Harvard Center for
Risk Analysis

February 2009
Volume 17, Issue 1

Risk in Perspective

An Overview of "Science and Decisions: Advancing Risk Assessment"

Jonathan Levy, ScD
Mark & Catherine Winkler Associate Professor of Environmental Health & Risk Assessment

"Risk assessment should be viewed as a method for evaluating the relative merits of various options for managing risk, not as an end in itself."

Introduction

While risk assessment has existed in various forms for many years, the process used by US EPA and others was formalized in the pivotal 1983 National Research Council (NRC) report known as the "Red Book[1]." The Red Book codified the well-known four steps of risk assessment (hazard identification, exposure assessment, dose-response assessment, and risk characterization) and emphasized the necessity of a conceptual distinction between risk assessment and risk management. Over the intervening quarter-century, risk assessment has evolved substantially, driven in part by additional NRC reports, EPA and other agency guidelines, and publications in the peer-reviewed literature.

However, concerns about the value and relevance of risk assessment for making policy decisions have grown over time, especially as risk-management issues that appear difficult to address with standard risk assessment methods (such as global climate change, endocrine disruption, nanotechnology, and environmental justice) have come to the fore. Risk assessments for some chemicals have taken decades to complete, in part because the presence of uncertainty has contributed to decision-making gridlock. At the same time, the underlying science has changed substantially in recent years, with advancements in genomics, analytical methods to measure biomarkers, and computational capacity for exposure models. In addition, there have been major changes in the expectations of the public and interest groups with respect to consultation and public participation, and risk assessments are increasingly integrated with other decision-making inputs such as regulatory cost assessments.

Against this backdrop, the EPA asked the NRC to form a committee to develop scientific and technical recommendations for improving the risk analysis approaches used by the EPA. The "Committee on Improving Risk Analysis Approaches Used by the U.S. EPA," on which I served, was charged to focus on human health risk analysis and to consider all environmental media (water, air, food, and soil) and all routes of exposure (ingestion, inhalation, and dermal absorption). The committee was asked to consider practical improvements that could be made in the near term (the next 2-5 years) and over a longer term (10-20 years). The committee released its final report in December 2008[2]. This issue of *Risk in Perspective* provides a brief overview of the key conclusions of the report, which can be obtained at www.nap.edu/catalog.php?record_id=12209. The text and figures below are largely based on the report.

Framework of the Committee's Evaluation

The committee determined that risk assessment could be improved either by improving the technical analyses (by incorporating improvements in scientific knowledge and techniques) or by improving the utility of risk assessment for decision-making. The latter can be achieved in several ways, including improving the ways in which risks are characterized and uncertainties expressed and ensuring that risk assessments are constructed in a manner that is maximally informative for decision-makers.

As a general principle, the committee recommended that risk assessment should be viewed as a method for evaluating the relative merits of various options for managing risk, not as an end in itself. This has a number of implications for the practice of risk assessment. It implies a greater need for upfront planning of the risk assessment, in which considerable discussion among risk managers, risk assessors, and other stakeholders helps to determine the risk-management questions that risk assessment should address. It also implies that the technical analyses within the risk assessment should be more closely aligned with the questions to be answered. For example, the level of detail of uncertainty and variability analyses should align with what is needed to inform risk-management decisions, rather than being defined as a task limited only by computational capacity. The committee's conclusions were therefore organized around measures to improve either the utility or the technical content of risk assessment, within a decision-oriented framework.

Design of Risk Assessment

The committee encouraged EPA to focus greater attention on design in the formative stages of risk assessment, including planning, scoping, and problem formulation, similar to the approaches articulated in EPA guidance for ecological risk assessment and cumulative risk assessment. With risk assessment considered as a decision-support product, it should be designed as the best solution to achieving multiple simultaneous and competing objectives while satisfying constraints on the process or the end product. For example, while use of the best scientific evidence and methods is a clear design objective, this may compete with objectives to be more expansive in scope, to provide timely outputs, and to have transparency in process.

One dimension of interest to the committee and EPA was the application of value-of-information (VOI) principles, which can be key components of the iterative design of risk assessments. When risk assessments are used within a decision-making environment, there is a need to determine whether information is adequate to make a decision or if more research is required. VOI analysis can help determine when investments in further information gathering are worthwhile. However, the committee concluded that formal quantitative VOI analysis may only be possible or desirable for a small number of decisions, in which decision rules are clear, estimates of uncertainty are comprehensive, and the stakes of the decision are high enough to warrant the effort. The committee offered two alternatives to formal quantitative VOI methods. The first alternative is to maintain the logic of the formal method by describing and evaluating, though in a qualitative manner, the impact of specific potential reductions in uncertainty on the choices facing the decision-maker. The second alternative is to apply an analogous "value-of-methods" approach to characterize the potential benefits of the many choices among risk assessment design options (e.g., consultative processes, peer engagement and review processes, means to improve transparency, methods for analyzing uncertainty) considered from the perspective of their ultimate impact on the overall quality of the agency's decision-making processes.

Uncertainty and Variability

Characterization of uncertainty and variability cuts across all elements of a risk assessment and many of the topics in the committee's statement of task. As a general principle, the committee concluded that EPA needs to characterize and communicate uncertainty and variability in all key computational steps of a risk assessment and noted that many risk assessments implicitly or explicitly omit multiple areas of uncertainty or variability. For example, emissions estimates are often treated as known and variability in cancer susceptibility is often ignored or isolated to defined subpopulations. That being said, the committee also emphasized that the level of detail with which uncertainty and variability are characterized should depend on the extent to which detail is needed to inform specific risk-management decisions and recommended that EPA adopt a "tiered" strategy for selecting the level of detail within the planning stage of the risk assessment.

Selection and Use of Defaults

One of the more vexing challenges involves the use of defaults within assessments and the decision to apply substance-specific data or default values. In the Red Book, it was recognized that there was a need for uniform inference guidelines (or defaults) that would specify the assumptions to be used generally within risk assessments in order to ensure consistency and avoid manipulation of assessment outcomes. While such guidelines are necessary for decision-making, the appropriateness of the use of a default in the face of data and theory that may support an alternative plausible assumption has been debated extensively, often leading to protracted delays. The committee concluded that established defaults need to be maintained for the steps in risk assessments that require such inferences, and that clear criteria should be made available for judging whether, in specific cases, data are adequate to support an inference in place of a default. The committee proposed that EPA should adopt an alternative assumption in place of a default when it determines that the alternative is "clearly superior" (that its plausibility clearly exceeds the plausibility of the default), while EPA should report additional risk estimates corresponding to alternative assumptions within the risk characterization whenever the alternative assumptions are of "comparable plausibility". Applying these criteria allows EPA to balance the need for comprehensive uncertainty characterization with the need for timely and consistent decision-making.

The committee also emphasized that there are many implicit or missing defaults within current risk assessment practice, such as the assumption that an untested chemical has no risk and the assumption that all humans (at the same life-stage) are equally susceptible to carcinogens. The committee concluded that EPA should develop explicitly-stated defaults to take the place of the implicit defaults.

A Unified Approach to Dose-Response Assessment

Historically, dose-response assessments have been conducted differently for cancer and non-cancer effects. For cancer, it has generally been assumed that there is no dose threshold of effect and dose-response assessments have focused on quantifying risk at low doses (although consideration of mode of action has led to some recent exceptions). For most non-cancer effects, a dose threshold has been assumed, below which effects are not expected to occur or are extremely unlikely. This dose is referred to as a reference dose (RfD), with an analogous definition for a reference concentration (RfC).

There are both scientific and operational limitations with these current approaches. Non-cancer effects do not necessarily have a threshold or low-dose nonlinearity. Background exposures and underlying disease processes contribute to population background risk and can lead to a non-threshold response when considered at the population level. In addition, because the RfD does not quantify risk at different levels of exposure but rather provides a bright line between possible harm and possible safety, its use in risk-management decision-making is both limited and prone to misinterpretation. For cancer risk, the mode of action of carcinogens varies and assessments usually do not account for differences among humans in cancer susceptibility other than possible differences in early-life susceptibility.

The committee concluded that both scientific and risk-management considerations support unification of cancer and non-cancer dose-response approaches. This unification can occur within a framework that includes formal systematic assessment of background disease patterns and exposures, possible vulnerable populations, and modes of action that may affect a chemical's dose-response relationship in humans (Figure 1). This approach redefines the RfD as a risk-specific dose that provides information on the percentage of the population that can be expected to be above or below a defined acceptable risk with a specific degree of confidence. The redefined RfD can still be used as the conventional RfD has been to aid risk-management decisions, but it provides additional information that allows for the inclusion of non-cancer endpoints in risk-risk and risk-benefit comparisons. The new definition also decreases the potential for misinterpretation when the value is understood as an absolute indicator of a level of safety.

Other characteristics of the committee's recommended unified dose-response approach include use of a spectrum of data from human, animal, mechanistic, and other relevant studies; a probabilistic characterization of risk; explicit consideration of human heterogeneity (including age, sex, and health status) for both cancer and non-

cancer endpoints; characterization (through distributions to the extent possible) of the most important uncertainties for both cancer and non-cancer endpoints; use of probabilistic distributions instead of uncertainty factors when possible; and characterization of sensitive populations.

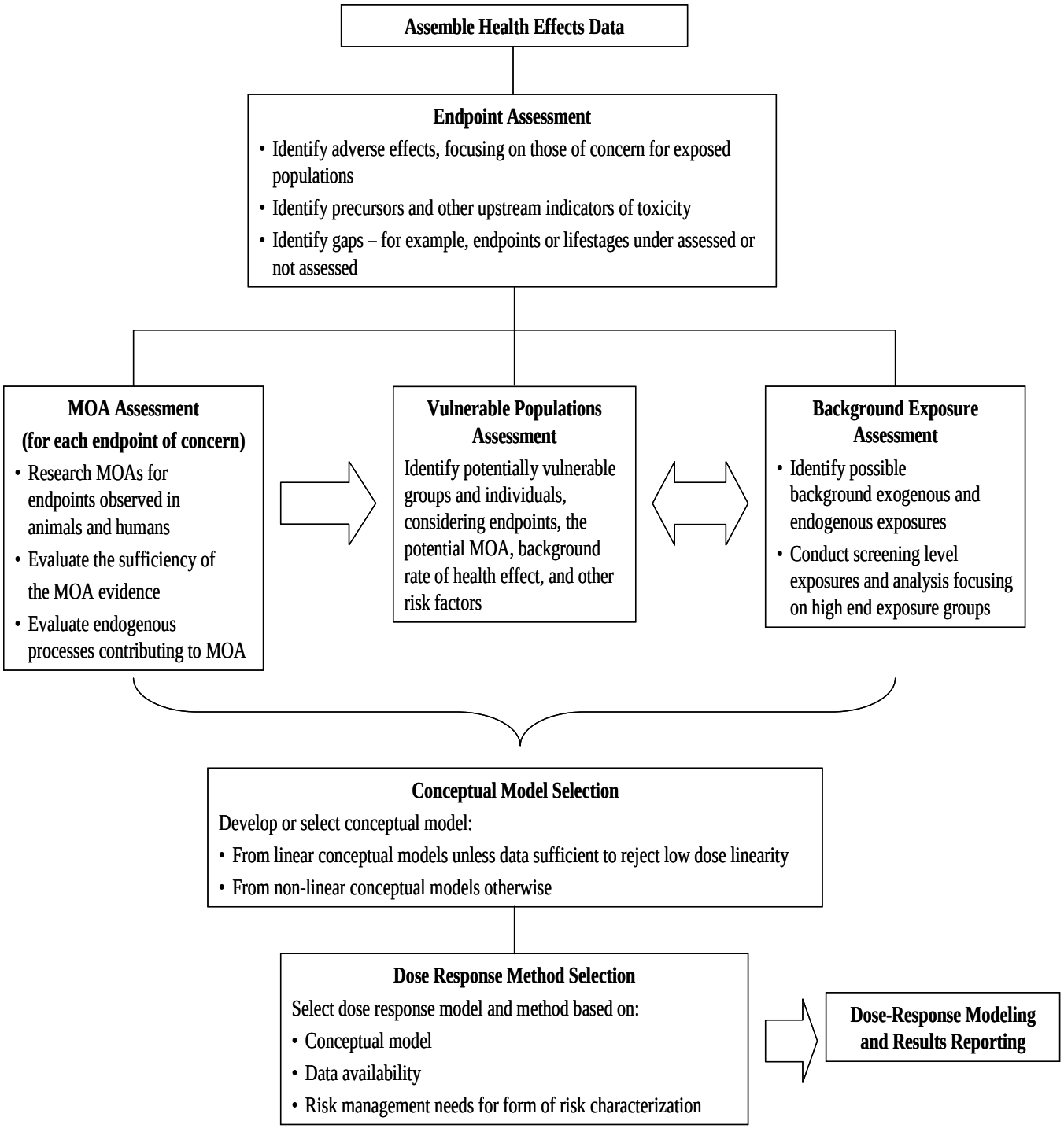

Figure 1. New unified process for selecting approach and methods for dose-response assessment for cancer and non-cancer endpoints involves evaluation of background exposure and population vulnerability to ascertain potential for linearity in dose-response relationship at low doses and to ascertain vulnerable populations for possible assessment.

Cumulative Risk Assessment

EPA is increasingly asked to address broader public-health questions that extend beyond individual chemicals to consider multiple exposures, complex mixtures, and vulnerable populations in a community setting. In response, EPA has developed cumulative risk assessment, defined as an evaluation of the combined risks posed by all routes, pathways, and sources of exposure to multiple agents or stressors. The committee applauded EPA's move toward this broader definition to make risk assessment more informative and relevant to decisions and stakeholders, but felt that EPA cumulative risk assessments fall short of what is possible and supported by agency guidelines. In particular, there has been little consideration of non-chemical stressors, vulnerability, and background risk factors. The committee concluded that conducting cumulative risk assessments within a risk-management context would allow for a more streamlined assessment, focusing on only those stressors that contribute to endpoints of interest for risk-management options and that are either differentially affected by different control strategies or influence the effects of stressors that are differentially affected. Insights from fields such as ecological risk assessment and social epidemiology, that have confronted similar complexities, should be leveraged. The committee also concluded that there was a need for simpler analytical tools that could allow for screening-level cumulative risk assessments and that databases and default approaches should be developed for non-chemical stressors in the absence of population-specific data.

Improving the Utility of Risk Assessment

Given the desire for risk assessments that are relevant to the problems and decisions at hand, and the corresponding need for assessments to be designed to ensure that the best available options for managing risks are considered, the committee proposed a framework for risk-based decision-making (Figure 2). The framework consists of three phases: I, enhanced problem formulation and scoping, in which the available risk-management options are identified; II, planning and assessment, in which risk-assessment tools are used to determine risks under existing conditions and under potential risk-management options; and III, risk management, in which risk and non-risk information is integrated to inform choices among options. The framework has at its core the risk assessment paradigm established in the Red Book, but differs from the Red Book paradigm primarily in its initial and final steps. The framework begins with a "signal" of potential harm (for example, a positive bioassay or epidemiologic study, a suspicious disease cluster, findings of industrial contamination). It focuses upfront on the options that are available to reduce the hazards or exposures that have been identified and on the structure of the risk assessments needed to evaluate the merits of the options being considered (that will generally include "no intervention" as an option). The framework also calls for formal stakeholder involvement throughout the process, with time limits to ensure that decision-making schedules are met and with incentives to allow for balanced participation of stakeholders, including impacted communities and less advantaged stakeholders.

Additional Dimensions and Conclusions

The committee's recommendations call for considerable modification of EPA's risk assessment efforts. Improving risk assessment practice and implementing the framework for risk-based decision-making will require a long-term plan and commitment to build the requisite capacity within EPA. EPA's current institutional structure and resources may pose a challenge to implementation of the recommendations and moving forward with them will require a commitment to leadership, cross-program coordination and communication, and training. That will be possible only if leaders are determined to reverse the downward trends in budgeting, staffing, and training and to making high-quality risk-based decision-making an agency-wide goal. The committee therefore recommended that EPA should initiate a senior-level strategic re-examination of its risk-related structures and processes to ensure that it has the institutional capacity to implement the committee's recommendations. The committee further recommended that EPA should develop a capacity-building plan that includes budget estimates required for implementing the committee's recommendations.

EPA is already taking steps to implement some of the key recommendations from this report[3], with staff preparing to meet and consider recommendations such as ways to harmonize cancer and non-cancer risk approaches and to increase the utility of assessments. Now that the Obama Administration and new Congress are in place, early senior-level leadership attention to several

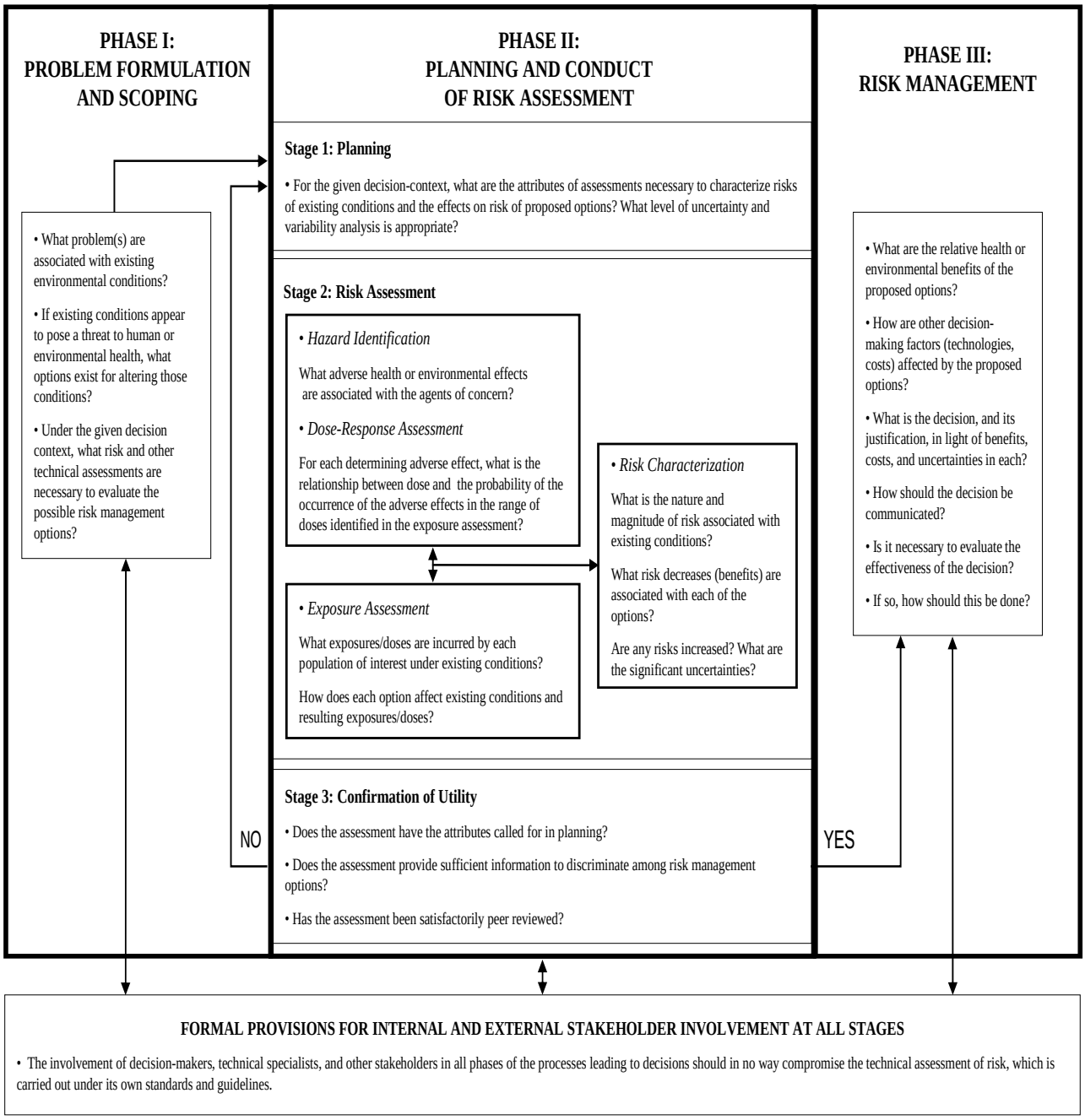

Figure 2. A framework for risk-based decision-making that maximizes the utility of risk assessment.
Reprinted with permission from Science and Decisions: Advancing Risk Assessment © 2008 by the National Academy of Sciences, Courtesy of the National Academies Press, Washington, D.C.

issues will be critical, including developing explicit policies that commit EPA to the revised framework, addressing funding levels, and adopting a set of evaluation factors for assessing the outcomes of policy decisions and the efficacy of the framework.

Because of the high financial and political stakes of risk-management decisions, there is unprecedented pressure on risk assessors and decision-makers at EPA. However, the committee felt that risk assessment remains essential to the agency's mission. The goal of the committee's recommendations was to provide a template for the future of risk assessment at EPA, strengthening the scientific basis, credibility, and effectiveness of future risk-management decisions.

7 — Conclusion *continued*

Although the committee's statement of task and report focused on practices at EPA, many aspects of the committee's recommendations should be relevant to other agencies and applications. While NRC committees have previously cautioned that risk assessment differs greatly across federal agencies and should not be approached identically[4], the general concept of designing a risk assessment to be aligned with risk-management needs should be broadly applicable. The framework for risk-based decision-making would also apply in many settings, especially given its emphasis on conducting assessments with appropriate scope and level of complexity for the decision context. This framework may be particularly helpful in settings where analytical and computational resources are limited, as it emphasizes that the most computationally complex model is not always the most appropriate. Turning to the technical content, the proposed unification of cancer and non-cancer dose-response approaches would be expected to have far-reaching impacts, potentially elevating the importance of non-cancer endpoints in risk-management decisions in many settings. Coupled with the revised approach toward defaults and cumulative risk assessment, the committee's technical recommendations should also stimulate new primary research that will enhance the scientific basis for risk assessment.

References:

[1] National Research Council. 1983. *Risk Assessment in the Federal Government: Managing the Process*. Washington, DC: National Academy Press.

[2] National Research Council. 2008. *Science and Decisions: Advancing Risk Assessment*. Washington, DC: National Academy Press.

[3] Hegstad M. EPA prepares to implement NAS advice to improve risk studies. *Inside EPA*, Vol. 29 No. 51. December 19, 2008.

[4] National Research Council. 2007. *Scientific Review of the Proposed Risk Assessment Bulletin from the Office of Management and Budget*. Washington, DC: National Academy Press.

Peer reviewer: Greg Paoli, Risk Sciences International, Ottawa and member of the NRC Committee on Improving Risk Analysis Approaches Used by the U.S. EPA.

Harvard Center for Risk Analysis
Harvard School of Public Health
Email: hcra@hsph.harvard.edu
Website: http://www.hcra.harvard.edu