risk assessments, they do warrant separate discussion.

On a related point, EPA has had a number of initiatives in recent years related to cumulative risk assessment (although often using different terms to describe it). Some of these are mentioned in the document in passing, but it would be helpful to the reader to have more information on these initiatives. I would suggest that several of these could be described in 2-3 page appendices to the Framework. Examples might include the EPA/OPP work on methods for cumulative risk assessment of pesticides, the OAQPS work on TRIM, and the Risk Assessment Forum's recent work on risk assessment of

mixtures.

There are some other issues that, I think, need to highlighted or added to the Framework:

Data Demands – Cumulative risk assessments will identify the need for many different kinds of data and, often, large quantities of such data. It needs to be clearly highlighted early in the document that this is likely to be a problem. In fact, it may be that, for the near term, identification of critical data and research needs will be the primary function of many cumulative risk assessments.

Variability – There is a section in the draft Framework on uncertainty, but variability is not discussed in any detail. With multiple stressors, the inherent variability in the factors affecting risk increases factorially. Temporal variation in combinations of exposures, spatial exposure variation within a community, and within-population variations in all of the factors affecting vulnerability are complex problems to address, even if extensive data sets were available for modeling. Section 3.2.2.2 talks about "variation of mixtures," but this is such a central issue that it deserves a full discussion and a clear recognition early in the document.

Interactions – There are some paragraphs in the draft talking about the critical issue of interactions. What would be helpful, I think, would be to add a few paragraphs giving the reader a flavor (a taste) of what is actually known about interactions – chemical/chemical, chemical/microbial, chemical/radiation, etc. There is a developing literature on this topic that should be acknowledged in the Framework. On the other hand, it should be made clear that this will continue to be a major research need for cumulative risk assessment (as suggested in Appendix F). This is not the same as developing methods for combining different kinds of risk.

PBPK/BBDR Models – In cumulative risk assessments of groups of chemicals, a key question is, What is the cumulative effective dose to the target tissue, and how can it be expressed for an individual or a population over time? Since this is the type of cumulative risk assessment for which we are closest to obtaining quantitative answers, it would be well to mention the potential value and encourage the development of physiologically-based pharmacokinetic (or biologically-based dose-response) models that can handle multiple chemicals simultaneously.

One of the questions asked of the peer consultants was whether some of the topics presented in the draft Framework are too generic. There certainly are a number of sections that are written in such a way that they could be lifted from this document and placed in any other discussion of risk assessment. Some of these sections probably could be deleted and replaced with an appropriate citation or two, or moved to an appendix; examples are Sections 3.2.1.1 and 3.2.1.2. However, other sections probably should remain in the document because, while the processes or issues they describe are applicable beyond cumulative risk assessment, they are extremely important in population- or community-based cumulative risk assessments; examples are several of the subsections of

Section 2.1. These latter sections do need to be linked to cumulative risk assessment, and one approach might be to add a sentence or two at appropriate points in each of these sections illustrating how the process might play out in such an assessment. It is recognized that this Framework provides an opportunity to pull together material that already exists in other EPA guidance documents but has never been laid out systematically in a single framework.

In fact, the draft document overall suffers from a lack of "for instance" and "for example." There are many broad statements that are indisputable and may bring to mind specifics for the cognoscenti but leave the average reader without a point of reference. More 1-2 sentence follow-ons to these broad statements that would give an example of what is meant or link the statement to cumulative risk assessment would add significantly to the readability of the document.

Even more important, it would greatly enhance the impact of the document if the authors could include in an appendix two or three samples (real or imaginary) of cumulative risk assessments. Details would not be necessary, and each sample could probably be limited to a couple of pages. The idea would be to walk through the process described in the Framework with a specific case, so that the reader could begin to get some sense of how the Framework might work and its practical utility. My impression was that there was a good deal of enthusiasm for this suggestion among the peer consultants.

I do want to acknowledge the evident efforts of the authors to "dejargonize" this document. I appreciate that one does not need 10 years experience at EPA to comprehend the ideas being presented and the approaches being discussed.

Another idea on which there seemed to be general agreement among peer consultants was the value of capturing the Framework in a figure, a process flow diagram that identifies the key components and generic steps involved in doing a cumulative risk assessment. Several models for such a diagram exist, and the outline of a diagram for cumulative risk assessment was drafted by one of the peer consultants during the consultation. Having a process diagram can help the reader to see how the parts fit together. It also provides a frame for building more detail into the process, as necessary, by expanding individual boxes within the diagram or illustrating how cumulative risk assessments with different objectives might play out differently in the Analysis and Interpretation stages.

Another question for the peer consultation was whether the Framework "adequately conveys the state of the science…and the areas that are in need of further research and development." Some suggestions have already been made to improve the coverage of the state of the science and more will be mentioned below, but overall the

draft document at least raises many of the key issues. It doesn't, and shouldn't attempt to, provide a comprehensive resource of scientific data or methodologies for cumulative risk assessment. It might be more complete in its citations of key references. In fact, it cites EPA documents extensively (which is fine) and is weak on non-EPA documents. For example, the discussion of interactions and of available methods would be greatly strengthened by a better coverage of the literature, identifying key papers and good reference books and reviews. [I provided a few examples during the peer consultation, but a focused literature search is needed.]

Appendix F is an excellent start on a list of critical areas of research for cumulative risk assessment. The development of biologically-based dose-response models might be added to the list, including both the "simple" case of multiple chemicals operating by a common mechanism and more complex cases.

Process Issues

The questions posed to the peer consultants on process focused primarily on stakeholder involvement. The draft Framework has a fairly thorough and thoughtful discussion of process for the Planning and Problem Formulation Phase, but the descriptions of the Analysis and Interpretation (Risk Characterization) Phases are focused almost entirely on the technical issues. More attention should be given to process in these latter phases. For example, the document acknowledges the importance of stakeholder involvement throughout a cumulative risk assessment but barely mentions stakeholders in the Analysis and Interpretation Phases. There is a good point made (in Section 2.3) about discussing possible outcomes of the risk assessment during the Problem Formulation Phase and revisiting those possible outcomes as a group (including all stakeholders) during the Interpretation Phase. However, the implication in Section 2.3 that unanimity must be reached among stakeholders on the plan for the risk assessment before proceeding, while certainly a goal, seems too restrictive; there may be cases where the risk assessment must proceed to meet the needs of most of the stakeholders, even if some disagreement remains of the scope or approach.

The document could benefit from further discussion of who are potential stakeholders (perhaps with some examples of how stakeholders may differ for different kinds of cumulative risk assessments). The table on p. 17 seems to me to be deficient in not clearly identifying "the affected industry" as a perennial stakeholder; "business owners" and "trade associations" are too vague.

Regarding the role of stakeholders in the later phases of the risk assessment, some ideas that could be considered, depending on the scope and approach agreed upon in Problem Formulation, are the following. In the Analytic Phase, stakeholders can: (1) suggest sources of data or provide data for the risk assessment; (2) help clarify issues identified during Problem Formulation; (3) work alongside the risk assessment expert to

see what data/assumptions are being used and why, and to understand better how the risk assessment process works; (4) suggest alternate scenarios that may reflect more realistic exposure conditions in the community. In the Interpretation Phase, stakeholders should: (1) understand the outcome of the cumulative risk assessment; (2) ask questions about how best to frame the interpretation; (3) confirm that the cumulative risk assessment has met the goals set in Problem Formulation, or if not, why not; (4) participate in the discussion of next steps and actions to be taken.

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

Technical Issues

I have only a few additional comments on the technical issues discussed in the draft Framework.

The use of biomarkers and biomonitoring in cumulative risk assessment is a good idea, but its application is likely to be limited to some specific cases for the near future. For example, information on the cumulative risks in a local population of a group of chemicals that are toxic to the liver might be provided by selective liver function tests, but causal inferences would have to take account of many other factors that may affect liver function. For more disparate stressors, we will have to learn how to evaluate and interpret broader measures of exposure and effect, a major challenge for cumulative risk assessment. Also, as noted in Section 3.1.3 of the draft document, the use of biomarkers as surrogates can lead to some loss of specificity in information.

The discussions in the document of approaches to cumulative risk assessment probably could benefit from further input from the biostatistics community. There has been some work done in recent years on the cumulative risk question and what is and is not appropriate methodology, and some acknowledgment of the potential pitfalls and problems would be helpful in the document.

The discussion of uncertainty needs to be carried through all three phases of cumulative risk assessment, and the Framework should include a few sentences in each Phase on how that might play out in practice. In addition, a brief discussion of different approaches to uncertainty analysis for cumulative risk assessment would add substance to the section already in the document. Also, as noted above, the significance of variability and its consideration at each Phase in the assessment should be discussed.

Vulnerability is, I think, a useful concept for cumulative risk assessment. Some further examples/discussion of its application in cumulative risk assessment would be helpful.

**********

Two final thoughts:

- Cumulative risk assessment is not only pushing the boundaries of what we are capable of doing technically in a risk assessment; it also is pushing the boundaries of risk assessment into what some have called risk analysis, a domain that begins to consider issues beyond the reach of science, issues of policy and societal values. These are important issues in public health decision making. But we should think about the potential effects of blurring the boundaries. Do we really want to call the broadest applications of the process described in this Framework "risk assessment"?

- A related cautionary reminder is that the planning, conduct, and characterization of a cumulative risk assessment must be perfectly transparent. The process, methodology, data, assumptions, and selection among alternate interpretations must be very carefully documented and very clearly stated in the report of a cumulative risk assessment. The complexity of the problem and the uncharted territory of this new land will demand the highest level of clarity, integrity, and openness if we are to reach our goal.

# Post-Meeting Written Comments From Bill Rhyne

Bill Rhyne

# Comments by W.R. Rhyne on the Draft Framework for Cumulative Risk Assessment

**Comment on whether the *Framework* adequately captures, describes, and reasonably organizes the key issues for cumulative risk assessment? Include in this discussion whether key terms have been identified and clearly defined.**

The concept of a "stressor" is introduced on page 1, but the term is not described until page 17 and much clearer on page 34. A glossary will be added to the document, but I suggest that this term deserves early, clear definition in the text. A discussion similar to that on page 34 is recommended for page 1, particularly the range of physical hazards. Before I got to page 17, it appeared that a stressor was limited to pollutants.

A statement is made on page 58 that the document devotes considerable time to the multiple chemical aspect. I suggest that this statement be introduced much earlier, e.g., in Section 1.1, including the statement that methods and data are not uniformly developed at the present time.

"Hazard Index" is mentioned on pages 25, 44, 45 and 52 but is not described.

**What additional issues, if any, should be covered?**

No comments in addition to those in several places below about physical and other stressors that produce the immediate effects of injury and fatality.

**Keeping in mind that the *Framework* is intended to address issues that are specific or unique to cumulative risk assessment, comment on whether some of the topics presented in the draft *Framework* are too generic for the intended purpose?**

No comments in addition to those in several places below about physical and other stressors that produce the immediate effects of injury and fatality.

**The *Framework* attempts to identify where methods and data are currently lacking or are underdeveloped for application to cumulative risk assessment. Based on a suggestion during the meeting with other Federal scientists, research oriented issues have been highlighted in an appendix to the *Framework*. Comment on whether the *Framework* adequately conveys the state of the science with respect to cumulative risk assessment and the areas that are in need of further research and development.**

Appendix F is a top-level discussion of the shortcomings in the science. It is somewhat abbreviated compared to the level of detail in Section 4.1, but seems to serve its intended purpose.

**Process Issues**

**Stakeholder Involvement Throughout the Cumulative Risk Assessment Process [*Framework* Section 2; especially 2.1.3 and 2.3] Stakeholder involvement is recognized as an important aspect of cumulative risk assessment. The draft *Framework* highlights this involvement in the Planning and Problem Formulation Phase of the assessment. Examples of interested and affected parties are provided and the importance of defining roles and responsibilities is discussed. In addition, the importance of discussing the possible outcomes of the assessment with stakeholders is emphasized. What suggestions do you have for engaging stakeholders early? What kind of background or ground rules would be helpful? What roles and responsibilities would be most appropriate for communities and interested parties?**

The stakeholder section is quite good but can be improved as suggested by panel members. However we should recognize that it is difficult to force meaningful stakeholder participation on an agency. If an agency wants it, they can and will seek it. Conversely, if any agency wants to avoid it, then there is nothing that can be added to this section of the document to force it. This document can heighten the need for such involvement.

A role/responsibility that can be very helpful to meaningful stakeholder involvement is to form subgroups of stakeholders to concentrate on various specific issues in order to (1) understand the technical information, (2) elevate and clarify the stakeholder issues as needed, (3) and convey the facts to their peers. The third item is the key, and this role/responsibility works best in situations in which the stakeholders are reacting to a lack of information and/or a belief that their issues are not being considered.

My experience with stakeholder groups runs from excellent (all the positive attributes discussed by the panel) to nonexistent stakeholder involvement. In the most positive case, the stakeholders are very diverse and spread across the U.S. The issue is not where facilities will be located, but what type of facility will it be. Approximately 80 representatives of a like number of stakeholder groups met and chose five of their members to attend technical meetings of the Army, the

competing contractors, and the National Research Council. The roles and responsibilities described above seem to be working to everyone's satisfaction.

As noted on page 18, technical assistance is being provided. The stakeholders have their own contractor, who as time passes is needed less and less. Substantial travel funds are also provided.

The assistance of an independent review group is invaluable. In my experience the citizens never fail to be impressed that the National Research Council committee is composed of unpaid volunteers, i.e., not contractors paid to support a specific position.

**Using the Results of Cumulative Risk Assessment [*Framework* Section 4.5]**

**The intended use of the cumulative risk assessment should be considered at each step of the process, from Planning and Problem Formulation through completion of the assessment. It is important to recognize that the cumulative risk assessment provides important information but is not the only contributor to the decision making process. How the cumulative risk assessment fits into the decision making process should be addressed when discussing possible outcomes with stakeholders during the planning phase. What kind of information could stakeholders contribute to cumulative risk assessments? Under what circumstances do you feel stakeholder participation is most effective?**

See the above comment.

**Cumulative Risk Assessment in the Broader Context of Environmental Analysis and Decision Making [*Framework* Sections 1.4 and 1.5 and Section 4; especially 4.4.2 and 4.5]**

**An issue related to using the results of cumulative risk assessment is understanding how these assessments fit, both conceptually and practicably, into broader contexts. For example, cumulative risk assessment may be a component of assessing cumulative effects under the National Environmental Policy Act (NEPA). Further, these assessment may support Community-Based Environmental Protection efforts. What are the most appropriate situations for conducting cumulative risk assessments?**

An example of the need for a community-based assessment in my community is the addition of another chemical/radionuclide processing facility, although perhaps

small, to an industrial park. NEPA does not apply in this case, so cumulative effects will not likely be addressed by any group

.

**Technical Issues**

**Approaches to Cumulative Risk Assessment [*Framework* Section 3, especially introduction]**

**There are a number of ways to approach cumulative risk assessment, either starting with the NRC paradigm or using a different approach. Each approach may present its own challenges in methods, data, and analysis. Four example approaches are discussed in the draft *Framework for Cumulative Risk Assessment*: combining toxicity before calculating risk, calculating risk factors, using biomarkers and biomonitoring, and calculating other types of probability statements. Are important approaches missing from this list? Comment on whether there is a better way to organize this discussion on approaches to cumulative risk assessment.**

The above list omits "calculating risks for individual stressors and then combining them" that is discussed on page 24.

I found Section 3 to be a little difficult to digest. Section 3.2 is 17 pages long and the three parallel sections (3.3, 3.4 and 3.5) are to be provided later. Some of the material in Section 3.2 is likely to apply to the missing sections, and it is likely that Section 3 will have to be recast for this reason alone. At a minimum, Section 3.2 needs a "tell 'um what you are going to tell 'um" introduction.

"Other" is too broad for the title to Section 3.1.4. "Reduction in Life Expectancy or Quality" would be better.

The penultimate sentence of Section 3.1.4 is confusing. It is not clear whether "this" refers to QALY or to both LLE and QALY. Also the "second approach" should be clarified to be the second of two approaches in Section 3.1.1 not the second general approach presented in Section 3.1.2.

**Using Biomarkers of Exposure or Effect [*Framework* Section 3.1.3]**

**Among the approaches to cumulative risk assessment discussed in the draft *Framework*, use of biomarkers and biomonitoring information shows promise for providing an integrated measure of where an individual falls on the continuum between exposure and effect. However, existing methods are**

**inadequate for assessing complex situations involving a large number of stressors. Further, experience using biomarkers and related information in decision-making is limited. Comment on the discussion of biomarkers of exposure and effects? Given the current state of the science, discuss the utility of this approach in the near term and in the future. Does the *Framework* include the appropriate level of discussion of this topic? How can the discussion be improved (consider, for example, whether the *Framework* discussion adequately characterizes how biomarkers can be used with more traditional risk estimates)?**

No comment.

**Uncertainty in Cumulative Risk Assessments [*Framework* Section 4.3]**

**Uncertainty analysis is an important aspect of risk assessment (and policy analysis in general). However, historically, dealing with uncertainty has been a short-coming 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 thought this section was a very good overview and contained about the right amount of detail. One way to improve it would be to give examples of each end of the uncertainty spectrum: (1) large but unknown uncertainty and (2) the ability to express various uncertainties as mathematical distributions.

**Vulnerability [*Framework* Section 3.2.1.6]**

**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. 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?**

This is not my area of expertise, but the discussion seemed reasonable.

**Combining Chemical and non-Chemical Stressors [*Framework* Sections 3.2.1.5 and 3.2.2.5]**

**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?**

These sections address a complex problem. Radiological effects can be, but are only rarely, large enough to be immediate, rather it takes years for cancer to develop. In this sense radiological risk is similar to chemical risk.

Physical hazards, on the other hand, are of concern due to their immediate effects: injury and fatality. Physical hazards include mechanical forces from accidents (both transportation and processing accidents) and the forces due to fireballs, explosions, and so forth. Chemical spills directly on the skin and airborne exposure greater than IDLH (immediately dangerous to life or health) are additional stressors that produce an immediate effect. The exposure can be occupational and public. I recommend providing the reader with a better understanding of this type of "other " stressor. A discussion similar to that on pages 48 and 49 for quality-of-life stressors is needed.

Analysis of immediate effects is relatively straightforward, whereas, as noted in Section 3.2.2.5, stress and quality-of-life issues are not straightforward to evaluate.

Appendix A is referenced in Section 3.2.2.5 as further reading relevant to determining exposures to non-chemical stressors. The last paragraph mentions the increased likelihood of vehicular accidents, but it is not clear whether the context is

transportation-induced chemical spills or the occurrence of physical stressors. It should be clarified.

Appendix A.2 addresses resources relevant to exposures to non-chemical stressors and is incomplete, i.e., no mention is made of physical stressors that result from transportation or process accidents. Data is generally available to address these stressors. References for process safety and risk could be added from Appendix D of 29 CFR 1910.119, *Process Safety Management of Highly Hazardous Chemicals*.

Transportation accidents may produce multiple stressors: small spills, large spills, and physical. The physical stressors can result in property damage, injuries, and/or fatalities. (Note that a spill can produce a physical stressor, e.g., an LNG spill can result in a fireball producing heat and mechanical forces.) To put these stressors in context, the conditional probabilities, given a heavy truck accident, are approximately: 0.2 for an injury, 0.05 for a small spill, 0.02 for a large spill, and 0.01 for a fatality. The truck injury and fatality data are good on a global large truck basis, but the spill values are soft (many packaging variables). The point is that transportation physical stressors can produce (1) an immediate end point, an injury, that is about the same probability as a small spill and (2) an immediate end point, a fatality, that is about the same probability as a large spill.

Process accidents can also produce small spills, large spills, and physical stressors; see 29 CFR 1910.119.

**Combining Different Types of Risk [*Framework* Section 4.1.3]**

**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 in this section capture the state of the science in the 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.**

The problems are stated at a level appropriate for this top level document. Some details on the indices in Section 4.1.3.2 would be helpful, but references are given for the curious.

**Limits on the Information Provided by Cumulative Risk Assessment [*Framework* Section 2.3]**

**There are many factors that place limits on what can be learned from a cumulative risk assessment. These include: how the problem is defined during the Planning and Problem Formulation phase, what data are available for the assessment, what models are available for the assessment, and what resources are available for the assessment (e.g., expertise, time, financial support, etc.). The adequacy of existing data may be a key factor limiting the results of a cumulative risk assessment. One outcome of the assessment may be the identification and prioritization of data gaps and research needs. This also applies to the availability of models for the assessment. Comment on the *Framework's* attempt to characterize the limits that may be encountered when using cumulative risk assessment in the decision making process. What can be added to improve this discussion?**

No comment.

**Distinguishing between Cumulative Risk and Cumulative Impacts [*Framework* Sections 4.4 and 4.5]**

**The *Framework* attempts to clarify how cumulative risk assessment relates to community assessments and decision making. In particular, the *Framework* emphasizes that cumulative risk assessment is only a portion of the information needed for decisions. Other factors such as employment and quality of life are considered for many decisions. When these other factors are brought into the assessment, the approach is often called cumulative impact assessment. Comment on how well the framework distinguishes between cumulative risks and cumulative impacts. Are the two concepts well characterized? How can the discussion be improved to clarify the role of cumulative risk assessment in the assessment of cumulative impacts?**

This section is quite good, but it does not discuss cumulative impacts - only cumulative risk.

# Post-Meeting Written Comments From Jennifer Sass

Peer Consultation Workshop -- Review Draft Framework for Cumulative Risk Assessment
(NCEA-F-1098; August 2, 2001)

Meeting held August 22, 23 2001.
Arlington, VA

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EPA deserves much credit for tackling this tremendous task, and as a draft document, the Framework is an extremely important initial step. The Framework is a very inclusive document, with an appropriately large amount of flexibility which will necessarily give it great utility in its applications. It draws from a number of previous documents, and provides a useful overview of the historical development of cumulative risk analysis. I commend the writers of this document for both tackling such a grandiose task, and for including peer review input so early in the process.

I felt that the Peer Consultation Workshop was extremely beneficial, and provided expertise drawing from technical, theoretical, and practical knowledge. Surprisingly, there was much consensus during the two day discussion, and many concrete suggestions for improvement. I feel confident that with the incorporation of the panel suggestions, and further work by EPA, the document will take on the shape of a Framework. I thank the EPA for including me in the consultation process, and look forward to future versions of the Framework.

*I. Overarching Issues*

The document needs to provide a framework that is clear. As it stands, the document provides a review of existing risk methodologies, but does not lay out a clear framework which is specific to cumulative risk assessment, and tangible. A schematic (flowchart, matrix, etc.) would be extremely helpful, possibly with some examples which might help the reader to grasp the utility of the framework. A framework must be something that both frames the methodology, and can be worked with.

The framework, when defined and presented, should be able to accommodate large and small scale cumulative risk assessments, such as community projects, chemical family assessments, etc. Within

the framework, each step could include both the question, the criteria which would constitute an answer to the question, and some examples of answers.

Variability and uncertainty should be defined at the beginning of the framework, and then carried throughout the framework, with the goal of providing a risk assessment which considers the protection of the population at all stages.

Given the Agency's desire to move towards a pro-active approach to Cumulative Risk Assessment, it would be prudent to establish a database or National registry in which information on morbidity and mortality were cross-referenced with information on occupation. This would require all death certificates to list primary occupation as standard information. After all, science has identified almost every known carcinogen from the death certificates of workers. This information, while so obviously important in identifying risk factors leading to disease and death, is noticeably absent from all cancer and occupation registries.

*II. The Process*

It is important to include stakeholders, particularly community groups, environmental activists, and public health professionals, early in the process of Cumulative Risk Assessment, to help define the problem, and to help identify stressors, sources, pathways, etc. However, while including stakeholders throughout the risk assessment process, it is important that EPA maintain discretionary power regarding the incorporation, if at all, of stakeholder input. Without this caveat, there is a concern that powerful stakeholders, with financial interests in the outcomes of the risk assessment, would have the potential to bias the assessment outcome towards profit goals rather than health or environmental protective goals.

It is important to provide a "level playing field" whereby all stakeholders have equal access to the resources required to play a meaningful role in the risk assessment. These resources would include access to software, technical expertise, consultants, etc.

The risk characterization step would be better placed early in the process, to ensure that the desired outcome of the assessment is identified early, and then the analysis process is designed/chosen to obtain the desired outcomes. The risk characterization process needs to focus on a given question, for a given application, early in the cumulative risk assessment. To this end, the time frame (deadlines, etc.) and criteria for acceptable outcome decisions should also be defined, to the level that this is possible. This would allow the cumulative risk assessment to be useful as a planning tool consistent with the EPA goal of moving towards more pro-active community planning.

*III. Technical issues*

Some discussion regarding methods for harmonizing cancer and non-cancer approaches is needed.

Some discussion regarding the use of epidemiology for use with analysis is needed. Ecological epidemiology might be particularly useful in providing estimates of population risks, and should be discussed. The use of ecological data for decision-making should be discussed. This may include its use in identifying and quantifying background exposure levels, from all sources, within a population.

Much discussion, and examples, regarding methods for assessing qualitative stressors (nutritional status, access to health care, etc.) is needed. Examples from European methods could be discussed. Methods and approaches for the inclusion of value judgments and qualitative data should be a key component of the Framework.

The importance of background or baseline exposure data should be more explicitly discussed, including methods for assessing it, and for incorporating this information into a Cumulative Risk Assessment Framework.

The Framework should include methodology and approaches for identifying uncertainty. This could be included within the schematic Framework, such that the limitations of the methods are identified initially, and then, given the limitations, what can be learned, and what cannot, with the given methods.

An expanded discussion of biomarkers is warranted, given their increasing usefulness. Their use early in the risk assessment process, to obtain a "basic health indicator" of the actual cumulative assault on a person, regardless of source, warrants discussion. Biomarkers may be used for surveillance and biomonitoring on a chronic basis, and can help define background exposures. Likewise, their current limitations deserves discussion.

# Post-Meeting Written Comments From Margo Schwab

Margo Schwab

# Peer Consultation on Technical Issues Associated with Developing a Framework for Cumulative Risk Assessment

## Margo Schwab's Comments, Ideas, Vision for Document

### I. Over Arching Issues

#### A. Title

In light of the extended process for achieving this framework, both from a process and from a technical perspective, consider changing the title to "*An Evolving Framework for Cumulative Risk Assessment*."

#### B. Goals

The goal(s) of the document should be stated clearly in the first section (see suggested reorganization below), and then reiterated in the concluding section of the document. As it currently stands, a variety of different goals are stated throughout the report. The conflict among the goals is confusing, and is reflected in the changing tone of the text in throughout the document. Keep the goals narrow.

#### C. The Framework

Currently it is not clear what the "framework" is. See comments under "proposed reorganization."

### Proposed Reorganization

***1. Introduction***:

i. Begin by *defining* what cumulative risk assessment is, rather than with history [the current beginning focus on the evolution of risk through various EPA documents is distracting and not useful until the concept is defined clearly.] Instead, focus defining cumulative risk assessment as a tool to inform the decision-making process. Discuss what is special about it: it is designed to take into account a broad variety of stressors. See proposed Figures 1 and 2 as aids in laying out the array of stressors that are of concern and the array of types of

cumulative risk assessments that might be conducted, from narrow to broad. In defining the concept of cumulative risk assessment, clearly state its goals and limitations (in a general way). The current discussion attempts to make cumulative risk assessment "all things to all people" and to answer to too many of our problems.

ii. Next, set the *need* for this framework in its policy and historical context. Set up the framework as the vision for the future. The movement in society toward a more inclusive (holistic) approach to defining problems, in part as a result of our realization that public values are as important as science; in part due to our improved scientific understanding of multiple routes of exposures, effects at low levels of exposure, and common mechanisms of action as well as understanding that many diseases are multifactorial, thus a multi-risk factor approach is needed. Talk about our increasing understanding of the importance of stress in the body's ability to fight disease, thus the importance of including multiple stressors.

It is here that the various EPA and NAS documents might be sited as evidence of the evolution in both science and process. It is here that the 1983 NAS Red Book paradigm should be introduced as being pivotal to defining the risk assessment process until now, but that conditions have changed, and the needs (stated here) require an evolving approach. In essence, ***emphasize that the cumulative risk framework is charting the future of risk assessment***. Introduce the idea that the goal of setting up a "framework" is to show how the concept of cumulative risk assessment can be applied in a wide variety of contexts (give a few examples, like FQPA and superfund sites, as well as community driven concerns).

iii. Next state the *goal*(s) of the document. Keep the goal narrowly focused on setting up a framework. Again, highlight what the document will cover (how one approaches a cumulative risk assessment) and will not cover (e.g. implementation/protocols/decision making frameworks).

iv. Present the *framework*. What is referred to as "The Framework" can be presented as having three levels of detail:

The first level is depicted in Figures 1 and 2 – the concept that multiple stressors define the context of a problem. . Give examples of classes of stressors: chemical, biological,

physical, economic, social/political, cultural, etc. Introduce the concept of vulnerability (Kasperson's four types).

The second level is depicted in the three steps: problem formulation, analysis, and interpretation/characterization (proposed Figure 3). Outline the key purpose of each of the three steps.

The third level depicts what is included in each one of these steps with respect to decisions that must be make and potential stakeholder roles (proposed Figure 4)

In this subsection, discuss *why* each component of the framework is important. Set this up as a guide for the next three sections of the report.

### *2. Problem Formulation Phase*

Walk through this section as a series of decisions that must be made, the purpose of those decisions, examples of decisions, and the implications of those decisions for the subsequent steps in the process. The current discussion of the importance of addressing the desired outcome during this phase is essential, and should be highlighted earlier. Specifically, it is important to emphasize that the purpose of the analysis determines the type of characterization that is appropriate, which in turn influences the type analysis approach chosen.

The current document talks about defining a conceptual model – this is very good; keep it and give some graphic examples of such models.

The current focus on process is good, but is sometimes distracting. Perhaps tie it all together by beginning the section by saying that there are three sets of issues that will be covered:

i. the decisions to be make.
e.g., the definition of the problem, the goals of the analysis, which stressors to included, the time frame for the entire process, etc. Most of these are included in the current discussion, however they get lost in too much text and not enough "to do" lists.

ii. the process for going about making the decisions.
e.g., discuss the definition and importance of stakeholder involvement and how to make determination regarding who it is appropriate to include in this situation, the role of

the stakeholders, and the need to provide technical and/or financial resources to allow this process (see comments below under "process issues").

iii. the criteria that should be used in making those decisions e.g., level of uncertainty that is acceptable, implications of vulnerability and variability, the state of science, how the results will be used, etc.

I'd like to see the detailed discussions of vulnerability and uncertainty that appear in the "Analysis" section of the current document moved up to this section. It should be made clear that both of these concepts/concerns must be addressed in this first phase, and their significance carried throughout subsequent phases.

### *3. Analysis Phase*

This section is currently twice as long as it needs to be. Keep the focus on the approaches available and their strengths and weaknesses of each . Discuss how these approaches advance the more traditional one-pollutant and one-stressor paradigm. Stay away from equations and jargon. See detailed comments under "technical issues."

### *4. Characterization and Interpretation Phase*

This section should be shortened to about one-third of its current length. It is highly redundant with other parts of the document, and contains too much speculation. Rather, tie it strongly the problem formulation phase – bringing the significance of the decisions made full circle. The specifics should reflect the organization of the "approach" section. If there is little technical detail/protocol in the analysis section (as I recommend above/below), then much of the technical detail can be removed from this section.

## E. Level of Detail

As commented upon by many of the reviewers, the level of detail is uneven. Suggestions include:

1) Remove much of the detail from Section 3.2 (see comments under technical issues).

2) Throughout the document, each of the issues discussed in "generic" terms (i.e., not specifically limited to

cumulative risk assessment), should be discussed in terms of how the issue is particularly relevant to cumulative risk assessment. An example here is with "stakeholder involvement" (see comments under process issues).

3) Finally, it is important throughout the document to use examples to illustrate each of the points made. You might choose to use two examples each time – one for a limited scope assessment (e.g., an FQPA type assessment) and one from a broad-based assessment that includes many types of stressors. This would show the range of applicability of the concepts. There should be few concepts in this document that are limited to only one end of this spectrum or the other.

**F. State of Science**

The state of science in unevenly documented. Areas that need improvement include:

1) Most of the science documented is quantitative. Little emphasis is put on the value of qualitative methods or the approaches available.
2) The value of community-based health studies and the role of epidemiology in general is missing.
3) Our recent understanding of how non-chemical stressors influence our ability to fight disease, thus the dose-response curve is not highlighted.

## II. Process Issues

### A. Stakeholder Involvement

The baseline information on stakeholder involvement is appropriate – i.e., the process is set out in a manner consistent with the Presidential/Congressional Commission Report (1997). However, I encourage you to articulate more clearly the *particular* importance of stakeholder involvement within the context of "the cumulative risk assessment framework." Specifically, that without stakeholder involvement in determining the problem that the assessment will address; which stressors to include; the level of uncertainty considered acceptable; the type of results (quantitative versus qualitative); and the schedule for completion of the assessment, the "cumulative risk assessment framework" is not only inadequate, it is destined for failure.

Given that this is a framework intended to provide EPA with guidance, the extent and limitations of stakeholder involvement should be specifically addressed. The issues identified below can help guide a *positive* involvement process rather than simply insuring involvement:

**Who is Involved:** The key issues associated with determining who is a stakeholder should be discussed: give examples of cumulative risk assessments in which the stakeholders do not include the "general public," for instance permitting processes, and other examples in which the stakeholders include multiple, competing community groups, multiple government agencies and levels of jurisdiction, etc. The point here is that the breadth of stakeholders invited to the table should be tailored to suit the situation.

It might also be worthwhile to provide a little guidance about which individuals are invited – that in order for the process to be productive, it is necessary to choose those who have a genuine interest in solving the problem and who are willing to engage in a dialogue.

**Extent of Involvement:** The trade offs between extent of involvement and delay in producing information should be discussed. Examples should be given to highlight situations in which there is an urgency for a decision, and thus extensive involvement can hinder the process and, at the other end of the spectrum, situations in which the schedule is more flexible and the stakeholders have the technical knowledge and understanding to participate at a very deep level.

The decisions which are *most* important for stakeholder involvement should be identified, and examples given as to why this involvement is essential.

The extent of involvement possible by community groups and the general public will depend upon their technical and financial resources. If a level playing field is sought, the Agency must provide a mechanism to support and/or facilitate contributions from groups without the necessary resources.

It should be explicitly stated that EPA is inviting stakeholders to provide input, but that the final decisions regarding each step in the process are the purview of the Agency.

**B. Using the Results of Cumulative Risk Assessment**

I agree with the gist of the discussion on pages 60-61 – that if the problem must be formulated to address a specific question; if this has been done, the results will provide guidance in addressing that problem. Currently, however, the section is not succinct; it is redundant. Since this section also serves as the conclusion to the report, it might be set up as Section 5 (rather than the last subsection of Section 4). As such, the format would be to link back into the points discussed in the first chapter, and the schematics used therein. The text currently does this – I a suggesting making the link even stronger and clearer. Similarly, the point about the "use of the results" should be made in Section 1, thereby ending the "framework" by going back to the "scope" set out at the beginning of the document.

**C. Cumulative Risk Assessment in the Broader Context of Environmental Analysis and Decision Making.**

See discussion under "overarching issues."

**D. Add A Section:**

Discuss the resources that the Agency must develop to facilitate the implementation of this framework, including expertise in epidemiology and social science, as well as collaboration with Federal and State agencies. Also discuss the need for a targeted research agenda to address specific questions raised in this document (gaps).

## III. Technical Issues

### A. Approaches to Cumulative Risk Assessment

Section 3, the description of the "analysis phase," might be reorganized as follows:

Begin with a one-page discussion of how the traditional "red book" paradigm is used to "analyze" risk [note: per my comments under organization in the "over arching issues section, the paradigm would have originally be introduced under the "historical context" subsection of Section 1.] Opposite this one-page description of how one analyzes risk per the red book paradigm should be two figures: one of the "four step" process, and one that lists the key activities and decisions associated with each of those four steps. The text would focus on describing these two figures. Concepts such as dose-response, extrapolation, exposure, pathways and sources would be introduced and defined in this document, but actual methods such as the RfD, the linear no-threshold model, BMD, etc would not be introduced or defined in this document. This page would end with a description of the limitations of this analysis approach, both for combining multiple chemical and for combining multiple stressors. These limitations would highlight the state of science regarding mechanism of action as well as combining chemical and non chemical stressors, etc. A brief introduction to the issues listed in Section 3.2 can be included here (e.g., temporal trends). Reiterate issues of uncertainty here – that the traditional red book paradigm is full of uncertainty; it is compounded each time another chemical and stressor is added.

The next section would begin with general approaches to the shortcomings of the traditional approach to risk assessment.

#### 1) Qualitative Approaches

A variety of qualitative approaches are available. Below I note two; a comprehensive review of the social ecology literature is likely to turn up more such indicators. Also see the Health and Environment Analysis for Decision Making project of the WHO/UNEP, discussed in "Linkage methods for environmental health analysis" WHO/ENG/95.26 ed by D. Briggs, C. Corvalan, M Nurminen. 1996.

The attached adaptation of Figure 2 from Sexton et al 1992 (see ref below) shows the conceptual paradigm underlying the prioritization of environmental health problems. The highest ranking problems are those with elevated exposures and very toxic pollutants; conversely, the lowest rankings are for contaminants with low exposures and low toxicities. This matrix approach can be expanded to include any number of additional

stressors, including underlying health status (e.g., based upon cancer statistics), demographic characteristics that influence sensitivity and susceptibility (e.g. % elderly), economic status, etc.

Look at the entire issue of Archives of Environmental Health from November/December 1992; volume 47, No. 6. Especially: Sexton et al "Estimating Human Exposures to Environmental Pollutants: Availability and Utility of Existing Databases, pg 398 and Burke et al., Role of Exposure Databases in Risk Management, pg 481

The qualitative indicators provided by such matrices can be communicated using geographic information systems. Displaying complex multi-dimensional matrices in a map can help visualize locations of areas with multiple stressors.

Furthermore, geographically based measures of hazard are potentially useful cumulative measures – although they do not provide information on the risks, the locations of hazards can be used as an indictor of cumulative exposures, thus risks from all of the potential chemicals associated with that site. The environmental justice literature has used this approach.

Within this context, a semi-quantitative approach to cumulative risk assessment was demonstrated by Dr. Jill Litt in her recent dissertation. She demonstrated that it is possible to identify high risk populations using information on the location of brownfields, in conjunction with health and demographic statistics. [additional information on this dissertation is available from her advisor, Dr. Thomas Burke].

**2) Inherently Cumulative Measures**

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

identifying the underlying vulnerability of a population and by generating hypotheses regarding the determining relative contributions of multiple stressors.

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

Biomarkers are inherently cumulative risk measures, thus they would be discussed under this category.

**3) Common Denominators**

This category of measures would include those associated with assigning a common measurement to all costs and benefits associated with a particular situation. Common metrics include money, time, and effort. Use of a monetary metric is based on an implicit faith in the markets. Examples of approaches to quantifying non-monetary costs and benefits include: expressed values (willingness to pay or willingness to accept); human capital costs (year potential life lost); or costs to society (friction costs).

The current discussions of the DALYs, etc. would feature in this section. These measures need to be described more clearly, and linked to the concept of cumulative risk.

**4) Mathematical Models**

Discuss options that range from the simple additive model of toxicity that uses traditional risk assessment methods, to complex synergistic approaches.

The recent dissertation of Dr. Mary Fox suggests that you can use cumulative toxicology to characterize community health. Dr. Fox uses a multiple health end point data base to characterize cumulative risk. She found that her total hazard ratio risk score, created from this data base was correlated with estimates to Years Potential Life Lost (YPLL) and

mortality rates at the census tract level. [information on this project is available from her advisor, Dr. Thomas Burke]

Another subtopic under mathematical models would be the use of epidemiologic studies to predict effects from multiple exposures. This is the "risk factor" method discussed in the current document. The current discussion requires a re-write by an epidemiologist, with particular emphasis on differentiating between conclusions at the individual level versus the population level. See my comments in the text of the document.

5) **Others**?

Emphasize here the need for new, creative approaches – that one should not feel tied to these approaches, as the science and process will only progress with innovation.

Each of the approaches set out here should be linked to a separate box that lays out the strengths and weaknesses for dealing with uncertainty, cumulating across types of stressors, vulnerability, variability, interpretation, and quantification of that approach. The text associated with each section (a maximum of two pages each) would just enough to provide the information necessary for choosing an approach, not implementing that approach. An example should be presented of a situation in which each of the approaches might be of value.

All of these approaches are amenable to application to a broadly defined assessment with multiple stressor or a narrowly defined assessment with a single stressor.

*General comments*:

The most of Section 3.2 should be eliminated. This section is too detailed for a framework document (the person reading this document should not have to understand dose response at this level of detail). This information is better presented elsewhere (in other guidance documents). Furthermore, this presentation puts too much emphasis on quantitative results and on using the techniques traditionally used instead of setting out a framework that provides the leeway for creative new approaches.

**B. Combining: Chemical and Non-Chemical, Risks and Impacts, Types of Risks**,

This should not be a separate section; rather the framework should be generic enough to apply to any such combination of stressors, risks, or impacts. Rather, what the document should do is identify approaches that are more likely to be of value in combining different sorts of information (e.g., if one is doing an FQPA type analysis, a mathematical model would be more appropriate than a qualitative matrix, whereas a qualitative approach may be the best option for an assessment designed to set priorities.) See above discussion of qualitative approaches; need for innovation, etc.

Note: Sixteen pages of unnumbered attachments follow. Next numbered page is G-111.

# Figure 1

Schwalis comments & articles received 8/30/01

Disease is multifactorial thus risk of disease is a function of multiple stressors. Some of these stressors influence underlying health status; others influence only ones vulnerability to a specific exposure.

risk = f ( economic, social/polit., behavior, psychosocial, physical, chemical, biological, etc ... )

Example:

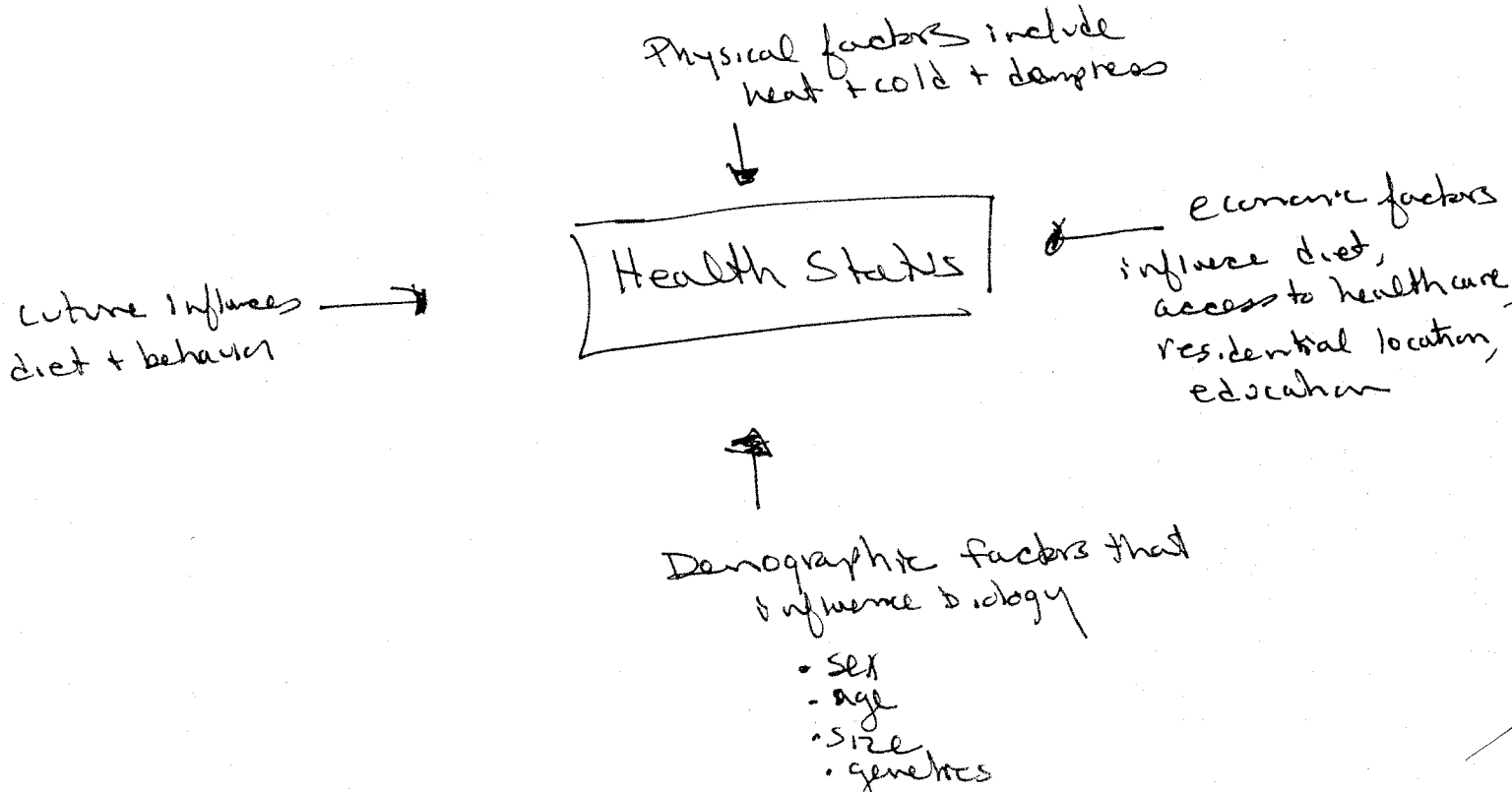
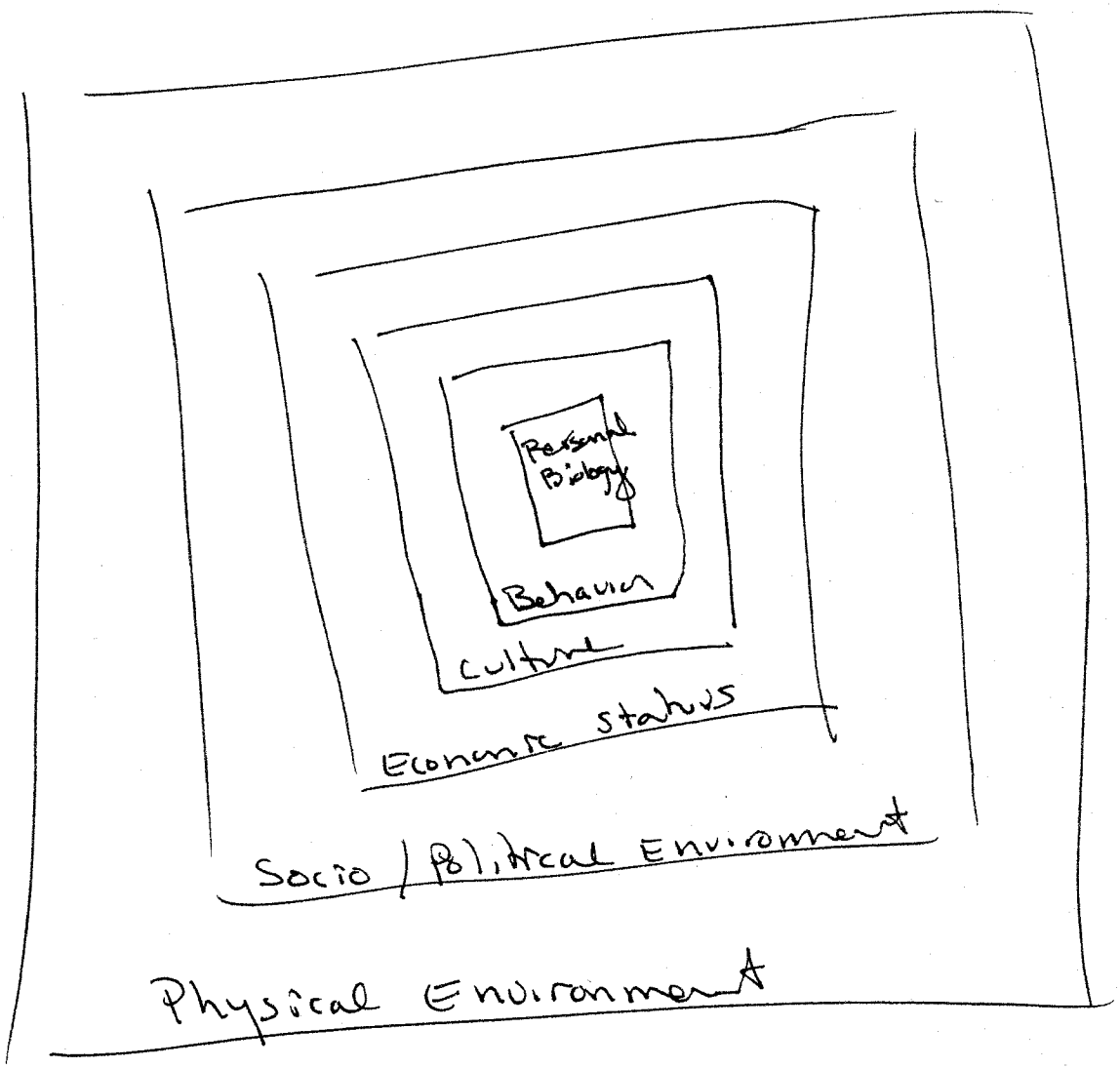


Figure 2




Each of these boxes contains a series of stressors that influence a progressively ~~smaller~~ more specific subpopulation. ^ Chemical Exposures must be considered within this broad context of the effects of one's total environment.

Figure 3

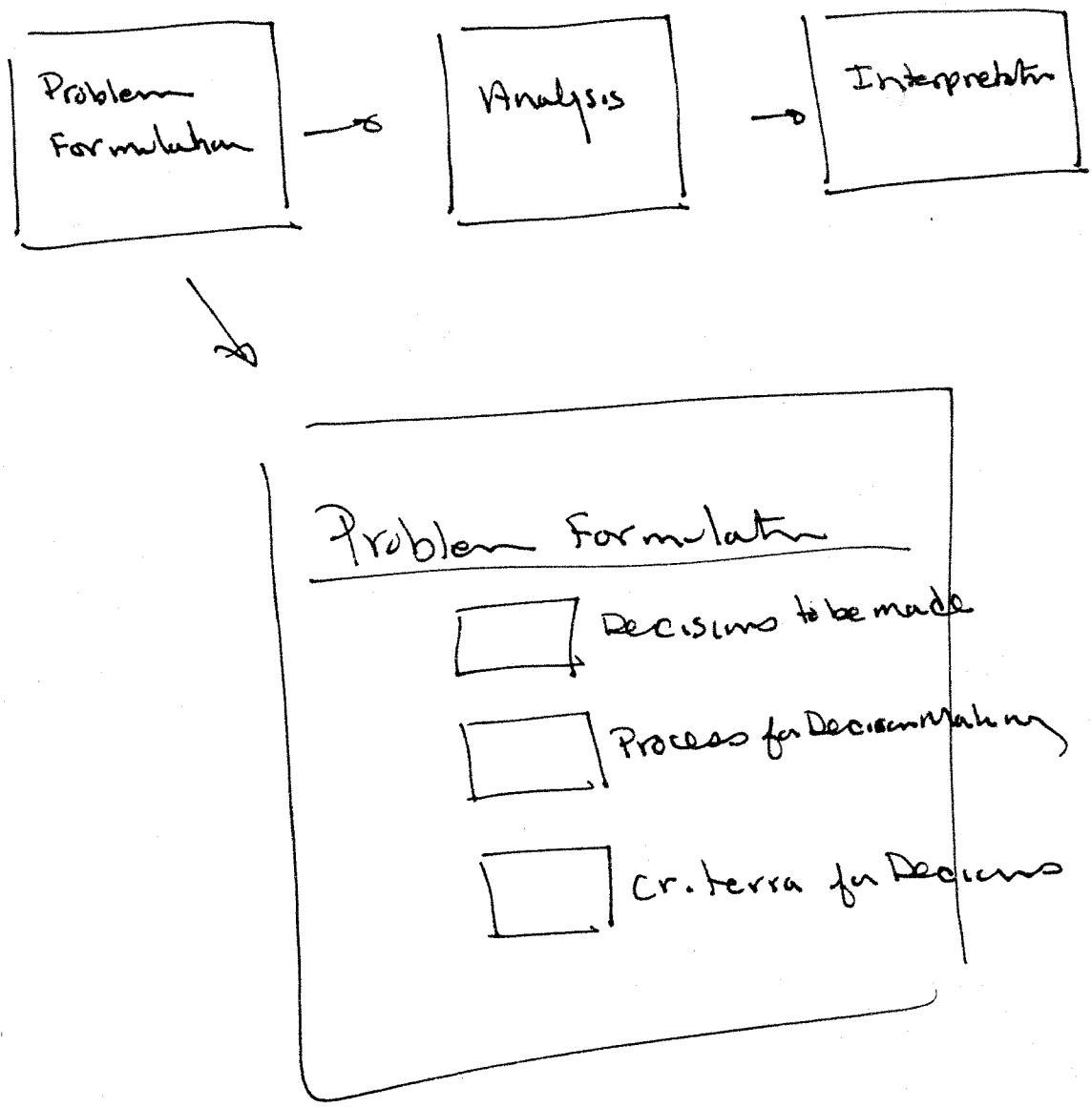
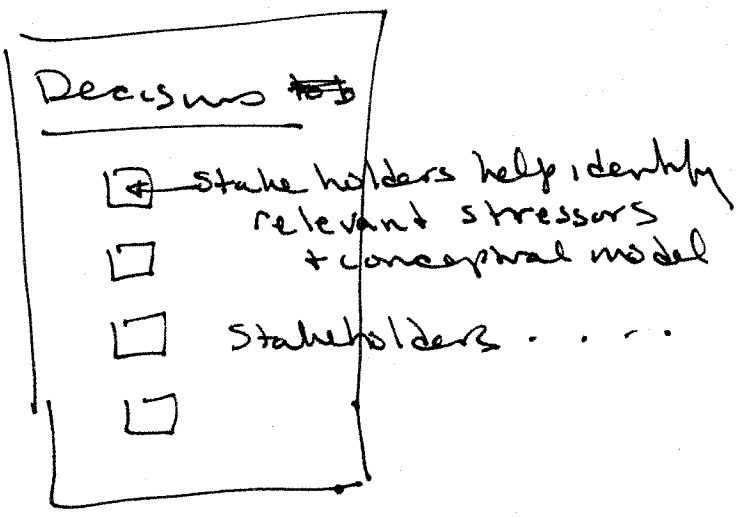



Figure 4



Model for Qualitative Approach

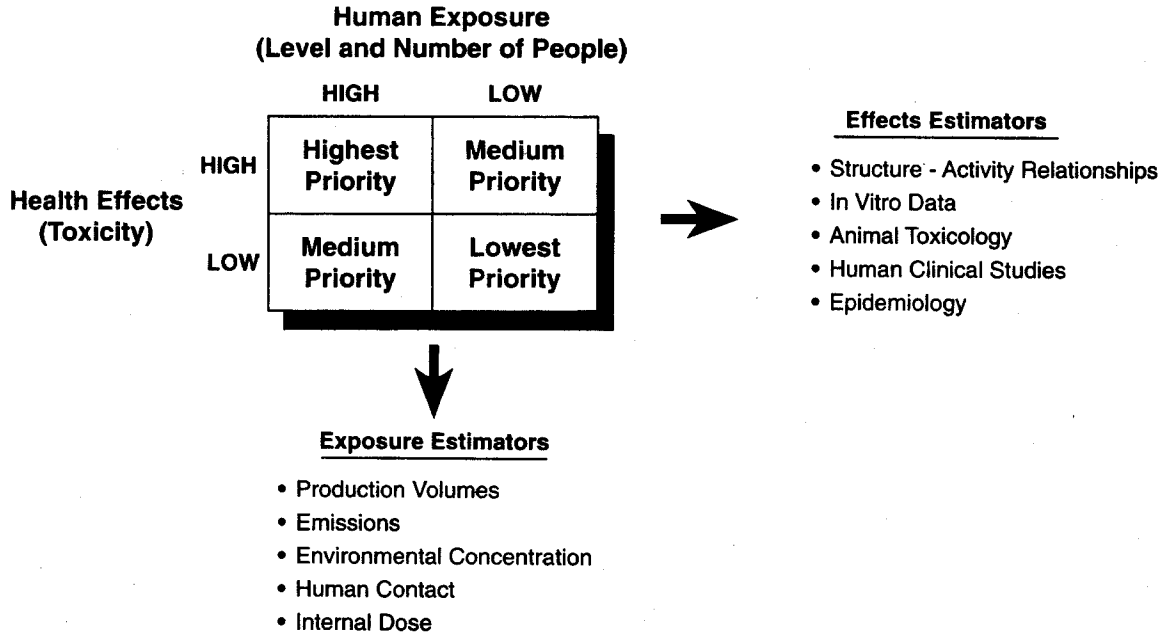
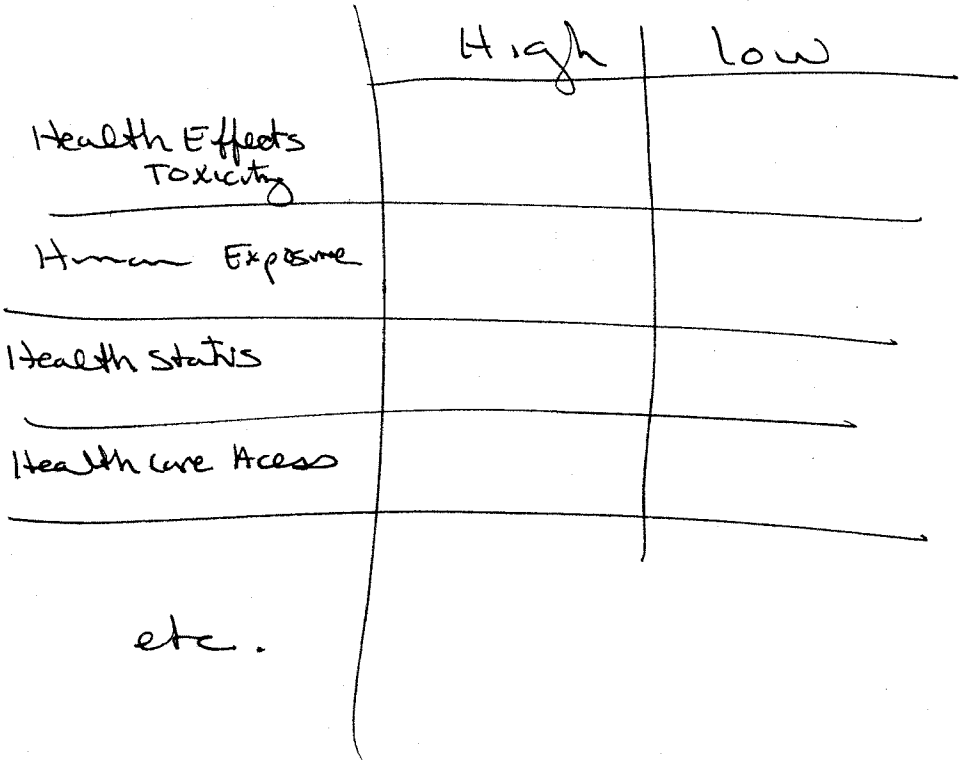



**Fig. 2. Conceptual framework for setting environmental health priorities.**



# Estimating Human Exposures to Environmental Pollutants: Availability and Utility of Existing Databases

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**ABSTRACT. Information about human exposures to environmental agents is a crucial component of informed decisions about protection of public health. Results from an inventory of exposure-related databases are used to examine the value of exposure information for risk assessment, risk management, surveillance of status and trends, and epidemiologic studies. Findings indicate that current and future exposure-related databases should include (1) standardized procedures for the collection, storage, analysis, and reporting of data; (2) an enhanced ability to compare data over time, i.e., conduct comparison studies of "old" and "new" methods; (3) mechanisms for coordination and cooperation among public and private-sector organizations with respect to the design, maintenance, exchange, and review of information systems; (4) measurements of actual exposures and dose for relevant human populations; and (5) data collection, storage, and retrieval methods that permit easy manipulation of information for both model building and testing.**

DURING normal day-to-day activities, everyone comes into contact with environmental pollutants, i.e., breathing of air, drinking of water, consumption of food, and encounters with soil or dust. This contact between people and pollutants, termed *exposure*, requires the simultaneous occurrence of two events: the presence of a pollutant in an environmental medium (e.g., air, water, soil, food) and contact between a person and that medium. More precisely, environmental exposure is defined as contact between the outer boundary of the human body (e.g., skin, nose, and throat) and a pollutant or pollutant mixture. It is quantified by reporting the concentration of the pollutant and the time of contact.[1]

Four basic characteristics describe exposure: (1) Route—do exposures occur by inhalation, ingestion, or dermal absorption? (2) Magnitude—what is the pollutant concentration (e.g., parts per million, micrograms per cubic meter, milligrams per liter)? (3) Duration—what is the duration of exposure (e.g., minutes, hours, days, lifetime)? and (4) Frequency—how often do exposures occur (e.g., daily, weekly, seasonally)? Although magnitude (i.e., concentration) is the most commonly reported parameter, exposure data are

more useful when expressed as a concentration over some specified time (e.g., ppm/h, mg/l · d).

Exposure is a key element in the chain of events that leads from release of pollutants into the environment to a concentration of the pollutant in one or more environmental media, to actual human exposure, to internal or delivered dose, and ultimately to environmentally induced disease or injury. This series of events (Fig. 1) serves as the conceptual basis for understanding and evaluating environmental health. Actions taken by society to protect its members from the harmful health consequences of pollution are based on established or postulated links between pollution sources, human exposures, and adverse health effects.

Estimation of health risks associated with environmental pollutants is composed of two primary activities: (1) exposure assessment and (2) effects assessment. During exposure assessment, the initial portion of the event chain is evaluated (Fig. 1), i.e., sources of pollutants, media concentrations, exposures, and dose. A major goal is to estimate exposure levels and the number of persons exposed (e.g., the population exposed to nitrogen dioxide concentrations that exceed the National Ambient Air Quality Standard). In addition, the relative contributions of all important sources and exposure pathways to the associated target dose are determined as part of exposure assessment.

Health effects assessment focuses on the final portion of the event sequence, i.e., exposure, dose, and adverse effects. The goals are twofold: (1) determination of intrinsic health hazards associated with the pollutant, including cancer and noncancer effects; and (2) quantification of the relationship between target dose or exposure and health effects (i.e., dose-response) in human populations.

The overlap between exposure and effects assessment, shown in Figure 1, reflects the importance of exposure and dose information to both activities. Exposure determination, a critical component of epidemiologic studies, is needed to examine associations between environmental exposures and potential health consequences. Measurement of internal dose is crucial for relating exposure to dose (i.e., pharmacokinetics—what the body does to the pollutant) and for relating dose to effects (i.e., pharmacodynamics—what the pollutant does to the body). Moreover, measurements of environmental pollutants or their biological consequences after contaminants have crossed one of the body's boundaries and have entered human tissues or fluids are increasingly used as "biomarkers" of exposure, effects, and susceptibility.[2]

Although often overlooked, exposure is an equal partner with effects for the determination of health risks of environmental pollutants. The simple two-by-two matrix in Figure 2 represents the conceptual paradigm that underlies prioritization of environmental health problems. The highest ranking problems are those that embody elevated exposures (i.e., elevated levels experienced by a significant number of people) *and* very toxic pollutants (i.e., harmful at low exposure/dose). Conversely, the lowest priority problems exhibit relatively low exposure and toxicity.

Despite their obvious importance, human exposure data are not collected in a systematic or comprehensive manner. Only limited information is available; therefore, understanding historical trends, estimating current levels, and predicting future directions for environmental exposures to populations and population subgroups is difficult. The available data tend to be anecdotal, fragmented, and focused narrowly on specific pollutants, media, and routes of exposure. Recently, several groups, including the Environmental Protection Agency's Science Advisory Board and the National Research Council, have pointed out the value of realistic exposure information; the current lack of adequate and appropriate data; and the concomitant need for better methods, measurements, and models.[3-7]

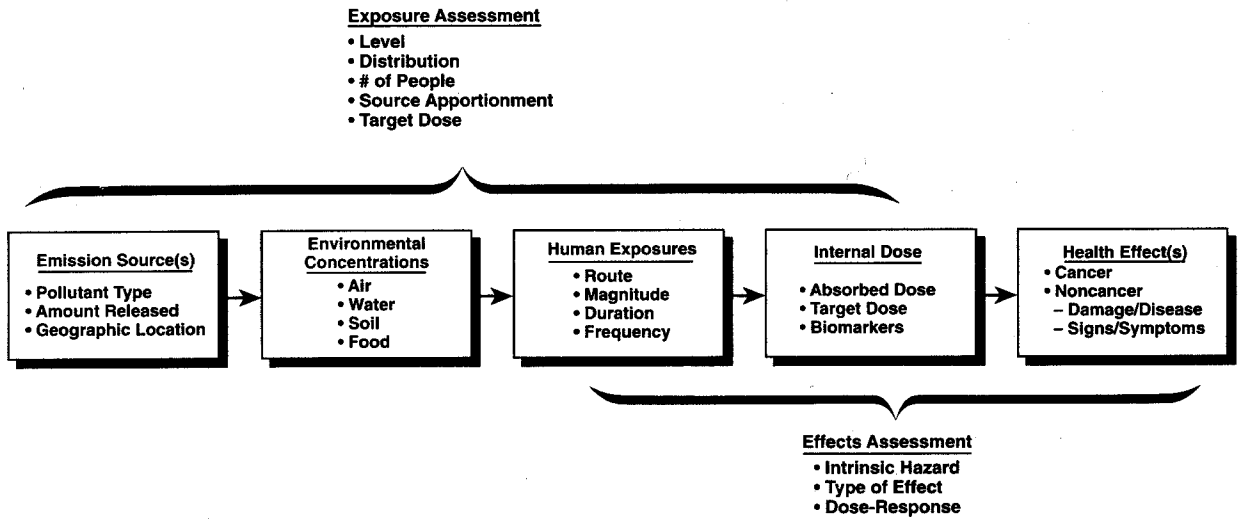


**Fig. 1. Relationship of exposure assessment and effects assessment to the Environmental Health Paradigm.**

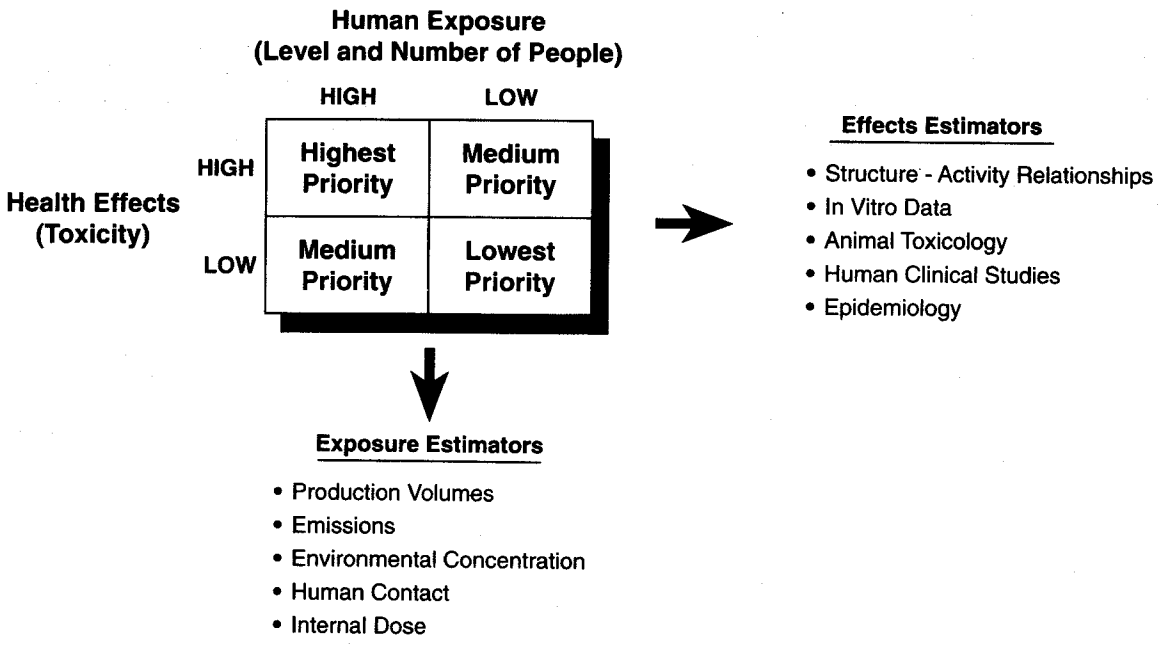


**Fig. 2. Conceptual framework for setting environmental health priorities.**

Concerns about the adequacy of available exposure-related information prompted a joint inventory (EPA, Centers for Disease Control [CDC]-National Center for Health Statistics [NCHS], and Agency for Toxic Substances and Disease Registry [ATSDR]) of federally sponsored databases and a consensus workshop that targeted the use of databases in risk assessment, risk management, epidemiology, and status and trends analyses. The objectives were to examine the existing exposure-related databases and to identify needed improvements. The following discussion highlights important issues that relate to the estimation of exposures, briefly examines results of the database inventory, and summarizes recommendations of the consensus workshop.

## Estimating human exposures

Pollutants can move along many different pathways between the emission point and subsequent contact with people. Some of these exposure pathways are displayed in Figure 3 for airborne and waterborne pollutants emitted from a hypothetical chemical plant. Although Figure 3 may appear complicated, it does not capture the complexity of the real world in which a plethora of sources (e.g., motor vehicles, industrial wastes, agricultural runoff, consumer products) release literally thousands of pollutants (e.g., chemicals, microorganisms, radionuclides) in a multitude of settings (e.g., residential, occupational, recreational, transportational) in which people can be exposed.

A more generic overview of the major pathways by which people come into contact with pollution is provided in Figure 4. Although Figure 4 does not explicitly show "nontraditional" pathways, e.g., infant exposures to contaminated breast milk or indoor air pollution exposures from the volatilization of water pollutants during showering, it does demonstrate the many possible ways that people and pollution connect.

Historically, these pathways have been examined individually. It is clear from Figure 4, however, that multiple pathways can contribute to exposures and dose for a single pollutant (e.g., lead in drinking water, indoor and outdoor air, paint, house dust, soil, and food—all of which contribute to blood-lead levels). Many human exposures (e.g., metals, dioxins and related compounds, pesticides, polycyclic organic matter) occur through a wide spectrum of environmental pathways and by different routes (e.g., inhalation, ingestion, and dermal contact). Acknowledgment of this reality and the need to account for it in exposure assessment are embodied in the "total human exposure" concept.[5]

The total human exposure approach to assessment accounts for all relevant pathways and routes when environmental exposures experienced by an individual or group are estimated. The information gained from application of this methodology can be used to construct and examine the "human exposure topology" (Fig. 5) for the pollutant of interest.[8] The total exposure approach to design, collection, analysis, and presentation of information provides a more realistic picture of exposure patterns.

Ideally, all exposure assessments would be based on data similar to that displayed in Figure 5. But in reality, the costs and, in some cases, the technical feasibility limit our ability to make the necessary measurements. Nevertheless, the only way to determine whether and to what extent people come into contact with specific environmental contaminants is to measure their exposure. This may be accomplished in three different ways: (1) use of microenvironmental samplers (e.g., passive

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# Protect Public From Chronic Diseases, Pew Commission Urges

## *Diseases, Environmental Exposures Must Be Tracked to Save Lives*

WASHINGTON, DC –Sept. 6, 2000 -- The Pew Environmental Health Commission at the Johns Hopkins School of Public Health today called on Congress and the White House to protect Americans from chronic diseases – the No. 1 cause of death in the U.S. – by tracking where and when these health problems occur and possible links to environmental factors.

In its third report, the Commission charged that the nation faces an environmental health gap and proposed a Nationwide Health Tracking Network to provide the critical information now lacking in nearly every state. Without this Network, the Commission said the U.S. will remain unable to mount effective prevention efforts for asthma, birth defects, developmental disabilities, cancers, and neurological disorders such as Alzheimer's and Parkinson's, among other chronic diseases.

"We responded quickly to the threat of West Nile virus, tracking and monitoring every report of infected birds and people, but 20 years into the asthma epidemic this country is still unable to track where and when attacks occur and what environmental links may trigger them," said Lowell Weicker Jr., the Commission chairman and former U.S. senator and Connecticut governor.

The recommended Network would include the following components:

1. Nationwide baseline tracking of priority diseases – asthma and chronic respiratory diseases; birth defects; developmental disorders; cancers, especially childhood cancers; and neurological diseases such as Alzheimer's, multiple sclerosis and Parkinson's – and priority exposures such as PCBs, and dioxin; heavy metals such as mercury and lead; pesticides and water and air contaminants.

2. Monitoring of immediate health crises such as heavy metal and pesticide poisonings to serve as an early warning system.

3. Establishing 20 state pilot tracking programs to address regional environmental health concerns.

4. Developing a federal, state and local rapid response capability to investigate clusters, outbreaks and emerging threats.

5. Supporting community interests and scientific research to further health tracking efforts.

The Commission estimated that the Network will cost $275 million annually – less than one-tenth of a percent of the $325 billion that chronic disease costs the U.S. annually in health care and lost productivity.

"It is time to make the investment in our public health that matches the threat from chronic disease," Weicker said.

As examples of the environmental health gap, the nation's failure to deal with chronic diseases and their potential links to environmental hazards, the Commission noted:

- More than half the states (27) lack ongoing tracking and monitoring of asthma even though it is a rapidly growing national epidemic;
- Most states fail to track developmental disabilities such as autism and mental retardation despite an estimated 50 percent rise nationwide in these disabilities in the last decade, and research indicating that 25 percent are related to environmental exposures. California, District of Columbia, Kentucky, Mississippi, Nebraska, New Jersey, North Carolina, South Carolina and South Dakota reported tracking at least some of these disorders.
- Only four states reported tracking autoimmune diseases such as lupus even though rates for these diseases are rising. The four states are: Arizona, Massachusetts, New Mexico and South Dakota.
- Less than half the nation's population is covered by birth defect registries even though birth defects are the leading cause of infant mortality in the U.S. and rates for certain birth defects and related conditions are increasing.

"This is Public Health 101, and as a nation we are flunking," said Louis Stokes, former 15-term U.S. House member from Ohio and a member of the Pew Environmental Health Commission.

In calling for the Nationwide Health Tracking Network, the Commission has the support of many voluntary disease support groups and national public health organizations, including: Allergy and Asthma Foundation of America; Allergy and Asthma Network, Mothers of Asthmatics; American Academy of Pediatrics; American Autoimmune and Related Diseases Association; American Cancer Society, Inc.; American Lung Association; American Public Health Association; Association of State and Territorial Health Officials; Candlelighters Childhood Cancer Foundation; Council of State and Territorial Epidemiologists; Joint Council of Asthma, Allergy and Immunology; National Association of City and County Health Officials; and Public Health Foundation.

"The support for health tracking is broad and deep. It should command the attention of every candidate for President and every candidate for Congress," Weicker said.

"Tracking on a nationwide basis will enable our medical system to focus on a critical area of health care that has long had insufficient emphasis, the prevention of the diseases that cause the most suffering and death," said Dr. Neil Schlackman, the senior corporate medical director for Aetna US Healthcare and a member of the Commission.

The Commission's recommendations were based on an analysis conducted under the guidance of Thomas A. Burke, associate professor at the Johns Hopkins School of Public Health and chairman of the Director's Advisory Committee to the National Center for Environmental Health at the Centers for Disease Control and Prevention (CDC). The analysis examined public health tracking capacity at the national, state and local levels.

"We need to know when and where diseases occur, what are the environmental hazards, and what are the actual exposures we have to those hazards," said Burke. "This is a basic right to know issue for our communities and our public health professionals."

"Americans have a right to this information about the health of their communities," said the Rev. Michael D. Place, STD, president and chief executive officer of the Catholic Health Association of the United States, representing the nation's largest group of not-for-profit healthcare systems, facilities and related organizations, and a member of the Commission. "These recommendations will enlighten our research and make possible disease prevention efforts that will save lives and spare much suffering."

Later this year, the Commission will release its final recommendations on improving the ability of the public health system to combat environmental threats to health. Its two previous reports examined the increases in birth defects and related conditions and the asthma epidemic, focusing on the need for national environmental health tracking.

The Pew Environmental Health Commission was launched in May 1999 to develop recommendations on improving the nation's ability to track and prevent health problems linked to environmental conditions. Its members include leaders from the public policy, health industry, environment, government, academic and nonprofit communities.

The Commission is funded by a grant from the Pew Charitable Trusts to the Johns Hopkins School of Public Health. The Pew Charitable Trusts support nonprofit activities in the areas of culture, education, the environment, health and human services, public policy and religion. Based in Philadelphia, the Trusts make strategic investments to help organizations and citizens develop practical solutions to difficult problems. In 1999, with approximately $4.9 billion in assets, the Trusts granted over $250 million to 206 nonprofit organizations.

*For the full report and appendices, visit the Commission's Web site at*

*http://pewenvirohealth.jhsph.edu*

**EMBARGOED FOR RELEASE**
**Until Noon EST Nov. 16, 1999**

**Contact: Donna Rohrer or Sara Sigelman**
**(202) 659-0330**

# Commission Study Finds Increases in Certain Birth Defects

## Nearly 59 Million Americans Not Covered by Birth Defects Tracking

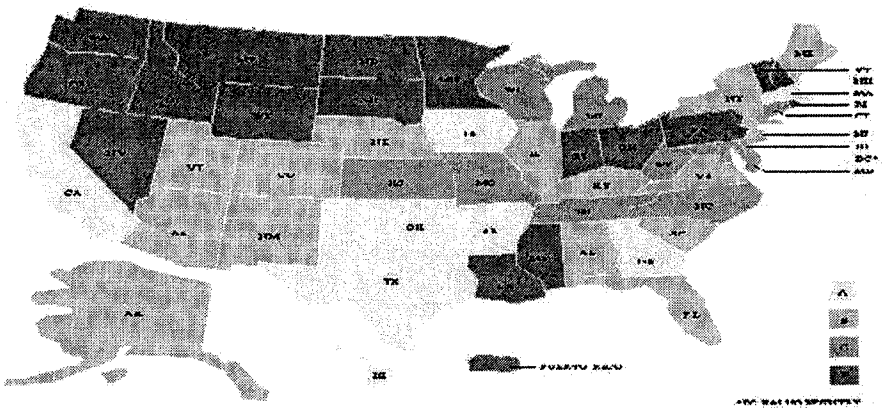
NEW YORK – Nov. 16, 1999 – A major analysis of national data on birth defects and the environment has found unexplained increases in certain birth defects and related conditions that point to the need for strengthening the public health system.

Even though birth defects are the nation's leading cause of infant death, one-third of the states, the District of Columbia and Puerto Rico – with a total population of nearly 59 million – fail to track birth defects, and 25 more states have systems that need improvement to better protect the public.

The study, conducted by the Pew Environmental Health Commission at the Johns Hopkins University School of Public Health, reported that only about 20 percent of birth defects have known causes, while the causes of the majority await further research. However, there is increasing evidence that environmental factors, including diet, personal behavior and exposure to toxic substances and pollutants, may play an important role in the development of birth defects and related conditions.

Commission researchers concluded that the unanswered questions about wide variations in certain birth defect rates reported over an eight-year period may be the result of improved diagnoses, variations in state tracking procedures or increases that are actual.

Researchers evaluated each state's monitoring effort and graded each on its quality. One-third of the states, the District and Puerto Rico – or 19 – received an "F" grade because they do not currently track birth defects at all. Only eight states were awarded an "A" for systems that can be helpful to future research on the causes of birth defects. The remaining 25 states have tracking systems that are in need of improvements.



SCORECARD OF STATE BIRTH DEFECTS SURVEILLANCE PROGRAMS, NOVEMBER 1999

"Without this information, public health officials are working in the dark," said Lowell Weicker, Jr., former Connecticut governor, three-term U.S. Senator and chairman of the commission. "We lack the key tool needed to identify emerging disease clusters and trends, making it tougher to tackle the environmental threats that may cause sickness and death in our children."

While federal and state investments in birth defects monitoring over the past two decades have produced some excellent systems, as observed in the commission's report, much more must be done.

"What we need is full funding of the Birth Defects Prevention Act of 1998," said Dr. Jennifer L. Howse, president of the March of Dimes and member of the commission. "This legislation called for more surveillance, research, education and services to prevent birth defects and protect children, but without full funding the job just won't get done."

The analysis examined data from the Centers for Disease Control and Prevention and states gathered from 1989-1996. Increases were found by analyzing information from those states with tracking systems for birth defects.

Among the study's findings about birth defects and related conditions:

- Rates of babies born with low birth weight and pre-term conditions have been rising steadily since the mid-1980s despite increased prevention efforts. Low birth weight and pre-term conditions in infants contribute to infant deaths and often accompany birth defects and related conditions such as cerebral palsy and mental retardation.
- The rate of infants born with one serious heart defect rose 2 _ times in less than a decade among states that track this defect.
- The rate of infants born with a blockage in the urinary tract rose more than 1 _ times in less than a decade among states that track this defect.

As a reflection of the variations in birth defects monitoring systems, researchers found inconsistencies even among the 33 states collecting data.

"Gaps in quality and consistency in state data prevent public health officials from answering the many disturbing questions raised by our analysis," said Dr. Lynn R. Goldman, principal investigator on the birth defects study.

"We know more about how much pollution we put in our physical environment than we know about the levels of those pollutants in our bodies and how they can affect the health of a developing baby," she said.

The Pew Environmental Health Commission was launched in May to develop recommendations to improve the nation's ability to track and prevent health problems linked to environmental conditions. Commission members include leaders from the public policy, health industry, government, academic and nonprofit communities.

In the coming months, the Commission will study two other children's environmental health issues, asthma and childhood cancers, and examine the quality of state tracking systems and other issues relating to the capacity of the public health system to combat new threats to health.

The Pew Environmental Health Commission is funded by a grant to the Johns Hopkins School of Public Health by The Pew Charitable Trusts. The Pew Charitable Trusts support nonprofit activities in the areas of culture, education, the environment, health and human services, public policy and religion. Based in Philadelphia, the Trusts make strategic investments to help organizations and citizens develop practical solutions to difficult problems. In 1998, with approximately $4.734 billion in assets, the Trusts granted over $213 million to 298 nonprofit organizations.

*For the full report and state-by-state analysis, visit the Commission's website at http://pewenvirohealth.jhsph.edu*

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# Tracking disease in America

search this issue

Chronic diseases are the leading cause of death in the U.S., yet the systems in place to combat this major public health problem are woefully inadequate. For example, more than half the states have no tracking and monitoring of asthma, which afflicts 17 million Americans, including 5 million children.

Existing efforts to gather information on asthma and other chronic diseases and their potential environmental links are highly fragmented and inadequate for collecting the kind of nationwide data that are needed to truly understand how often, in what locations and why these diseases occur. This information could also help to eventually prevent the incidence of some of these diseases in the future. Lacking such information, it is difficult for health care professionals, the public and government officials to grasp the magnitude of the problems we face and how to prevent them.

Home > Tracking disease

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**Contact: Donna Rohrer (202) 659-0330**
**Dave Woodruff**

# ASTHMA CASES PROJECTED TO DOUBLE BY 2020; WILL HIT 29 MILLION AMERICANS; 1 IN 5 FAMILIES

## Commission Charges Federal Government Is Failing to Stop Asthma Epidemic

WASHINGTON – May 16, 2000 – The nation is in the grip of a rapidly growing asthma epidemic whose victims will more than double by 2020, according to a study released today by the Pew Environmental Health Commission at the Johns Hopkins School of Public Health.

An analysis by the Johns Hopkins researchers concludes that new cases of asthma among Americans are increasing so rapidly that by the time another generation of children is born, asthma will strike 29 million Americans – more people than the projected 2020 population of New York and New Jersey combined.

The report sharply criticized the federal government for shortchanging both research efforts to find the causes of asthma and public health strategies to prevent its spread. Two weeks ago, the federal government released its action plan on asthma, 15 years into the epidemic.

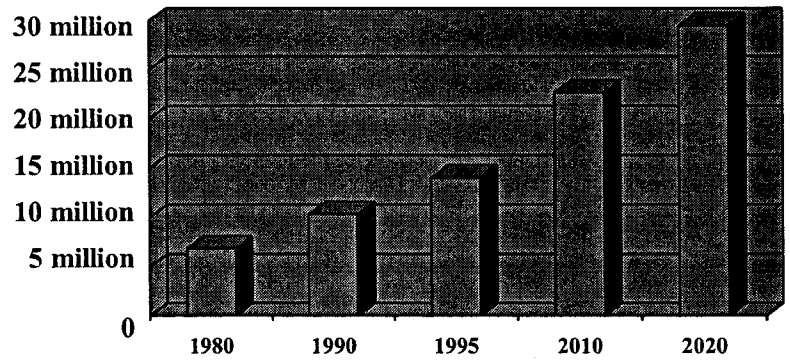
"While the federal government acknowledges that there is an asthma epidemic, it has so far failed to devote sufficient resources to tracking and preventing asthma," said Lowell Weicker, Jr., former governor and three-term U.S. senator from Connecticut and chairman of the Commission.

"The real tragedy of this asthma epidemic is that the federal government's response has been too little, too late," said Weicker. "If asthma were an infectious instead of a chronic disease, we wouldn't be having this discussion, because the full power of the federal government would be aimed at preventing it."

The Johns Hopkins researchers concluded that in fiscal year 1999, less than 10 percent of federal asthma research spending – approximately $14 million – is directed at monitoring or preventing the disease. This year, asthma will cost the U.S. economy at least $11 billion and afflict more than 14 million Americans.

The Commission determined that unless the rates are slowed, asthma will strike 1 in 14 Americans and 1 in 5 U.S. families by the year 2020.

**Total number of persons with asthma, computed and projected, 1980-2020**



Asthma rates are going up dramatically across all demographic groups, all across America. For example, between 1980 and 1994, they rose by 75 percent – and by 160 percent for those under age 4. In just one year, 1995, asthma accounted for 1.8 million visits to hospital emergency rooms, and more than 10 million missed school days.

That makes asthma the number 1 cause of school absenteeism.

"Asthma affects some groups in our society more than others, including the very young, very old and very poor," said Dr. Lynn Goldman, principal investigator and adjunct professor at the Johns Hopkins School of Public Health. "This is why tracking is so very important – it will help us understand why some groups are hit harder by asthma and help find the keys to preventing the disease."

"While a higher percentage of African Americans have asthma, the disease is rapidly rising everywhere and is affecting everyone," said Louis Stokes, former 15-term U.S. congressman from Ohio and member of the Commission. "Despite what you may have heard, it is America's problem."

"It's time for the federal government to declare a War on Asthma," Stokes said.

Asthma is a chronic disease whose causes are largely unknown, but genetic predisposition and environmental triggers in both indoor and outdoor air are known contributors to asthma's development and severity.

To win this War on Asthma, the Commission called for a five-part campaign for Congress and the Administration to:

- Establish a 15-state tracking system within two years – and a nationwide system in five years – to provide public health officials with the information necessary to analyze trends, determine causes, better understand the role of the environment, and prevent asthma.
- Deploy a "9-1-1 Force" at the Centers for Disease Control and Prevention within one year to conduct thorough, targeted investigations into asthma deaths in order to identify causes and learn how to prevent asthma.
- Begin short- and long-term environmental health studies to determine what causes asthma, the best strategies for prevention, and why asthma rates are higher in low income and minority communities.
- Begin a comprehensive public education program within two years on the immediate steps we can take to combat asthma, beginning with the environmental factors that contribute to the development or severity of the disease.
- Give the U.S. Surgeon General the authority to marshal all federal efforts on behalf of the War on Asthma.

"The findings of the Pew Environmental Health Commission's report underscore the importance of dramatically escalating the nation's War on Asthma," said John M. Coruthers, Jr., President of the American Lung Association. "The American Lung Association strongly supports the Pew Commission's recommendations for improving our national response to this public health crisis."

"We can win the War on Asthma in the United States by investing in the public health infrastructure in response to this epidemic-with an emphasis on prevention," said Mary Worstell, executive director of the Asthma and Allergy Foundation of America. "The Pew Environmental Health Commission's report is a call to action in this vital life-saving effort."

The Pew Environmental Health Commission was launched in May 1999 to develop recommendations on improving the nation's ability to track and prevent health problems linked to

environmental conditions. Commission members include leaders from the public policy, health industry, environment, government, academic and nonprofit communities.

The Commission released a report in November 1999 on birth defects and the environment that concluded that although there are unexplained increases in certain birth defects nationwide, a third of all states fail to track birth defects, and half of the states have monitoring systems that need improvement.

In the coming months, the Commission will examine the quality of state and federal health tracking systems in more detail, and issue its final recommendations on the capacity of the public health system to combat environmental threats to health.

The Pew Environmental Health Commission is funded by a grant to the Johns Hopkins School of Public Health from The Pew Charitable Trusts. The Pew Charitable Trusts support nonprofit activities in the areas of culture, education, the environment, health and human services, public policy and religion. Based in Philadelphia, the Trusts make strategic investments to help organizations and citizens develop practical solutions to difficult problems. In 1999, with approximately $4.9 billion in assets, the Trusts granted over $250 million to 206 nonprofit organizations.

*For the full report and appendices, visit the Commission's website at http://pewenvirohealth.jhsph.edu*

# # #

# Post-Meeting Written Comments From Ken Sexton

**8-25-01**

**Comments on an early draft of**
**EPA's Framework for Cumulative Risk Assessment**

**by Ken Sexton**

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## General Comments

The document is a reasonable early draft that does (1) lay out a framework for thinking about cumulative risk assessment, (2) highlight many of the important issues that must be addressed, and (3) begin the process of building a common language. EPA is to be commended for both the attempt and the quality of this work in progress.

The Framework should state clearly that *cumulative risk assessment is a tool for organizing and analyzing information in a way thatt will be useful for the decision at hand*. It is not a decision rule that constrains decisionmakers' discretion.

As I understand it, the "essence" of the framework involves (1) 3 phases – formulation, analysis, interpretation, (2) an analytic-deliberative process, (3) up front consideration of key issues including identification of the "risk management team" and the "risk assessment team," (4) explicit consideration of both values (value judgments about scope, combining risks, etc) and facts (data, data quality, uncertainty) throughout the process, (5) specification of the vital activities that are performed as part of each phase, (6) identification and brief discussion of key technical and science policy issues that are intrinsic to cumulative risk assessment, and (7) definitions for important terms, concepts, and principles. However, it took several readings and substantial effort to discern this framework.

A major problem with the current version has to do with style (as opposed to substance). It desperately needs a professional editorial presence to (1) punch up the verbiage describing the key ideas, concepts, and principles, (2) provide suitable diagrams that summarize significant elements of the framework and provide the reader with a better road map of the document, and (3) restructure and rearrange the narrative so as to make crucial points early and to reduce redundancy throughout (for example, several statements describing the goals are spread randomly throughout the current version). I strongly encourage EPA to retain a good editor and work with him/her to make the document more focused, more concise, and less redundant. As it is, the draft framework is uneven (much detail about some important issues and almost none about others), inappropriately even in

tone/style (doesn't draw attention to the essential elements of the framework because all issues, major and minor, get about the same level of description/discussion), and unbalanced (meant to be generic but virtually all examples are human health, at the very least it needs a couple of ecological examples; it also emphasizes quantitative approaches and gives short shrift to qualitative methods). It is important, to the extent practicable, that the discussion and descriptions relate directly to cumulative risk assessment (much of the current version is too generic and non-specific).

I question whether the Framework needs to be so historical in terms of describing the wide range of EPA documents/guidelines (many still in draft), some of which are only tangentially related in one way or another to the Framework. For me this detracts from the impact of the Framework itself and needlessly adds to the length of the narrative. I recommend putting this sort of review of earlier EPA work (unless it relates directly to cumulative risk) in an appendix. An explicit decision should be made about whether to reference these draft documents at all.

One area where I think a formal peer review will find fault is the reference list. The selection of references is always a difficult one, especially in this context. It is obvious that a comprehensive literature review is inappropriate, so to the extent that the scientific literature is cited at all the authors must be selective. The key question for future reviewers is "have the authors cited the "best" primary or secondary source for the point being made"? It is not apparent to me that the answer is necessarily "yes".

**Process Issues**

The Framework makes it clear that stakeholders are important and that they need to be involved, as appropriate. However, virtually all of the discussion of stakeholders is found in the formulation phase, and it is not easy to understand what roles they play, if any, in the analytical and interpretation phases. The Framework could do a better job of making it clear that (1) stakeholder involvement creates the need for specific resources to be set aside up front for this purpose (e.g., funding for transportation, child care, reimbursement for time), (2) there is a variety of different roles stakeholders might play (e.g., listeners, respondents, advisors, partners, joint decisionmakers) and it is critical to decide at the outset which role(s) are appropriate, (3) regulatory agencies need effective methods to gather information, test ideas, and obtain opinions from stakeholders without necessarily relinquishing their statutory role and responsibility to make the final decision; and furthermore, that they cannot allow the decision-making process to be sidetracked or delayed by a futile search for unanimous agreement (the reality is that regulators should not feel obliged in every instance to offer stakeholders either a vote or veto). It would be helpful if the Framework would be more specific about the value of stakeholder involvement. Among the many reasons to involve stakeholders are the following: (1) stakeholder acceptance (buy in) is critical for some cumulative risk assessments, (2)

stakeholders often have unique knowledge of local conditions and can complement specialized knowledge of risk assessment experts, and (3) including stakeholders as equals in cumulative risk assessments is an important social value that builds social capital and promotes the concept of environmental democracy.

In order for community members to participate meaningfully, the Framework should explicitly acknowledge that they often need (1) financial support to attend meetings (e.g., parking, transportation, child care, time off from work), (2) independent technical/scientific assistance, and (3) help understanding their rights and responsibilities as equal participants in a cumulative risk assessment.

There are several prosaic yet critical questions that must be discussed and resolved during the formulation phase, including:

When is the cumulative risk assessment to be completed? (timeliness issues)
How much money is available to conduct it? (fiscal/budgetary issues)
Which government agencies (federal, state, local) will be involved?
What are their respective roles and responsibilities?
Which stakeholders (business, NGOs, community) will be involved?
What are their respective roles and responsibilities?
How are decisions going to be made? (unanimity vs consensus vs other)

The Framework should do a better job of emphasizing the importance in the formulation phase of directly confronting the almost overwhelming complexity associated with cumulative risk assessment, and deciding what compromises need to be made so that the agreed upon task can be completed within budget and time constraints.

The Framework should be more specific about the challenges of successful stakeholder participation, and the fact that we don't know yet what works and what doesn't across the spectrum of possible cumulative risk situations. Although there is much anecdotal information, it should be made clear that this issue is as much art as science. I suggest that the document reference a couple of key overview/summary articles and books, such as:

Chess, C. and K. Purcell (1999). Public Participation and the Environment: Do We Know What Works? *Environmental Science & Technology* 33(16): 2685-2692.

Frewer, L. (1999). Risk Perception, Social Trust, and Public Participation in Strategic Decision Making: Implications for Emerging Technologies. *Ambio* 28(6): 569-574.

Thomas, J. (1995). *Public Participation in Public Decisions: New Skills and Strategies for Public Managers*. San Francisco, CA, Jossey-Bass Publishers.

It would be helpful if the Framework explicitly recognized the literature on the different dimension of risk (e.g., Slovic, Covello, Sandman, NRC) and reminded the reader that

experts and community stakeholders are likely to approach risk-related issues from different frames of reference. This relates directly to decisions by the risk management team about (a) combining chemical and non-chemical stressors and (b) combining different types of risk.

**Technical Issues**

The issue of qualitative versus quantitative cumulative risk assessment deserves more attention. As currently structured, the Framework focuses almost exclusively on methods to arrive at a quantitative outcome, while giving the impression that qualitative methods are somehow less useful and less desirable. I believe that qualitative approaches are valuable for cumulative risk assessment and, in the near-term, the only practical way to address the complexities involved. Rather than being discouraged, they should be advocated as a way to overcome the complexity and data deficiencies that hinder quantitative approaches. The discussion should describe qualitative methods (giving examples) and mention related techniques for dealing with uncertainty/variability. It is vital for the Framework to make clear that *risk is not an inherently quantifiable variable*.

Relevant topics like Expert Judgment techniques, Focus Groups, Opinion Surveys, Citizen Juries, Alternative Dispute Resolution, etc. are not mentioned.

The Framework should more clearly state the obvious: cumulative risk assessments, either qualitative or quantitative, are likely, on average, to require more time, more money, and a broader skill mix than traditional risk assessments. There will be an expanding need for social scientists, urban planners, philosophers, and ethicists, among others, to become involved.

Variability should be discussed along with uncertainty in the document, and the importance of each in all three phases should be made clear. The need to be consistent about how uncertainty/variability is addressed (qualitatively or quantitatively) should be stressed. It is important to state that this attention to uncertainty/variability is an essential element of characterizing our ultimate “confidence” in the final product(s).

It should be stated explicitly that it might be either impossible or inadvisable to combine (1) chemical and non-chemical stressors and (2) different types of risk, depending on the situation and circumstances of the cumulative risk assessment.

Instead of talking about “Four General Approaches to Cumulative Risk Assessment” (Section 3.1), it would be better to talk about “Four Examples ….” It would also help to add one or two qualitative approaches as examples.

The distinction between cumulative risks and cumulative impacts is blurred and confusing. The Framework should do a better job of defining these terms, using them consistently,

and discussing how they are related or unrelated for the purposes of cumulative risk assessment.

Much has been published on the strengths and weaknesses of biomarkers (e.g., NRC), and at least a summary needs to be included. The most glaring need, however, is for a concise description (with examples) of the role of biomarkers in cumulative risk assessment, including data collection, analysis, and interpretation issues.

All of the forgoing comments have ramifications for describing related research needs; therefore, it will be necessary to revise and enhance this section. Also, it is necessary to comment on the equally important implications of the Framework for exposure and effects surveillance activities (e.g., routine monitoring, determination of background levels).

A key point that comes through in the Framework is the need to consider, blend, and balance both facts and values throughout the 3 phases of cumulative risk assessment. This is significantly different that the conventional risk assessment paradigm described by the National Research Council (NRC, 1983, 1994), although more similar to the paradigm for ecological risk assessment and impact assessment for NEPA. The document should confront these differences directly and comment on their ramifications for conducting cumulative risk assessment. It is also important for the framework to put cumulative risk assessment in the broader context of its relationship to (1) risk management, (2) risk communication, and (3) risk-related research and surveillance.

# APPENDIX H - DRAFT FRAMEWORK FOR CUMULATIVE RISK ASSESSMENTS

# Framework for Cumulative Risk Assessment



**IMPORTANT NOTICE:**

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

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

**Table of Contents**

**Acknowledgments** [to be completed later]

**Foreword** [to be completed later]

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

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

The EPA Science Policy Council has asked the Risk Assessment Forum to begin developing Agency-wide cumulative risk assessment guidance that builds from these ongoing activities. As a first step, a technical panel convened under the Risk Assessment Forum has been working to develop a Framework for Cumulative Risk Assessment. Building from the Agency's growing experiences, this Framework is intended to identify the basic elements of the cumulative risk assessment process. It should provide a flexible structure for the technical issues and define key terms associated with cumulative risk assessment.

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

William P. Wood
Director, Risk Assessment Forum

**Preface**

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

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

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

of adults. Public criticisms documented in this report note that EPA does not often consider the possibility of synergistic interactions when multiple chemical exposures occur, nor does it consider extreme variability among individuals in their responses to toxic substances. A related issue is the problem of how risks associated with multiple chemicals are to be combined. Finally, the FQPA [P.L.104-170, August 3, 1996], requires research on the influence of complex exposures on non-cancer human health effects of pesticides and other toxic substances.

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

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

**Authors, Contributors, and Reviewers** [to be completed]

**List of Abbreviations and Acronyms**

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

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

**Executive Summary** [to be completed last]

## 1. INTRODUCTION

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

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

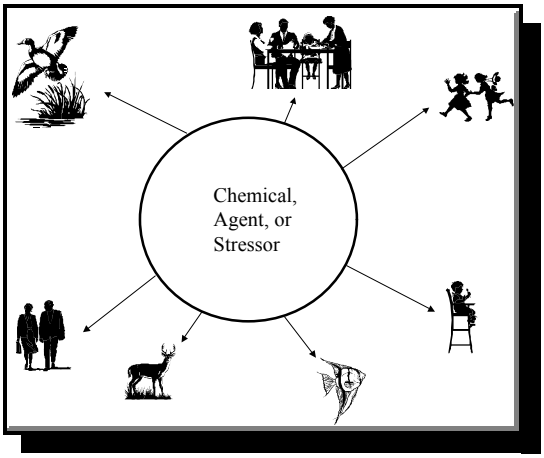


**Figure 1.** Chemical (or stressor) focused assessment starts with a source and evaluates how the chemical gets to various populations or ecological targets. Individual assessments may choose to pursue some or all pathways, media, or population segments.

Risk assessment methodology of the 1970s and early 1980s, for this reason, tended towards single chemical assessments (see Figure 1). The 1983 National Research Council report *Risk Assessment in*

*the Federal Government* (NRC, 1983) was largely focused on the single chemical risk assessment approach when it spoke of the four parts of a risk assessment: hazard identification, dose-response assessment, exposure assessment, and risk characterization. EPA's *1986 Risk Assessment Guidelines* (USEPA 1986a), with the exception of the mixtures guidelines (USEPA, 1986b), were also largely focused on single chemical assessment.

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

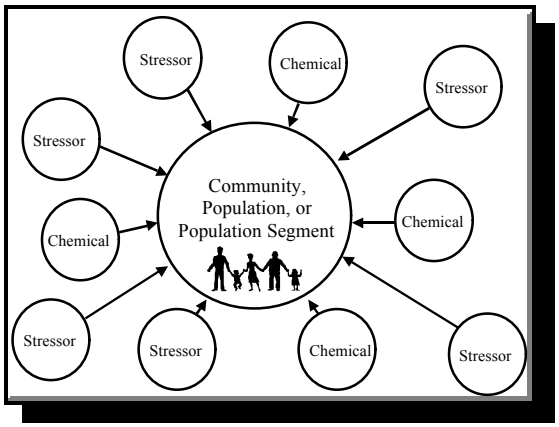


**Figure 2.** Population-based assessments start with the receptors, and determine what chemicals, stressors, or other risk factors are affecting them.

The challenges posed by the population-based assessment can be daunting. Taken to the extreme, Figure 2 represents a concept of "total risk" for the population or population segment being evaluated, with each chemical, biological, radiological, or other stressor adding some fraction of the total risk. Looking at the problem from an individual stressor viewpoint, to do this type of assessment would require not only evaluating each individual stressor, but developing a way to add up all the risks among stressors across a population of individuals with different exposures, susceptibilities, etc. In the early 1980s, the state of the science was unready for virtually any part of the methods for doing this type of assessment.

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

Also in the early 1980s, some progress was being made toward the question of how to add the risks from different chemicals or stressors. The 1986 *Risk Assessment Guidelines* (USEPA, 1986a) included a guideline on chemical mixtures (USEPA, 1986b), which discussed how the risks from multiple chemicals could be evaluated as a whole. The work on this guidance has continued most recently with a draft chemical mixtures guidance document (USEPA, 2001a) which expands and supplements the 1986 beginnings.

About the same time the Agency made some progress on single chemical and chemical mixture risk assessment with the 1986 *Guidelines,* some different kinds of risk assessment problems began to catch the Agency's attention. In 1986, eleven Chicago-area community groups joined together to file a petition under Section 21 of the *Toxic Substances Control Act* asking for a community assessment in Southeast Chicago. A series of community-based actions which started in 1982 and grew throughout the 1980s focused on disparities of risk among various population subgroups, calling specific attention to cumulative effects of pollution on minority subgroups (GAO, 1983; Lee, 1987). This series of community-based actions, chronicled in the 1990 book *Dumping in Dixie: Race, Class and Environmental Quality* (Bullard, 1990) eventually became known as the Environmental Justice movement. The issues raised by the Environmental Justice movement were the basis of a 1994 Presidential Executive Order [Executive Order 12898, February 11, 1994] which told Agencies, among other things, that "Environmental human health analyses, whenever practicable and appropriate, shall identify multiple and cumulative exposures." In the 1990s, Environmental Justice cases, including the cases which have been filed under Title VI of the *1964 Civil Rights Act*, [P.L. 88-352, July 2, 1964] have added to the demand that a population-based human health risk assessment methodology be developed.

Even before Executive Order 12898 was issued, it was apparent that population-based assessments were going to be needed, in addition to the chemical-based assessments, if EPA was going to be able to answer the questions and issues being raised by the public. Community spokespersons and other "stakeholders," as well as scientific panels, were increasingly coming to the Agency with problems that demanded a multi-stressor, population-based approach (e.g., NRC 1994). Ecological problems, especially, were demanding a "place-based" context (such as the Chesapeake Bay watershed) in which the various populations within the area were looked at from a "total system" viewpoint. This place-based focus was a part of the 1992 *Framework for Ecological Risk Assessment* (USEPA 1992b) and the 1998 *Guidelines for Ecological Risk Assessment*. (USEPA 1998b)

Also by the early 1990s, it was becoming clear that the population-based assessments being contemplated for EPA's cumulative risk needs and the type of assessments done under the *National Environmental Policy Act* of 1969 (NEPA) were related. NEPA [P.L. 91-190, 42 U.S.C. 4321-4347, January 1, 1970, as amended by P.L. 94-52, July 3, 1975, P.L. 94-83, August

9, 1975, and P.L. 97-258, §4(b), Sept. 13, 1982], which was passed at about the same time EPA was established, requires assessments on the impacts of federal or federally-funded projects (such as roads, dams, power lines, military projects, and infrastructure development) on natural ecosystems, endangered species, habitats, and opportunities for public enjoyment and natural resource use. A primary concern for NEPA is "cumulative effects analysis," defined as "the incremental impact of the action when added to other past, present, and reasonably foreseeable future actions... Cumulative impacts result from individually minor but collectively significant actions taking place over a period of time" (CEQ, 1997). Much of the NEPA cumulative effects analysis is qualitative, but risk assessments and cause-and-effect relationships are key parts of the analysis process for controversial projects.

The projects or actions that NEPA addresses can be viewed as sources of stressors. Environmental impact assessment under NEPA contains a description of the affected environment that contains four types of information: (1) data on the status of important natural, cultural, social, or economic resources and systems; (2) data that characterize important environmental or social stress factors; (3) a description of pertinent regulations, administrative standards, and development plans; and (4) data on environmental and socioeconomic trends. In addition to health effects on populations and susceptible individuals as part of the affected environment, the NEPA cumulative effects analysis would consider effects on historic and archaeological resources, socioeconomic factors like employment, human community structure, and quality of life changes. These may be among the types of effects EPA may be asked to include in future cumulative risk assessments. As EPA moves toward cumulative risk assessment, there is some parallel with the NEPA methods for cumulative impact analysis, which may be applied to cumulative risk assessments.

By the first decade of the twenty-first century, cumulative risk assessment needs have become relatively common, especially in EPA's Regional Offices and in the Office of Civil Rights. Much like the "place-based" ecological assessments, communities are asking for community-based assessments which include human health risk assessments, ecological risk assessments, and sometimes, assessments of "quality of life" factors. It is the demand for population-based human health risk assessments that has driven the need for research into cumulative risk assessment, aggregate exposure assessment, and risk from chemical mixtures.

### 1.1. Purpose and Scope of the Framework Report

An understanding of the finite purpose and scope of this Framework Report is important. EPA, other regulatory agencies, and other organizations need detailed, comprehensive guidance on methods for evaluating cumulative risk. Before such detailed Agency-level guidance can be developed on a relatively new field of risk assessment, it has been the recent policy of the Agency

to first develop a simple framework as a foundation for later comprehensive guidance. This *Framework for Cumulative Risk Assessment* will emphasize chemical risks to human health in its discussion, but will do so in the context of the effects from a variety of stressors, including non-chemical stressors. Some important topics that could be characterized as "cumulative risk", such as global climate change, are beyond the scope of this Framework.

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

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

This Framework is meant to lay out broad areas where analysis might be done if needed. It does not suggest that cumulative risk assessment is a tool that should be used with every issue, nor does it suggest that when cumulative risk

**EPA's Risk Assessment Guidelines**

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

**Selected Policy and Guidance Documents**

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

assessment is applied, that all areas of analysis outlined or discussed here must or even should be done in every assessment. The scope of the assessment will define the areas to be analyzed. In some areas discussed in this Framework, the methodology for doing the risk analysis may not yet exist.

## 1.2. Intended Audience

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

## 1.3. Key Definitions in Cumulative Risk Assessment[1]

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

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

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

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

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

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

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

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

**FQPA's Terminology Interpretations**

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

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

*Aggregate exposure assessment:* An analysis, characterization, and possibly quantification of exposure of an individual (or defined population) to a specific agent or stressor via relevant routes, pathways, and sources.

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

The Food Quality Protection Act also discusses "cumulative effects" from different pesticides which act by the same mechanism of action (or as interpreted, mode of action).

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

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

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

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

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

**NEPA's "Cumulative Impact" Definition**

CEQ Regulation 1508 for Implementing the *National Environmental Policy Act* of 1969 [P.L. 91-190, 42 U.S.C. 4321-4347, January 1, 1970, as amended by P.L. 94-52, July 3, 1975, P.L. 94-83, August 9, 1975, and P.L. 97-258, §4(b), Sept. 13, 1982] defines "cumulative impact" as "the impact on the environment which results from the incremental impact of the action when added to other past, present, and reasonably foreseeable future actions regardless of what agency (Federal or non-Federal) or person undertakes such other actions. Cumulative impacts can result from individually minor but collectively significant actions taking place over a period of time."
Source: CEQ, 1997

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

We also believe that the definition used here is consistent with the sense of most definitions of "cumulative" such as are included in NEPA, FQPA, or defined by other groups such

as the EPA Science Policy Council's Cumulative Risk Subcommittee[3].

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

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

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

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

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

Source: USEPA, 1999b

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

[3] The Council Cumulative Risk Subcommittee has developed the following working definitions for cumulative risk, which incorporate both the accumulative and integrative aspects of cumulative risk assessment: *Cumulative Risk:* The combined risks from aggregate exposures to multiple agents or stressors. *Cumulative risk assessment:* An analysis, characterization, and possible quantification of the combined risks to health or the environment from multiple agents or stressors.

Cumulative risk assessment is also applied in ecological assessments. The definition of cumulative ecological risk assessment, as given in the EPA's 1998 *Guidelines for Ecological Risk Assessment* is: A process that involves consideration of the aggregate ecological risk to the target entity caused by the accumulation of risk from multiple stressors (USEPA, 1998b). A recent Society of Environmental Toxicology and Chemistry publication (Foran and Ferenc, 1999) discusses multiple stressors in ecological risk assessment, and gives a good overview of the topic of cumulative ecological risk assessment.

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

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

Decisions can be at a wide variety of levels, from a neighborhood group evaluating ways to improve or safeguard their health and environment, to a Federal official weighing options for action at a much broader geographical level. Although the decision-making method is beyond the scope of this Framework, such decisions usually involve more than the basic science and analysis that make up the "scientific" part of risk assessment. Robert T. Clemen, in his book *Making Hard Decisions* notes that in one type of decision-making approach (called decision analysis):

> Managers and policy makers frequently complain that analytical procedures from management science and operations research ignore subjective judgments. Such procedures often purport to generate "optimal" actions on the basis of purely objective inputs. But the decision-analysis approach allows the inclusion of subjective judgments. In fact, decision analysis *requires* personal judgments: they are important ingredients for making good decisions. (Clemen, 1996, page 5)

Regardless of the type of decision being made or the decision-making approach, a cumulative risk assessment's analytic part is not the decision-making vehicle in itself, that is, "cranking out the numbers" will not be the sole basis for a decision. Although in some cases, the estimated risks can weigh heavily in the decision, understanding the risk estimate is but one factor in a broader decision-making process. The U.S. EPA's Science Advisory Board (SAB) in their August, 2000, publication *Toward Integrated Environmental Decision-Making* (USEPA, 2000a), constructed a framework for what they termed Integrated Environmental Decision-making (IED). They noted that "The IED Framework recognizes that risks often are experienced simultaneously and are cumulative...". They speak of risk assessments in a very broad way, including human health effects, ecological effects, and quality-of-life effects. The first two phases of the IED, "Problem Formulation" and "Analysis and Decision-making" essentially correspond to the three

phases we discuss in this *Framework for Cumulative Risk Assessment*. The SAB's third phase, "Implementation and Performance Evaluation," is beyond the scope of this framework.

The SAB's report (USEPA, 2000a) gives a good insight into the broader context for cumulative risk assessment, and some of the aspects of the analytic-deliberative parts of the assessment. These will be discussed in Chapters 2-4, as these phases of the cumulative risk assessment process are examined.

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

## 1.6. Organization of this report

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

## Some Thoughts on Risk Characterization

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

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

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

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

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

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

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

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

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

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

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

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

1

# 2. THE PLANNING AND PROBLEM FORMULATION PHASE

The first step in any risk assessment process is to define the problem to be assessed. This step has been called "problem formulation" in the *Framework for Ecological Risk Assessment* (USEPA, 1992b), the NRC book *Understanding Risk* (NRC, 1996), *Toward Integrated Environmental Decision-Making* (USEPA, 2000a) and elsewhere (e.g., USEPA, 1997a). It is a phase where, according to NRC, "public officials, scientists, and interested and affected parties clarify the nature of the choices to be considered, the attendant hazards and risks, and the knowledge needed to inform the choices" (NRC, 1996) . Planning and Scoping of the assessment are often thought of as being part of the Problem Formulation phase, although the 1997 *Planning and Scoping* guidance treats Planning and Scoping as a separate activity before problem formulation begins (USEPA, 1997a). Whether it is considered a separate phase or not, it takes place at the very start of the process of doing a cumulative risk assessment. For convenience, this section incorporates both Planning and Scoping and Problem Formulation into the Planning and Problem Formulation Phase.

## 2.1. Planning and Scoping

Risk assessments are done within some context, that is, they are usually done because of a regulatory requirement, a community need, a health crisis, or some other "driving force." This context generates individuals or groups with interest in having the assessment done. They may be public officials, risk experts, community leaders, or any number of other "interested parties." Planning and scoping begins with a dialogue among these interested parties.

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

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

As part of the initial discussions concerning the need for a risk assessment, other "interested and affected parties" besides the risk manager and risk assessor may help define purpose, scope, and approach. The risk manager, risk assessor, and interested and affected

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

In the SAB's report *Toward Integrated Environmental Decision-Making*, they explain some of the roles of the various participants on the risk assessment planning team during the Planning and Problem Formulation phase:

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

Another role of the risk assessment planning team is documentation. The activities of the following sections are important, and should be documented by the team for several reasons. Written records can be referred to by assessors and people at public meetings. They can also help prepare for response to comments, and begin establishing a peer-review record for any later decisions or plans that need to be peer reviewed (USEPA, 2000b).

2.1.1. Defining the Purpose of the Assessment

As discussed in section 1.5 above, the risk assessment should be developed to inform the risk management decision by constructing an appropriate, decision-relevant risk characterization. After the risk assessment planning team is assembled, the risk manager must explain why the assessment is being performed, and what questions need to be answered. If interested and affected parties are part of the risk assessment planning team, it is especially important that the entire team agree on the purpose of the assessment, since differing sense of purpose among the team will lead to problems later.

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

**Possible Management Goals**

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

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

They may be economic, aiming to:

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

They may involve public values, aiming to:

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

Source: Presidential/Congressional Commission..., 1997

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

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

### 2.1.2. Defining the Scope of Analysis and Products Needed

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

Reasons for choosing the particular scope of the assessment, and how it will address the questions posed in the purpose statement, must be stated explicitly. Defining the scope of the assessment should include details on limitations on resources, limitations of data, the impact of risk elements on the risk estimate (i.e., some pathways may be seen as having negligible impact on the risks related to the questions being addressed), and methods available. In cases where an element of risk is likely to be important, but no valid data are available, the assessor must highlight this deficiency or use judgment or assumed values to approximate the missing data. Such judgments and approximations should be clearly documented, and explained to the manager in the risk characterization.

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

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

As examples of some of these scoping elements, stressors can include physical (including radiological) stressors or chemical or biological agents that may cause an adverse effect. The sources of the stressors can be human activities in sectors of society (e.g., manufacturing, transportation, agriculture, land development), personal human activities (e.g., smoking, other so-called "lifestyle activities") or natural phenomena. Stressors that are not physical, chemical, or biological, such as economic or other quality-of-life stressors may also be identified.

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

### 2.1.3. Agreeing on participants, roles and responsibilities

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

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

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

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

For community-based assessments, in particular, it is important that community involvement be sought and encouraged. The Presidential/Congressional Commission on Risk Assessment and Risk Management

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

- Who might be affected by the risk management decision? (This includes not only groups that already know or believe they are affected, but also groups that may be affected but as yet do not know it.)

- Who has information and expertise that might be helpful?

- Who has been involved in similar risk situations before?

- Who has expressed interest in being involved in similar decisions before?

- Who might be reasonably angered if not included?

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

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

**Guidelines for Stakeholder Involvement**

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

if any, such incentives can be provided, based on the scope, level of effort, and financial constraints of the risk assessment project.

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

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

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

The analysis approach (discussed further in section 2.2.3 and chapter 3) may fall anywhere on a continuum from relatively simple methods which rely heavily on conservative simple assumptions, and consequently have greater uncertainty, to increasingly refined assessments in which data are substituted for assumptions and uncertainty is reduced. Some of the factors that go into deciding on the approach include what level of uncertainty in the risk estimates is acceptable to the participants, the intended use and audience, time and money resources available, and the amount, quality and accessibility of data. In making the decision on approach, there will need to be an understanding of both the level of effort necessary for conducting an assessment of the sort selected, with an insight to alternatives, and the features and limitations of the selected approach, in comparison to other approaches.

#### 2.1.5. Agreement on the Resources Available and Schedule

Schedule and resources are often interrelated. They may also affect whether the work is performed in-house by the organization or team desiring the assessment, or by contractor or other external source. The need to meet external deadlines or coordinate with schedules of other organizations may become an overriding factor in defining what will be prepared. Assessments requiring short-term, low budget efforts, or preliminary screening assessments, may not have the

scope, time or resources where extensive stakeholder involvement is necessary or beneficial. For assessments, especially those where there is extensive stakeholder involvement, a budget and time schedule should be developed and known by all participants.

## 2.2. Problem Formulation, Conceptual Model, and Analysis Plan

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

### 2.2.1. Problem Formulation.

Problem formulation is a systematic planning step that identifies the major factors to be considered in a particular assessment. It is linked to the regulatory and policy context of the assessment. Problem formulation is an iterative process within which the risk assessor develops preliminary hypotheses about why adverse effects might occur or have occurred. It provides the foundation for the technical approach of the assessment. The outcome of the problem formulation process is a conceptual model that describes the relationship between the stressors, the population exposed, and the assessment endpoint that will be addressed in the risk assessment.

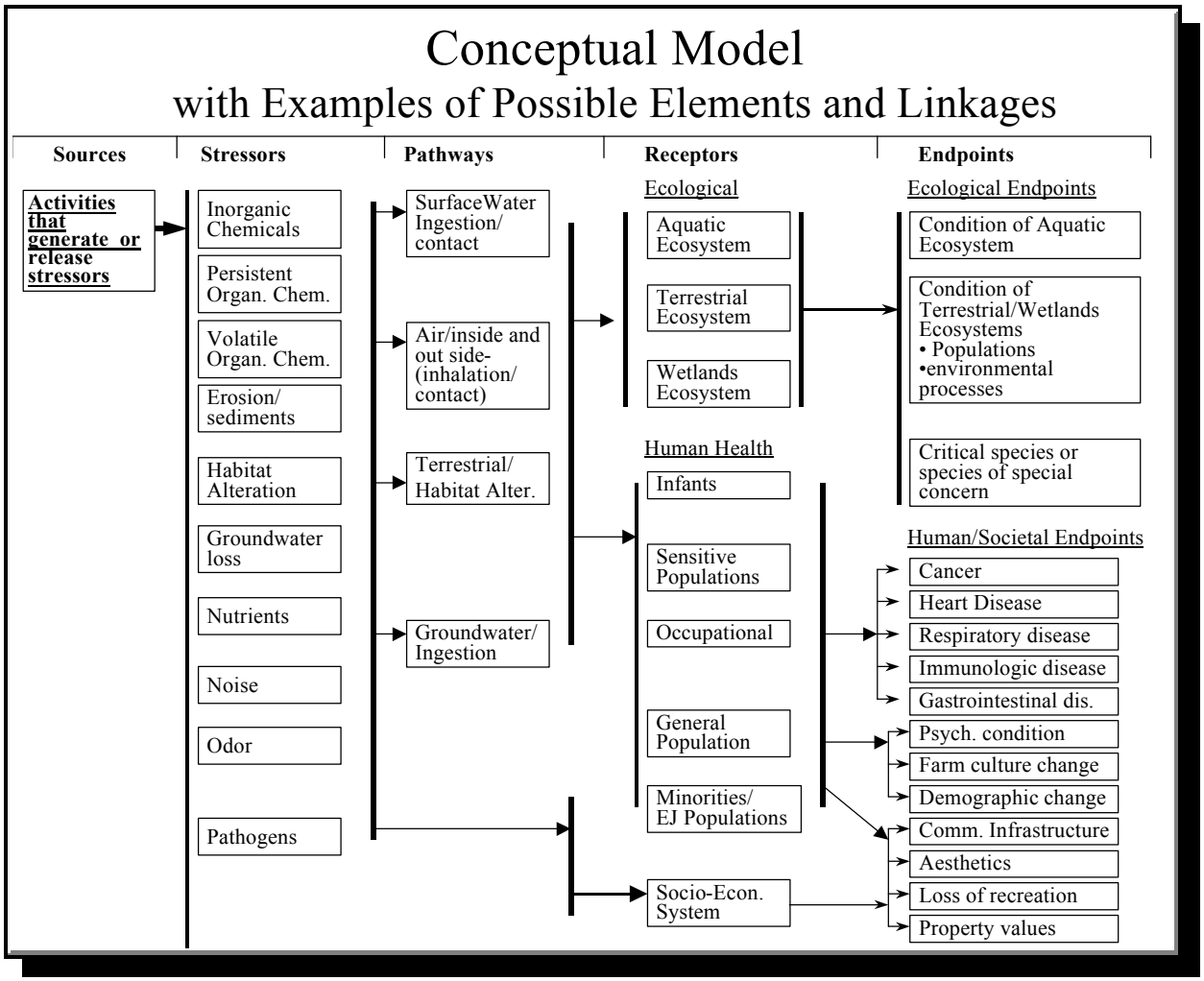


**Figure 3**. Generic conceptual model (from USEPA, 2001c).

2.2.2. Developing the Conceptual Model

A conceptual model is both a written description and a visual representation of actual or predicted relationships between humans (or populations, population segments) or ecological entities and the chemicals or other stressors to which they may be exposed. Conceptual models represent many relationships, and may describe primary, secondary, or tertiary exposure pathways. The model is developed by the risk assessor and may include input from other experts (including stakeholders). The model needs to distinguish between what is known or determined and what is assumed. Also, it needs to include a discussion of uncertainties in the formulation of the assessment. In some cases, conceptual models will be submitted for peer review. A general

conceptual model is provided in Figure 3 (previous page).

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

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

**Desired Outputs for Problem Formulation**

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

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

### 2.2.3. Constructing the Analysis Plan

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

needs and evaluate which analytical approach is best. When new data are needed, the feasibility of obtaining them can be taken into account.

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

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

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

It is useful for the entire team to hold some preliminary discussions, before the analytical efforts of the assessment are started, about the various possibilities of the cumulative risk assessment results and their implications. What conclusions will be associated with various results or risk levels? For example, for a risk assessment team with members from the community, industry, and the local and other government entities, what would happen if the assessment shows risk levels to be "low"? Would members accept this? Conversely, if "unacceptable" risks are determined, will all team members accept the results and their possible responsibility to do something about that risk?

Discussions like these will help determine if the assessment can really address the questions of the team. If not, the assessment may not be worth doing as planned. If members of the team will not accept the possibility of a range of results of the analysis, then it is important to reopen the entire planning and scoping discussion before anything is done in the analysis phase, since the planning and scoping phase has not been satisfactorily completed.

## 3. THE ANALYSIS PHASE

The risk assessment paradigm most widely used during the past two decades was first documented by the National Research Council (NRC, 1983). It consists of four parts: hazard identification, dose-response assessment, exposure assessment, and risk characterization. This

paradigm was developed when almost all risk assessments were being done on single chemicals. Nevertheless, it is a useful place to start when considering cumulative risks. There are a number of ways to approach cumulative risk, either starting with the NRC paradigm or using a different approach. Each may present its own challenges in methods, data, and analysis. Four examples of general approaches are described below. There will undoubtedly be others developed as the science advances.

## 3.1. General Approaches to Cumulative Risk Assessment

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

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

### 3.1.1. Combining Individual Stressor Risks.

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

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

Calculating individual stressor risks and then combining them presents largely the same challenges as combination toxicology, namely, taking interactions into account. Toxicity addition, independence, synergy, or antagonism still need to be evaluated, but since risk estimates for various stressors are often presented as values on the same numeric scale (e.g., as probabilities or as fractions of an RfD or RfC), cancer risks are often just added together, as are non-cancer risks

as part of a Hazard Index. Addition of cancer risk estimates or hazard indices without consideration for how these stressors may interact is making an (implicit or explicit) assumption of dose additivity, which requires explanation in an assessment. This will be discussed further in Chapter 4.

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

3.1.2. Use of Risk Factors Developed from Epidemiologic Associations.

The medical profession has long used "risk factors" to predict the chances of particular health effects in individual patients. In this approach, the characteristics of individuals within the population are correlated with the incidence of specific diseases or effects. For example, the risk factors for stroke are: increasing age, heredity (family history) and race, prior stroke, high blood pressure, cigarette smoking, diabetes mellitus, carotid and other artery disease, heart disease, transient ischemic attacks (TIAs), high red blood cell count, sickle cell anemia, socioeconomic factors, excessive alcohol consumption, and certain types of drug abuse (American Heart Association, 2000). Each of these factors can be correlated with stroke incidence, and then the risk of stroke from various combinations of these factors can be explored. Physicians use models containing effect-specific risk factors to advise patients of the probabilities of future effects (e.g., stroke, breast cancer) based on their medical history. Although the medical data upon which these factors are based have been well developed for many effects in humans, there are substantial data gaps remaining in terms of the role played by exposures to many chemicals in the environment in the development of human disease. This approach may be built on links between stressors and effects for more well-studied stressors, but may be limited in both capability for quantification, and coverage for stressors with less robust health effects data bases.

3.1.3. Biomarkers and Biomonitoring.

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

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

(biomarkers of exposure) or the current health status of individuals (biomarkers of effect). Use of biomarkers for a group of chemicals or stressors which act upon individuals in the same way can give the assessor a picture of where an individual currently falls on the continuum from exposure to effects, making it much easier to predict risks if additional exposure occurs. A few biomarkers (or even a single one) can represent exposure to a suite of chemicals. Although this reduces the analytical burden and simplifies the process of estimating cumulative risk, the approach loses some of the advantages of single-chemical assessment (especially being able to quickly discern the importance of different pathways and routes of exposure contributing to the risk). This may be the approach of choice in the future, but the state-of-the-science is not developed enough to make this practicable today in an assessment with large numbers of diverse stressors (although it may be possible to do this for more simple cases). One of the benefits of this method, the development of data which show the actual current exposure and risk status of a population, is also its major impediment: it can require extensive (or for humans, possibly invasive) monitoring. This can be not only costly, but difficult to obtain. This approach uses primarily measurement methods, and also can develop statements of probability of adverse effects of additional incremental exposures. This approavch holds great promise for simplification of a cumulative risk assessment, but few methods exist at this time for applying this approach in a cumulative assessment.

#### 3.1.4. Other Types of Probability Statements.

Not all statements of probability of harm are expressed as probabilities of specific health effects. Bernard Cohen, in his *Catalog of Risks Extended and Updated* (Cohen, 1991), uses mortality ratios to derive "loss of life expectancy" (LLE) estimates for a wide variety of risk-related activities. For example, workers in all occupations have a 60 day LLE as a result of working, but workers in agriculture have a 320 day LLE, construction workers a 227 day LLE, etc., as a result of their particular occupation. These types of statements are empirically derived, probability-based statements of harm that do not use "probability of adverse health effect" as the basis for the risk statement. For estimates such as LLEs, one could theoretically add up the various activities and the corresponding LLEs in days to estimate a cumulative risk in terms of loss of life expectancy. Other bases for risk statements include the quality-adjusted life year (QALY), which has been used extensively in the medical field for cost-benefit analysis and also has been proposed for use in comparative risk analysis (USEPA, 1998f). In a sense, this approach is similar to the second approach, where risks are added, but it differs qualitatively in the types of risk statements derived. These "other" types of probability statements could conceivably be used in cumulative risk assessment.

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

The approach of combining toxicities or individual stressor risks to come up with an

estimate of cumulative risk is most similar to traditional health risk assessment for chemicals, and provides a quantitative analysis, yet may include a large degree of uncertainty.

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

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

### 3.2.1. Characterization of Hazard Identification and Dose-Response.

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

Dose-response assessment is the characterization of the relationship between the concentration, exposure, or dose of a pollutant or pollutant group and the resultant health or environmental effects. The nature of quantitative dose-response assessment varies among pollutants. Sufficient data exist for a few pollutants, such as the air pollutants ozone or carbon monoxide, so that relatively complete dose-response relationships can be characterized. In such cases, there is no need for extrapolation to lower doses because adequate health effects data are available for humans at environmental levels. Such is not the case, however, for most pollutants. Most epidemiologic and toxicologic data on toxic pollutants typically result from exposure levels that are high relative to environmental levels. Consequently, dose-response assessment methods for most toxic pollutants generally consist of two parts. First is the evaluation of data in the observable range, and second is the extrapolation from the observable range to low doses/risks.

Recent terminology refers to the result of analysis in the observable range as the "point of departure," from which extrapolation begins. The approaches used for evaluation in the observable range are similar for all types of effects, while the Agency's current extrapolation methods differ considerably for cancer and non-cancer effects. Efforts are underway to harmonize these two methods.

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

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

3.2.1.1. Current Methods for Assessing Noncancer Effects.

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

For identification of long-term (chronic) hazards other than cancer, EPA reviews the health effects literature and characterizes its strengths and weaknesses, using a narrative approach rather than a formal classification scheme. Available data on different endpoints are arrayed and discussed, and the effects (and their attendant dose/exposure levels) are described. Particular attention is given to effects that occur at relatively low doses or that may have particular relevance to human populations. Information is presented in a narrative description that discusses factors such as the methodological strengths and weaknesses of individual studies (as well as the overall database), the length of time over which the studies were conducted, routes of exposure, and possible biological mechanisms. EPA considers the severity of effects, which may range from

severe, frank, effects that can cause incapacitation or death, to subtle effects that may occur at the cellular level but are early indicators of toxic effects. Not all effects observed in laboratory studies are judged to be adverse. The distinction between adverse and non-adverse effects is not always clear, and considerable professional judgment is required in applying criteria to identify adverse effects. All of these observations are integrated into a presentation that gives a concise profile of the toxicological properties of the pollutant.

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

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

The RfC or RfD is then derived by consistent application of uncertainty factors (UFs), generally a 1, 3 or 10, to account for recognized uncertainties in the extrapolation from the experimental data and exposure conditions to an estimate (the RfC or RfD) appropriate to the assumed human lifetime exposure scenario (Barnes and Dourson, 1988; USEPA, 1994). The standard UFs are applied as appropriate for the following extrapolations or areas of uncertainty: 1) Laboratory animal data to humans; 2) Average healthy humans to sensitive humans; 3) Subchronic to chronic exposure duration; 4) LOAEL to NOAEL; and 5) Incomplete data base. The composite UF will depend on the number of extrapolations required. RfCs have been derived using composite UFs that range from 10 to 3,000, with most RfCs using factors of 100 to 1,000.

The use of order-of-magnitude uncertainty factors for RfCs and RfDs and the definition of the RfC or RfD as having "uncertainty spanning perhaps an order of magnitude" are indications of the general lack of precision in the estimates.

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

3.2.1.2. Current Methods for Assessing Cancer Risks.

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

In 1996, EPA proposed major revisions of the carcinogen hazard identification scheme. The proposed revision to the cancer risk assessment guidelines (USEPA, 1996c), which has undergone subsequent revisions as a result of Scientific Advisory Board reviews (e.g., USEPA, 1999e), focuses on narrative statements describing the main lines of evidence and their interpretation, replacing the current alphabetic designations. The proposed guidelines also replace the system of stepwise consideration of different types of data with a single comprehensive

evaluation process that stresses the coherence of various data elements. The result is a single scientific interpretation that evaluates, to the extent possible, how well the commonality of mode of carcinogenic action between human beings and the various test systems has been established. Emphasis is also placed on defining the qualitative conditions under which carcinogenic hazards might be expected. If warranted, limitations to the finding of carcinogenic hazard can be drawn based on route of exposure, existence of other factors needed for tumorigenesis, and doses below which elevation of cancer risk is not expected.

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

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

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

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

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

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

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

In the case of linear carcinogens, this cumulative exposure assumption has been carried into the risk assessment step. Regardless of the details of the exposure circumstances for the study on which the cancer potency was based, it is assumed that there is a linear relationship between amounts of exposure and associated cancer risk For non-linear carcinogens assessed in cumulative risk assessments[6], the details and sequence of exposure may be important, both in developing the dose-response relationship and in predicting risk associated with exposures of interest.

As some chemicals may have the ability to affect an organism's response to other chemicals, consideration of the time sequence of exposure may take on an additional layer of

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

complexity in multiple chemical cumulative risk assessments.

3.2.1.4. Issues Associated with Assessing Mixtures of Stressors.

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

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

To address concerns over health risks from multi-chemical exposures, EPA issued *Guidelines for Health Risk from Exposure to Chemical Mixtures* in 1986 (USEPA, 1986b). Those Guidelines described broad concepts related to mixtures exposure and toxicity and included few specific procedures. In 1989, EPA published guidance for the Superfund program on hazardous waste that gave practical steps for conducting a mixtures risk assessment (USEPA, 1989a). Also in 1989, EPA published the revised document on the use of Toxicity Equivalence Factors for characterizing health risks of the class of chemicals including the dibenzo-dioxins and dibenzofurans (USEPA, 1989b). In 1990, EPA published a Technical Support Document to provide more detailed information on toxicity of whole mixtures and on toxicologic interactions (e.g., synergism) between chemicals in a binary (two-chemical) mixture (USEPA, 1990a). The concept of toxicologic similarity was also discussed, and is expanded upon in the recent *Guidance for Conducting Health Risk Assessment of Chemical Mixtures* (USEPA, 2001a).

The prediction of how specific mixtures of toxicants will interact must be based on an

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

Risk assessment on mixtures usually involves substantial uncertainty. If the mixture is treated as a single complex substance, these uncertainties range from inexact descriptions of exposure to inadequate toxicity information. When viewed as a simple collection of a few component chemicals, the uncertainties include the generally poor understanding of the magnitude and nature of toxicologic interactions, especially those interactions involving three or more chemicals. Because of these uncertainties, the assessment of health risk from chemical mixtures must include a thorough discussion of all assumptions and the identification when possible of the major sources of uncertainty.

3.2.1.5. Hazards Other than Chemical Hazards.

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

The context of a risk assessment might lead a risk assessor to consider the adverse effects

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

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

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

3.2.1.6. Vulnerability.

One of the concepts that can be used in risk assessments (both for human health and ecological assessments) is that of *vulnerability* of the population or ecosystem. Vulnerability has been a common topic in socioeconomic and environmental studies. The European Commission's TEMRAP (The European Multi-Hazard Risk Assessment Project), studying vulnerability to natural disasters such as floods, windstorms, fires, earthquakes, and others, defines "vulnerability" as "the intrinsic predisposition of an exposed element to be at risk of suffering losses (life, health, cultural or economic) upon the occurrence of an event of [a specific] intensity" (European Commission, 2000).

Vulnerability of a population places them at increased risk of adverse effect. The Agency's risk characterization policy and guidance (USEPA, 2000c) touches on this concept by recommending that risk assessments "address or provide descriptions of [risk to] ... important subgroups of the population, such as highly exposed or highly susceptible groups". Further, the Agency's guidance on planning and scoping for cumulative risk assessments (USEPA, 1995b) recognizes the importance of "defining the characteristics of the population at risk, which include individuals or sensitive subgroups which may be highly susceptible to risks from stressors or

groups of stressors due to their age, gender, disease history, size or developmental stage". That guidance also recognizes the potential importance of other social, economic, behavioral or psychological stressors that may contribute to adverse health effects (e.g., existing health condition, anxiety, nutritional status, crime and congestion). These same concepts may also be discussed as a group in terms of "population vulnerability." The various ways in which a population may be vulnerable are discussed below in four categories.

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

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

The third category of vulnerability is *differential preparedness* to withstand the insult of the stressor, and the fourth is the *differential ability to recover* from the effects of the stressor. These last two are linked to what kind of coping systems and resources an individual, population, or community has. Preparedness or recovery is often a crucial factor in ecological assessments. In human health assessments, lack of access to health care, income differences, unemployment, or lack of insurance, for example, may affect a community's ability to prepare or recover from a stressor. One aspect of differential ability to recover is illustrated by differing survival rates for the same disease (e.g., Lantz, et. al 1998).

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

3.2.2. Characterization of Exposure.

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

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

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

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

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

**Components of Exposure Assessment**

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

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

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

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

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

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

3.2.2.1. The Time Dimension of Exposure.

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

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

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

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

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

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

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

**Some Examples of Exposure Models which Consider Time Aspects**

Calendex (Novigen Sciences, Inc), integrates different pathways e.g., dietary (food and water), and residential, and routes (oral, dermal, inhalation) of exposure using a calendar-based probabilistic approach . One of the important factors of this approach is it provides estimates of risk which reflect aggregate and cumulative exposure to discrete individuals with exposure pathways and routes appropriately linked for the scenarios being assessed. Calendex also allows one to estimate exposure pre- and post use of a chemical, as well as degradation periods**.** Calendar based assessments maintain the integrity of the individual by capturing: the location of the exposed individual, the time of year in which he or she was exposed, and the patterns of exposure. Calendex also allows for a variety of time-breakout options for analysis of exposure. For example, specific, single day exposures which are multipathway (e.g., one could perform an assessment on June 21 if one knew of specific exposure timing with which we were concerned).

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

Other models include the LifeLine Model, developed under a cooperative agreement between EPA/OPP and Hampshire Research Institute (Hampshire Research Institute, 1999, 2000); the Stochastic Human Exposure and Dose Simulation Model (SHEDS), under development by EPA's Office of Research and Development (Zartarian, *et al.*, 2000), and the Cumulative and Aggregate Risk Evaluation System (CARES), under development by member companies of the American Crop Protection Association (APCA, 1999).

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

3.2.2.2. Variation of Mixtures.

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

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

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

3.2.2.3. Sources and Pathways of Exposure.

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

These chemicals can reach the receptor by a variety of pathways. For example, application of an agricultural pesticide can potentially contribute to a farm-worker population's

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

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

3.2.2.4. Subpopulations with Special Exposures.

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

Subpopulations at risk of high exposure due to geographic proximity could include workers at a facility which is a source of a stressor or residents near such sources. Specific examples might be people living in the plume from a coal burning power plant, those near and using a polluted water body (for example, for fishing or recreation), or along roadways with high levels of vehicular traffic.

Occupational exposures may be either direct (occurring in the workplace) or indirect (occurring at home). Indirect occupational exposures include those experienced by family members of those occupationally exposed, who may be exposed to occupational chemicals brought into the house by the worker (e.g., on clothes, breath, etc). Thus, workers or family

members may be subject to greater exposures than others in the population without this additional burden.

Examples of subpopulations at high exposure due to activity patterns may include people who exercise heavily in polluted air, recreational or subsistence fishers or hunters who consume large quantities of fish or wild animals, farmers or others who get a large percentage of their food from a location near a source of pollution and live in areas with high pesticide use, individuals with long commutes in automobiles, or children (because they consume a larger amount of food, drink, and air relative to their body weight, and because of additional exposure routes such as incidental soil ingestion).

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

It is important to recognize that some heavily exposed populations may also be particularly vulnerable. Examples of those who could be particularly vulnerable to certain stressors include children during certain stages of development, people with chronic respiratory problems, the elderly, and those economically disadvantaged without access to medical care. A cumulative risk assessment may need to take into account potential combinations of high exposure and high vulnerability.

3.2.2.5. Exposures to Non-chemical Stressors.

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

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

## 3.3. Issues Related to the Approach of Using Risk Factors

[To be added]

### 3.4. Issues Related to the Approach of Biomarkers and Biomonitoring

[To be added]

### 3.5. Issues Related to Other Approaches

[To be added]

## 4. THE INTERPRETATION (RISK CHARACTERIZATION) PHASE

### 4.1 Risk Estimation

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

#### 4.1.1. Methods for Combining Chemical Risks

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

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

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

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

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

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

4.1.2. Other Impacts or Effects

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

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

In trying to assess all of these different types of stressors, it is helpful to determine what types of effects the stressors produce, and then to try to group stressors by like effects. In an ideal situation – one quite remote from today's state of the science, to be sure – one would also know the mechanism or mode of action by which the stressor causes the effect, allowing more refined grouping by mechanism/mode of action.

4.1.2.1. Stress-Induced Risks.

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

The Agency for Toxic Substances and Disease Registry (ATSDR) held an expert panel workshop in 1995 on the subject of psychological responses to hazardous substances (ATSDR, 1995). In this report, the panel noted that there is "a significant lack of information" about how often communities near hazardous waste sites or spills suffer chronic stress reactions, but that psychological stress causes both psychological changes that can be measured by self-reports and objective tests, as well as physical changes such as increased blood pressure, heart rate, and biochemical parameters such as changes in stress hormones. Assessing the levels of stress, and their potential contribution to risk, is difficult for a variety of reasons. The report notes that "unlike the damage and injuries caused by a natural disaster, many toxic substances are invisible to the senses.... In the face of no external cues and uncertain circumstances, each person affected by a hazardous exposure develops their own beliefs about the nature of the resultant harm. These beliefs are based on the facts available to them, pre-existing opinions, cultural factors, sensory cues, and the beliefs of leaders and others in the community. On the other hand, scientists tend to rely on objective data produced by specialized testing that is subject to statistical analysis.... Unlike a natural disaster, which hits and has a low point after which recovery can begin, the response to a hazardous waste site can take 12 to 20 years."

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

> A methodology does not exist that would allow for discrimination between stress or neurotoxicant-mediated effects in community-based studies.... Experimental animal data exist to suggest that stress levels can modulate a toxic response; however, the question of specificity remains. Given that stress can induce or unmask a latent effect of a toxicant, there is the possibility that chronic stress could alter basal levels of neurofunctioning and shift the threshold for neurotoxicity. Indeed, one may find a shift in the dose response to a neurotoxicant; however, a specific effect of the neurotoxicant needs to be examined in greater detail than the generalized non-specific endpoints. Detecting such a shift would require the knowledge of toxicant-specific biological mechanisms of actions, which most often are not known. (ATSDR, 1995, page 30)

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

4.1.2.2. Quality-of-Life Risks.

Another group of stressors and effects whose evaluation may require a different approach

from the traditional NRC risk paradigm are the quality-of-life issues. To evaluate the effects from these types of stressors, a more deliberative approach is needed than is used in, say, cancer risk analysis. EPA's *Guidebook to Comparing Risks and Setting Environmental Priorities* (EPA, 1993b) suggests a six-step process in Quality-of-Life Analysis:

1. Identify impacts and determine the values of the community.

2. Identify and define evaluative criteria.

3. Collect and analyze data on impacts.

4. Characterize impacts for all problem areas.

5. Present findings and rank problem areas for quality-of-life impacts.

6. Analyze future environmental conditions and risk management considerations.

Quality-of-Life impacts are determined by analyzing a set of criteria developed for each community, depending on what they value. Stressors are those things that threaten to degrade the quality-of-life criteria for that community. An example of a set of quality-of-life criteria, and their descriptions, is given below. These criteria were developed by the State of Vermont's Agency of Natural Resources (State of Vermont, 1991):

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

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

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

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

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

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

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

Vermont's experience in evaluating these criteria was described as a qualitative description of risk:

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

Quality-of-life issues can encompass much more than the criteria used here as an example. Some cumulative risk assessments may include quality-of-life criteria as measures of effects, in addition to human health effects or ecological effects. How these very different types of risks may be included in a cumulative assessment is discussed in the following section.

#### 4.1.3. Combining Different Types of Risk

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

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

exposures may be presented as the percent of a reference dose (%RfD) or other chronic dose believed to be without adverse effects. Finally, if the same stressor is associated with cancer, risks may be presented as a probability of developing cancer.

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

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

4.1.3.1. Converting Adverse Effects to a Common Metric

As discussed at the beginning of Chapter 3, there are several different theoretical approaches to cumulative risk assessment. Some of these require synthesizing a risk estimate (or risk indication) by "adding up" risks for different parts of the risk picture. Actual mathematical addition, of course, requires a common metric. Finding a common metric for dissimilar risks (cancer vs. non-cancer, human vs. ecological, etc.) is not strictly an analytic process, since some judgments must be made as to how to link two or more separate scales of risks. These judgments often involve subjective values, and because of this, it is a deliberative process.

As an example of combining different effects into a common metric and the consequent judgment needed to achieve a common metric, the EPA Office of Pollution Prevention and Toxics in 1999 released its CD-ROM called "Risk-Screening Environmental Indicators Model, Version 1.0" (USEPA, 1999h)[14]. In this model, emissions for both carcinogens and non-carcinogens are weighted by a toxicity factor so that they can be combined in a risk-based screening "score" for a particular geographic area. The scale for this weight for carcinogens is related to the unit risk factor, and the weight for the non-carcinogens is based on the RfD. According to the authors, it is possible to relate these two scales by making a judgment as to how they relate. They note that in their case, "when combining cancer and noncancer endpoints, it is assumed that exposure at the RfD is equivalent to a $2.5 \times 10^{-4}$ cancer risk" (Bouwes and Hassur, 1998).

Obviously, as Bouwes and Hassur acknowledge, equating an Hazard Quotient value of 1.0

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

(exposure at the RfD) with a cancer risk of $2.5 \times 10^{-4}$ is a judgment that is outside the strictly analytic part of an assessment; the equating of the two points in the respective scales represents a value judgment and as such can be debated. This particular part of the assessment is deliberative in nature. In most cases, construction of a single scale for different types of endpoints will involve *comparative risk,* a field where different types of risks or endpoints are ranked, compared, or converted to a scale based on the judgments and values of the persons doing the assessments (USEPA, 1993b, 1998f, 1999f). When converting such diverse endpoints as human health, ecological, and quality of life, comparative risk is almost always involved, and this makes combining of diverse risks a *deliberative* rather than an analytic process.

There have been some attempts to quantify diverse risks in a common metric without resorting to the values needed as input for comparative risk. It has been suggested that "time is the unit of measure for the burden of disease"; whether the disease results in disability or premature mortality (Murray, 1994). Based on this premise, economic analyses of the costs and benefits of disease intervention strategies have used Quality Adjusted Life Years (QALYs) and Disability Adjusted Life Years (DALYs) as the metrics for the adverse effects of disease. These metrics are intended to reflect the years of life spent in disease states and the years of life lost due to premature mortality resulting from disease as a surrogate measure or risk from a variety of different types of effect.

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

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

Categorical regression may provide another tool for combining disparate effects using a

common metric. In this approach, adverse effects are assigned to severity categories (again, a judgment making the process deliberative) and the ordered categories are regressed against increasing dose (Teuschler et al., 1999). The results of the regression analysis may provide an RfD that can reflect a variety of effects. Furthermore, the probability of experiencing effects associated with a particular severity category at doses above the RfD can be determined. To date, categorical regression has been applied to data for individual chemicals and has been used to compare chemicals with similar effects (see Dourson et al., 1997 and Teuschler et al., 1999). The use of categorical regression as a tool for combining disparate effects will require considerable methods development research.

4.1.3.2. Translating Adverse Effects into an Index

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

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

Various environmental risk indices have been developed and applied to ranking and comparative analyses. Often, these indices employ surrogate measures for risk rather than using actual calculations of the probability of adverse effects. One such index is the Hazard Ranking System (HRS) [47 *Fed. Reg.* 31219, dated July 16, 1982, and amended 55 *Fed. Reg.* 51532, dated December 14, 1990], used to place uncontrolled waste sites on the National Priorities List (NPL) for Superfund. This index is based on the likelihood of off-site movement of waste, the toxicity of the waste, and the people and sensitive environments that may be affected. It also uses corrosivity, toxicity, fire hazard and other factors, all scored and combined into one numerical indicator of overall hazard potential. Such an approach for a composite index has been suggested for communication of cumulative risk (Hertzberg, 2000).

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

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

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

#### 4.1.3.3. Other Approaches

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

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

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

4.1.3.4. General Issues with Combining Risks

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

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

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

## 4.2. Risk Description

The ultimate useable product in the risk assessment process is the risk characterization, in which the information from all the steps is integrated and an overall conclusion about risk is synthesized that is complete, informative, and useful for decision-makers. The nature of the risk

characterization will depend on the information available, the regulatory application of the risk information, and the resources (including time) available. It is important to identify and discuss all major issues associated with determining the nature and extent of the risk. Further, the EPA Administrator's March 1995 *Policy for Risk Characterization* (U.S. EPA, 1995a) specifies that a risk characterization "be prepared in a manner that is clear, transparent, reasonable, and consistent with other risk characterizations of similar scope prepared across programs in the Agency." In short, estimates of health risk are to be presented in the context of uncertainties and limitations in the data and methodology.

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

**RISK CHARACTERIZATION GUIDING PRINCIPLES**

Regarding information content and uncertainty aspects:

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

Regarding risk descriptors:

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

Source: USEPA, 1995b.

Risk assessments are intended to address or provide descriptions of risk to one or more of the following: (1) individuals (including highly susceptible individuals) exposed at average levels and those in the high-end portions of the risk distribution; (2) the exposed population as a whole; and (3) important subgroups of the population such as highly susceptible groups or individuals (e.g., children), if known. Risk predictions for sensitive subpopulations are a subset of population risks. Sensitive subpopulations consist of a specific set of individuals who are particularly susceptible to adverse health effects because of physiological (e.g., age, gender, pre-existing conditions), socioeconomic (e.g., nutrition), or demographic variables, or significantly greater levels of exposure (USEPA, 1992a). Subpopulations can be defined using age, race, gender, and other factors. If enough information is available, a quantitative risk estimate for a subpopulation can be developed. If not, then any qualitative information about subpopulations gathered during hazard identification should be summarized as part of the risk characterization.

## 4.3. Uncertainty Analysis

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

- when one is performing an analysis in which people's attitude toward risk is likely to be important, for example, when people display significant risk aversion;

- when one is performing an analysis in which uncertain information from different sources must be combined. The precision of each source should help determine its weighting in the combination; and

- when a decision must be made about whether to expend resources to acquire additional information. In general, the greater the uncertainty, the greater the expected value of additional information.

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

**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.

Cumulative risk assessment will usually be used in a decision-making process to help inform the decision-maker(s). For this reason, it is important that the decision makers be made explicitly aware of any assumptions that may significantly affect the conclusions of the analysis

(item #6 in the box above). Morgan and Henrion suggest that these assumptions include:

- the main policy concerns, issues, or decisions that prompted the assessment to be done;
- the evaluation criteria to be used to define issues of concern or options;
- the scope and boundaries of the assessment, and ways in which alternate selections might influence the conclusions reached;
- soft or intangible issues that are ignored or inadequately dealt with in the quantitative analysis (e.g., intrinsic value of wilderness, equity of distribution of risks and benefits);
- approximations introduced by the level of aggregation or by level of detail in models;
- value judgments and tradeoffs; and
- the objective function used, including methods of combining ratings on multiple criteria (or combining risk scales). [adapted from Morgan and Henrion, 1990]

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

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

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

In Item #8 in the box on the previous page, Morgan and Henrion suggest that an assessor needs to find out which assumptions and uncertainties may significantly alter the conclusions, and that process can be done using sensitivity and uncertainty analysis. Techniques for these include:

- deterministic, one-at-a-time analysis of each factor, holding all others constant at nominal values;
- deterministic joint analysis, changing the values of more than one factor at a time;
- parametric analysis, moving one or a few inputs across reasonably selected ranges to observe the shape of the response; and
- probabilistic analysis, using correlation, rank correlation, regression, or other means to examine how much of the uncertainty in the conclusions is attributable to which inputs.

Finally, Morgan and Henrion answer the question of why we should consider uncertainty analysis with the following point. "Policy analysts have a professional and ethical responsibility to present not just "answers" but also a clear and explicit statement of the implications and limitations of their work. Attempts to fully characterize and deal with important associated uncertainties help them to execute this responsibility better." (Morgan and Henrion, 1990)

## 4.4. The Information Provided by Cumulative Risk Assessment

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

### 4.4.1. Making Sense of Multiple Stressor Effects

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

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

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

4.4.2. Cumulative Risk Assessments in a Public Health Context

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

Health statistics, including death rates and incidence of various diseases, illustrate the impact of a variety of risk factors (e.g., smoking as well as environmental pollutants) and risk reduction factors (e.g., exercise and good nutrition, as well as pollution control measures). Indeed, population health statistics are reflective of *all* risk and risk reduction factors in a population's history-to-date. Even the best cumulative risk assessment given today's state of the science would fall short of being able to include an evaluation of the magnitude and interactions of *all* stressors and effects. At best, the risk estimates of a cumulative risk assessment will reflect *some* of the risks which may be reflected in community health statistics. With rare exceptions[16], cumulative risk assessment estimates would not be expected to match exactly with community health statistics, even for specific health endpoints such as specific cancers.

4.4.3. How Scope and Purpose of the Assessment Affect Results

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

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

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

Finally, much of the activities and data needed for cumulative risk assessment overlap with the jurisdiction of other public health agencies, and academia. The most successful cumulative risk assessments of the future are likely to be those where cooperation among organizations (Federal, State, private, environmental, academic, etc.) leads to use of the best data and tools for the various parts of the assessment.

### 4.5. Using the Results of the Assessment

Once the results of an assessment are in hand, the assessment participants will usually focus primarily on the use of those results. The intended use of the assessment was considered at the beginning, in the Problem Formulation Phase, both to plan the assessment work and to set the framework for what possible actions might be taken at this point.. A detailed discussion of the use of the results of a cumulative risk assessment is beyond the scope of this document, but in deciding on a course of action, other considerations will need to be taken into account along with the results of the cumulative assessment.

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

If the goals of a cumulative risk analysis are to estimate the total risk from multi-chemical and multi pathway exposure to individuals living within a geographical area of concern, then an important objective is to identify the major risk contributors in order to understand the sources, pathways, and stressors which contribute most to that overall risk. The results of a cumulative risk assessment provide an additional tool for the risk manager, one that permits a more complete accounting and more explicit analysis to target follow-up risk mitigation strategies toward those stressors which most contribute to the population's risk.

If action to mitigate or prevent risk is the goal of the stakeholders, then options for action

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

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

## 5. GLOSSARY

[to be added]

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

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

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

## A.1. Resources Relevant to Chemical Exposures

*General guidelines:* [to be completed]

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

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

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

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

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

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

*Biological stressors:* [to be added]

*Radiological stressors:* [to be added]

*Noise, vibration, and congestion:* Increases in noise levels, e.g., from truck and/or rail traffic, could result in increased stress to local residents, as could the additional traffic congestion. Increased vibrations from additional truck or rail traffic could also increase or accelerate damage to local roads and other structures such as residences (foundation cracks), water and sewer lines, etc.. These types of damage could result in additional costs and stress to the local population. The U.S. Department of Housing and Urban Development has issued *The Noise Guidebook* (HUD, 1991), which implements the existing noise regulations [24 CFR 51-B] and includes the HUD Noise Assessment Guidelines. (The *Guidebook* is available in hard copy only.) The Federal Railroad Administration has developed a manual called *High-Speed Ground Transportation Noise and Vibration Impact Assessment* (DOT, 1998) which provides the theory, equations, and applications of noise and vibration analysis for high-speed railroads. Much of the theory and information is also applicable to other noise and vibration problems. Appendix A of the DOT *Guide* is a general discussion of noise concepts, with references. The *Guide* is available on-line.

*Odor:* EPA's Office of Wastewater Management has issued a report called *Guide to Field Storage of Biosolids* (USEPA, 2000e) which contains an appendix on "Odor Characterization, Assessment, and Sampling." Odor assessment is an analytic-deliberative process, involving both science-based analytical methods and more subjective analysis. The appendix of the *Guide* discusses sensory characterization of odors (character, intensity, pervasiveness, quantity), some practical options for assessing odors in a community, and the chemistry of odors (including range

of odor thresholds). It also discusses odor sample collection and analysis, and has several dozen references for further information. This report is available on-line.

*Other non-chemical stressors:* [to be added]

## APPENDIX B: ASSESSING ACCIDENTAL CHEMICAL RELEASE EXPOSURE

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

The *process analysis* is a formal, systematic analysis of the process where a chemical is handled to determine the probabilities and consequences of acute, catastrophic failures of engineered systems leading to an accidental release of the chemical. This analysis is often called a Process Hazards Analysis (PHA). For example, if a process temperature control fails, allowing pressure to build in a reactor system, an emergency pressure relief valve may open, venting chemical to the atmosphere. More severe hypothetical scenarios are often also evaluated, such as the failure of a storage tank, leading to a massive spill. Several formal PHA evaluation techniques are available including "What-If," "Failure Mode and Effect Analysis," "Event-Tree", or "Fault-Tree." (USEPA 1998c, AIChE, 1992)

The *likelihood or frequency of accidents* step is an evaluation of each of the scenarios uncovered in the process analysis step for likelihood or frequency of occurrence. For example, equipment failure rate data or accident histories can be used to judge how frequently certain accidental releases might occur.

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

*Dispersion or consequence modeling* is performed once the source terms (rate and duration of the release) are known. In this step, the consequences associated with those predicted releases can be evaluated. If the chemical released is a gas and toxic by inhalation, the consequence assessment would involve an analysis of the downwind dispersion, or the distance the chemical will travel downwind to a particular toxic concentration. If the chemical is flammable, the consequences of an explosion or fire might be analyzed. A wide variety of dispersion and consequence modeling tools, ranging from simple screening models to

sophisticated and complex computer applications, are available for this step (USEPA 1999d, AIChE 1996, USEPA 1993a). In addition to the source terms generated above, several other data elements are needed, such as physical/chemical properties (e.g., whether the vapor cloud is heavier than air or water reactive), meteorological conditions (e.g., wind speed and direction, temperature, humidity), and terrain surrounding the facility (e.g., buildings or valleys that may channel or disperse a vapor cloud). Physical/chemical properties can be found in chemical reference texts such as *Kirk-Othmer's Encyclopedia of Chemical Technology* (Kroschwitz and Howe-Grant, 1994), *Perry's Chemical Engineers' Handbook* (Perry, et al., 1997), on Material Safety Data Sheets (MSDS)[17], or in the *Guidance for Offsite Consequence Analysis* (USEPA 1999d). Meteorological conditions are often collected on-site or at local airports; information about terrain can be collected from topological maps or by visual inspection. Guidance on all these parameters is available in USEPA 1999d.

The final step in a chemical accident exposure analysis is the *exposure assessment.* The exposure assessment is related to, and builds from, the dispersion or consequence modeling step. The dispersion or consequence modeling depends on a health endpoint and the exposure level related to that endpoint. The endpoint reflects the health effect of concern; e.g., if lethality resulting from an acute toxic exposure is the concern, then the endpoint would be the airborne concentration necessary to cause acute lethality. Besides lethality, concentrations for certain health effects (e.g., odor thresholds, eye irritation) are available for several common toxic substances (NIOSH 1997, ACGIH 1998, AIHA 2000). These established concentrations, however, may be based on toxicity studies that are weak, derived by consensus, or may not be the most representative of actual exposure effects. Further, little is known about the chronic or long-term effects associated with an acute, non-lethal accidental exposure, so most assessments of the risk from chemical accidents focus on acute or short-term effects. Work is currently underway to develop more appropriate emergency exposure concentrations for a number of common toxic substances.

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

The results of all of these steps can be combined to generate a number of measures of risk

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

introduces greater uncertainty to the analysis being performed.

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

## APPENDIX E: SOME THOUGHTS ON BACKGROUND EXPOSURES

When looking at aggregate exposures or cumulative risks of citizens, so-called "background exposures" to specific chemicals are no less "real" exposures than the pollution usually studied for regulatory purposes. Whereas in historical single-chemical assessments done for limiting pollution, background sources of the chemical were often irrelevant to the questions being asked of the assessment (or ignored as having negligible effect on risk), background sources are rarely irrelevant with cumulative risk assessments[18].

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

Assessments of morbidity incidence and death rates, market basket surveys, and pesticide residue surveys also provide information which can be reflective of background chemical concentrations as well as overt pollution. Background issues extend across all media, beyond

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

regulated sources, and beyond direct exposure. Many chemicals are naturally present in the environment (e.g., soils, water, vegetation and other biota) and are consequently part of dietary, dermal and inhalation exposures. In some cases, naturally-occurring substances may occur at levels that exceed health-based or risk-based regulatory standards (e.g., drinking water standards), or other levels established to protect human health and the environment. Since cumulative risk assessments are population based, exposures due to naturally-occurring background concentrations should usually be of importance.

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

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

## APPENDIX F: RESEARCH AND DEVELOPMENT NEEDS

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

*Understanding the Timing of Exposure and its Relationship to Effects*

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

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

*Understanding the Composition and Toxicity of Mixtures*

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

EPA's *Guidance for the Health Risk Assessment of Chemical Mixtures* (USEPA, 2001a) presents approaches for combining the toxicities of multiple chemical stressors. These approaches necessarily involve a number of simplifying assumptions when the mixtures are complex. Although the current methods provide a valuable resource for assessing cumulative risks, future cumulative risk assessment will need a more complete understanding of the interactions among chemicals in complex mixtures. Some current research efforts are seeking to identify toxicologic principles of joint action that are applicable to mixtures involving many chemicals.

*Applying the Risk Factor Approach to Environmental Health Risks*

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

substantial data gaps in terms of the role played by exposures to environmental stressors in the development of human disease, and correlations of environmental exposures with disease outcomes are generally not available.

*Using Biomarkers and Biomonitoring*

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

*Considering Hazards Presented by Non-Chemical Stressors*

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

*Considering Psychological Stress as Part of Cumulative Risk*

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

*Considering All Aspects of Vulnerability*

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

*Methods for Combining Different Types of Risk*

Another key concept in the definition of cumulative risk assessment is that it represents the integration of effects from stressors acting together. This implies that, in some cases, it may be necessary to combine disparate measures of risk (i.e., different types of effects) to simplify the expression of cumulative risks. There have been some attempts to collapse complex arrays of risk into a few or even a single measure. These approaches have involved the use of common metrics (e.g., Quality Adjusted Life Years, Disability Adjusted Life Years, Loss of Life Expectancy, etc.), indices (e.g., Hazard Ranking System, etc.), and the categorization of effects (e.g., as for categorical regression). Alternatively, Geographic Information Systems (GIS) and mapping techniques can be used to graphically portray integrated information on risks without mathematically combining disparate measures. Much methods development work remains to be completed in each of these areas.