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Science and Decisions: Advancing Toxicology to Advance Risk Assessment

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In 2009, the National Research Council (NRC) released the latest in a series of advisory reports on human health risk assessment, titled *Science and Decisions: Advancing Risk Assessment*. This wide-ranging report made a number of recommendations related to risk assessment practice at the U.S. Environmental Protection Agency that could both influence and be influenced by evolving toxicological practice. In particular, *Science and Decisions* emphasized the scientific and operational necessity of a new approach for dose-response modeling; addressed the recurring challenge of defaults in risk assessment and the question of when research results can be used in place of defaults; and reinforced the value of cumulative risk assessment, which would require enhanced understanding of the joint influence of chemical and nonchemical stressors on health outcomes. The objective of this article is to summarize key messages from *Science and Decisions*, both as a stand-alone report and in comparison with another recent NRC report, *Toxicity Testing in the 21st Century: A Vision and a Strategy*. Although these reports have many conclusions in common and reinforce similar themes, there are important differences that merit careful consideration, such as the move away from apical endpoints in *Toxicity Testing* and the emphasis on benefit-cost analyses and related decision tools in *Science and Decisions* that would be strengthened by quantification of apical endpoints. Moving risk assessment forward will require toxicologists to wrestle with the implications of *Science and Decisions* from a toxicological perspective.

Key Words: **risk assessment; default; dose-response model; cumulative.**

Risk assessment is the interpretive and analytical framework used to evaluate research findings related to environmental threats for public health decision making. It is the best approach for systematically dealing with the available scientific information, and its associated uncertainties, and for identifying research needed to reduce those uncertainties.

The various elements of risk-based decision making are the subjects of a report from the National Research Council (NRC), *Science and Decisions: Advancing Risk Assessment* (Committee on Improving Risk Analysis Approaches Used by the U.S. EPA, 2009). The study leading to the report was undertaken in response to a request from the U.S. Environmental Protection Agency (EPA). The report recognizes that the scientific credibility and public standing of risk assessment are under continuing attack and makes numerous recommendations for improvement.

This review of *Science and Decisions* emphasizes features of relevance to the toxicology community. *Toxicological Sciences* published an article by two members of the NRC committee (Committee on Toxicity Testing and Assessment of Environmental Agents, 2007) that produced *Toxicity Testing in the 21st Century: A Vision and a Strategy* (hereafter, *Tox21*) (Andersen and Krewski, 2009), and then, over the following year, published eight invited commentaries. The authors of the original paper then reviewed and discussed those commentaries (Andersen and Krewski, 2010). Although a similar forum will not occur with respect to *Science and Decisions*, we hope that this review will stimulate commentary and discussion. Because the matters to be discussed here are being actively pursued at the EPA and other agencies, it is important that they be seriously discussed within the toxicology community.

The article begins with an outline of the major features of *Science and Decisions*, followed by a close look at the role of toxicology in risk assessment as envisioned in *Science and Decisions* and *Tox21*. Dose-response modeling is discussed in detail, as are the issues of "defaults" and the emerging and difficult problem of cumulative risk. The concluding sections discuss improving the utility of risk assessment and the dynamic relationship between toxicology and risk assessment.

MAJOR FEATURES OF SCIENCE AND DECISIONS

The major challenges to risk assessment are both scientific and process related. Features of *Science and Decisions* of greatest importance to the toxicology community are summarized in Table 1 and discussed below.

TABLE 1
Major Features of *Science and Decisions* Affecting the Toxicological Sciences

Advancing risk analysis requires
• Re-examination of scientific basis for generic defaults, including incorporation of some that are now missing.
• Development of clear criteria for replacing generic defaults with chemical-specific data.
• Research and analysis that provides quantification of cross-species and interindividual variabilities in response.
• Development of conceptual models for dose-response analysis based on mode-of-action information and relevant information on background processes and exposures.
• Quantification of risk for all endpoints to aid understanding of health benefits achieved under various risk management options.
• Incorporating cumulative risk assessment where appropriate.
• Conducting risk assessment within a new framework (Fig. 3) that requires substantial advance planning, early development of management options, and application of risk assessment only after scope, level of detail, and required uncertainty analysis are specified.

Central to the science questions dealt with in the report is the long-standing problem of biological variability, affecting cross-species extrapolation and interindividual differences in response among members of the human population (human heterogeneity). Toxicology research continues to provide valuable insights, particularly with regard to cross-species extrapolation, but there remain serious disagreements regarding the appropriateness, in some circumstances, of using chemical-specific data instead of defaults. Apart from the question of departures from defaults, the report emphasizes the need for more explicit and quantitative measures of variability in risk assessment. The report also features a discussion of uncertainty as it relates to all aspects of risk assessment and the ways it can quantitatively be assessed and expressed to ensure that it plays an appropriate role in decision making.

A second major scientific feature of the report concerns the need to examine many false distinctions made between cancer and noncancer toxicity endpoints. The chapter dealing with a unified approach to dose-response assessment, in which assessments are driven by mode-of-action information and consideration of background exposures and vulnerability attributes rather than endpoints, has drawn much attention from the toxicology community and is likely to remain controversial. We treat the issues it raises at length below because they are critical to the scientific foundations of risk assessment and the related role of toxicology. Perhaps the most difficult scientific challenge taken on in the report is the increasingly discussed problem of cumulative risk—the quest for understanding the cumulative impact of multiple threats or "stressors."

The report also deals with the problems associated with technical analysis seemingly undertaken for its own sake, with decision-making goals pushed aside. These process issues are particularly important in research planning and ensuring that research results can be produced on a schedule in keeping with defined objectives for decision making. The report recommends implementation of a new decision-making framework, which could have a profound influence on the way public health and regulatory decisions of all types are made.

ROLE OF TOXICOLOGY IN RISK ASSESSMENT

Science and Decisions argues that risk assessment is at a crossroads, as the increased sophistication of analytical techniques raises increasingly challenging policy and science questions. The same can be said of toxicology—the techniques by which health impacts can be toxicologically characterized continue to grow in sophistication. Indeed, *Tox21* explicitly indicates that toxicity testing is approaching a scientific "pivot point," where technological advances in fields such as toxicogenomics, and computational toxicology may drastically change the ways in which toxicity is evaluated (Committee on Toxicity Testing and Assessment of Environmental Agents, 2007). Although these advances may be the future of both toxicity testing and risk assessment, there are challenging questions about how the information derived from new tools can be best utilized (Andersen and Krewski, 2009; Krewski *et al*., 2009). Some of these questions might be resolved by the *Science and Decisions* paradigm; others could force a decision between competing approaches to risk assessment and management.

Although the two reports have many commonalities, including emphases on approaches to resolving the issue of untested chemicals, recognition of the need for risk assessments to meet risk management objectives, the importance of mixtures and mode of action, and the need to prioritize among chemicals, they do not concur on the centrality of risk quantification for apical endpoints. *Tox21* calls for a move away from apical endpoints in animals to perturbations of critical cellular responses in human cell lines (Committee on Toxicity Testing and Assessment of Environmental Agents, 2007). Although this transition leverages advanced technologies, facilitates a movement away from animal testing, and provides a stronger mechanistic understanding of health effects, it is challenging to quantitatively link such perturbations with the health outcomes emphasized in *Science and Decisions* and central in many forms of decision making. Although this paradigm shift may be viable, it raises challenges for the new dose-response modeling approach proposed in *Science and Decisions*, discussed in detail below.

More generally, there is a fundamental tension between the novel approaches that *Tox21* rightly emphasizes and the decision-theoretic context that *Science and Decisions* proposes. Potential bridges exist, such as through the application of physiologically based pharmacokinetic (PBPK) models and the use of biomarker measurements or by the use of high-throughput assays as screening tools to formulate more focused *in vivo* testing. Recent efforts by EPA (http://www.epa.gov/risk/nexgen/) have started to connect the two paradigms, explicitly citing the risk-based decision-making paradigm from *Science*

and Decisions in constructing a tiered approach for incorporating new insight from molecular systems biology. This does not resolve all fundamental tensions but demonstrates how aspects of both visions can be incorporated. Although this article focuses on the implications of *Science and Decisions* for toxicological practice, it is important to keep in mind the implications of these two major NRC reports for toxicology, as risk assessment practice will undoubtedly rely on aspects of both reports over time.

DOSE-RESPONSE MODELING

Chapter 5 of *Science and Decisions* calls for significant changes to the way that dose-response modeling is done in risk assessment. If implemented, this could have a wide-ranging impact on how toxicology is conducted and interpreted. We briefly describe the key features below.

The committee had both a scientific and an operational rationale for the proposed changes. The current dose-response paradigm involves an immediate separation between cancer endpoints and all other endpoints. For noncancer outcomes, a point of departure (POD) is established, based on a dose that exhibited a defined and observable response in the underlying toxicological study, and this value is divided by a series of "uncertainty factors" to determine a reference dose. This approach has a number of operational limitations, including the fact that no quantitative risk information is produced. No insight is provided into the magnitude of population risk considered "acceptable" by decision makers, defeating the goal of transparency in such decisions, and it is challenging to conduct tradeoff analyses or to evaluate the benefits of incremental changes in exposure. The "uncertainty factors" represent a combination of interspecies and intraspecies variability, along with true uncertainty related to an absence of scientific knowledge, complicating the interpretation of the output. From a scientific perspective, this approach also does not consider the possibility of noncancer endpoints for which low-dose linearity could be present. EPA commonly considers pollutants such as lead, ozone, or fine particulate matter to exhibit noncancer health effects at low doses, yet it does not systematize this logic across other pollutants and outcomes.

In *Science and Decisions*, the committee argued that risk quantification was feasible for noncancer endpoints, proposing approaches by which risk-specific reference doses could be estimated, following studies in the peer-reviewed literature (Evans *et al*., 2001; Hattis *et al*., 2002; Woodruff *et al*., 2007). In addition, in situations in which background processes and background exposures could potentially linearize an otherwise nonlinear response (conceptual model 1 in Fig. 1), the committee proposed an approach for low-dose linear extrapolation. To be clear, the committee did not propose that all pollutants would be linear at low dose for all endpoints, but rather that risk assessors should develop a conceptual model in each case only after formally considering the evidence for background exposures, significant heterogeneity in response, and so forth.

For cancer endpoints in the current dose-response modeling framework, chemicals with a mode of action that would imply low-dose linearity or with an unknown mode of action are treated as low-dose linear. A POD is established, and a slope factor is constructed by drawing a line from that point to the origin.

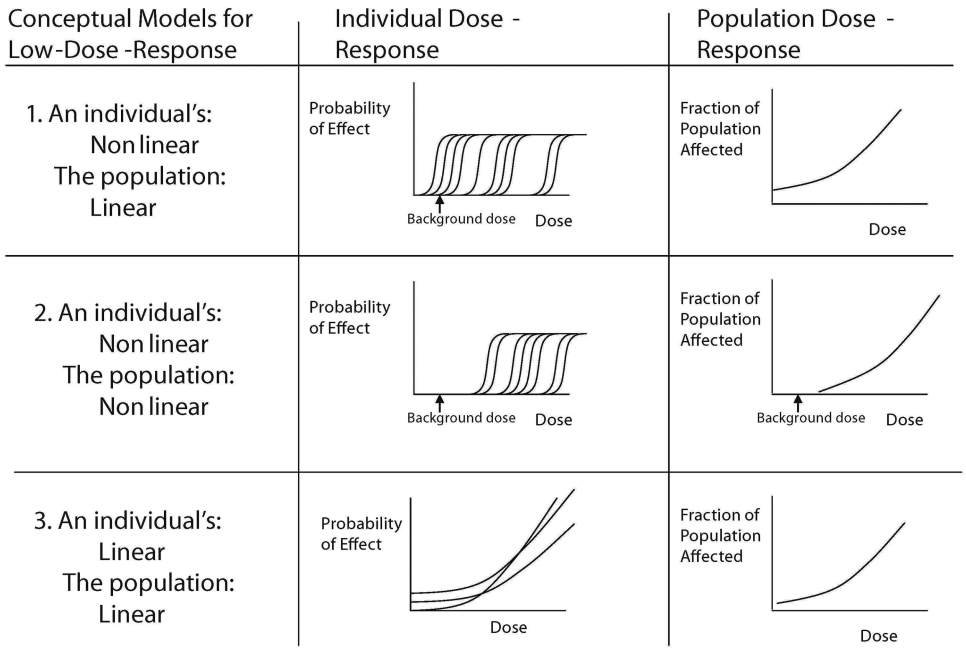

FIG. 1. Examples of conceptual models to describe individual and population dose-response relationships. Reprinted with permission from Science and Decisions: Advancing Risk Assessment, © 2009 by the National Academy of Sciences, courtesy of the National Academies Press, Washington, DC.

Interindividual variability in response is not typically considered. For chemicals with a mode of action that could imply a threshold response, a reference dose approach is used. The committee concluded that the consideration of threshold responses for carcinogens was a valuable recent refinement by EPA, but that quantitative insight was lacking, as seen in the current noncancer paradigm. The committee recommended that cancer dose-response modeling follow the unified approach for conceptual model development cited above, using mode of action and other information to determine the appropriate shape of the dose-response function, with specific recommendations to establish a default to include interindividual variability in cancer susceptibility. The new unified dose-response modeling approach in *Science and Decisions* does not ignore the important differences between cancer and other diseases but recognizes that development of dose-response models in either case requires understanding of background exposures and susceptibility factors, explicit consideration of human heterogeneity in response, and the goal of a probabilistic quantification of risk. The unified approach provides a logical framework within which these factors can be systematically incorporated and is presented in Figure 2.

The implications for toxicology are too numerous to articulate, and there has already been extensive debate and discussion in the literature, including clarification from committee members (Ginsberg *et al.*, 2010), critiques regarding the likelihood of low-dose linearity (Rhomberg *et al.*, 2011), and technical concerns regarding aspects of the calculation approaches (Crump *et al.*, 2010). Some of the key issues for toxicology include the following:

- approaches to characterize mode of action across numerous chemicals, including explicit consideration of endogenous processes;
- strategies for formalizing the diagnostic questions to determine the likelihood of low-dose linearity, which includes detailed consideration of the magnitude of interindividual variability, other chemicals that are structurally similar, and interactions between various disease processes and the chemicals in question; and
- methods for adjusting animal POD to human POD and for extrapolating from human POD to low-dose response, which rely on well-characterized distributions from toxicology studies and data on pharmacokinetic and pharmacodynamic variability.

To address these issues and many others raised in *Science and Decisions*, toxicological studies may need to either be conducted or be interpreted differently, and determining the optimal path forward will require some careful planning and case examples.

DEFAULTS

An understanding of the quantitative relationships between dose and risk, in risk ranges beyond those that are directly measurable with currently available methods, is critical for most public health decisions related to chemical toxicity. In the absence of direct measures, these important relationships must be modeled based on scientific inferences arising from knowledge of the chemical and biological processes underlying toxic phenomena. As described above, adequate knowledge of a chemical's mode of action, coupled with an understanding of relevant background processes, would allow for the development of dose-response models with an acceptable degree of accuracy and precision. Similar knowledge relating to the relevance of specific animal findings to humans, and of inter- and intraspecies variability, is necessary to complete such model building. Developing knowledge in these complex areas is central to the science of toxicology.

Although chemical-specific models would ideally be available for all risk assessments, such an outcome is unimaginable. The necessary research is complex, very costly, and time consuming, and its results almost always subjected to multiple and conflicting interpretations. Because of this, regulatory agencies (and EPA in particular) have dealt with the problem by adopting generic models and assumptions ("defaults"), applicable to all chemicals.

Toxicological research provides valuable insights into toxic modes of action and inter- and intraspecies variability associated with specific chemicals. Such research often has as its objective the replacement of one or more generic defaults by chemical-specific information. Serious and persistent questions have, however, created something of a deadlock regarding the use of chemical-specific findings in risk assessments. The EPA and other regulatory agencies have been reluctant to move away from defaults because of the identifiable uncertainties that accompany all research results. Such movement is especially problematic for regulators if the research findings suggest less risk than that suggested by the generic defaults the research data are intended to replace. This deadlock is a source of considerable frustration for research scientists when their efforts have no or little influence on risk assessment and for the regulatory scientists called upon to make decisions in the face of uncertainty.

The *Science and Decisions* committee was by no means the first to recommend that regulatory agencies offer clear criteria for judging the adequacy of specific research findings to replace generic defaults. This goal has proven difficult to achieve, and no generally usable criteria have appeared. The authors of *Science and Decisions* made it clear that this matter is too important to continue to ignore, and the report recommends that such criteria be developed by the EPA, following the general precept that "… departures should occur only when the evidence of the plausibility of the alternative is clearly superior to the evidence of the value of the default."

Although this criterion is broad, it should be a sufficient starting point for elaboration of departure criteria. Toxicologists have a clear role in planning and conducting relevant research, but they have a large stake in the resolution of this issue. Toxicologists need to take on this challenge and assist the EPA in arriving at

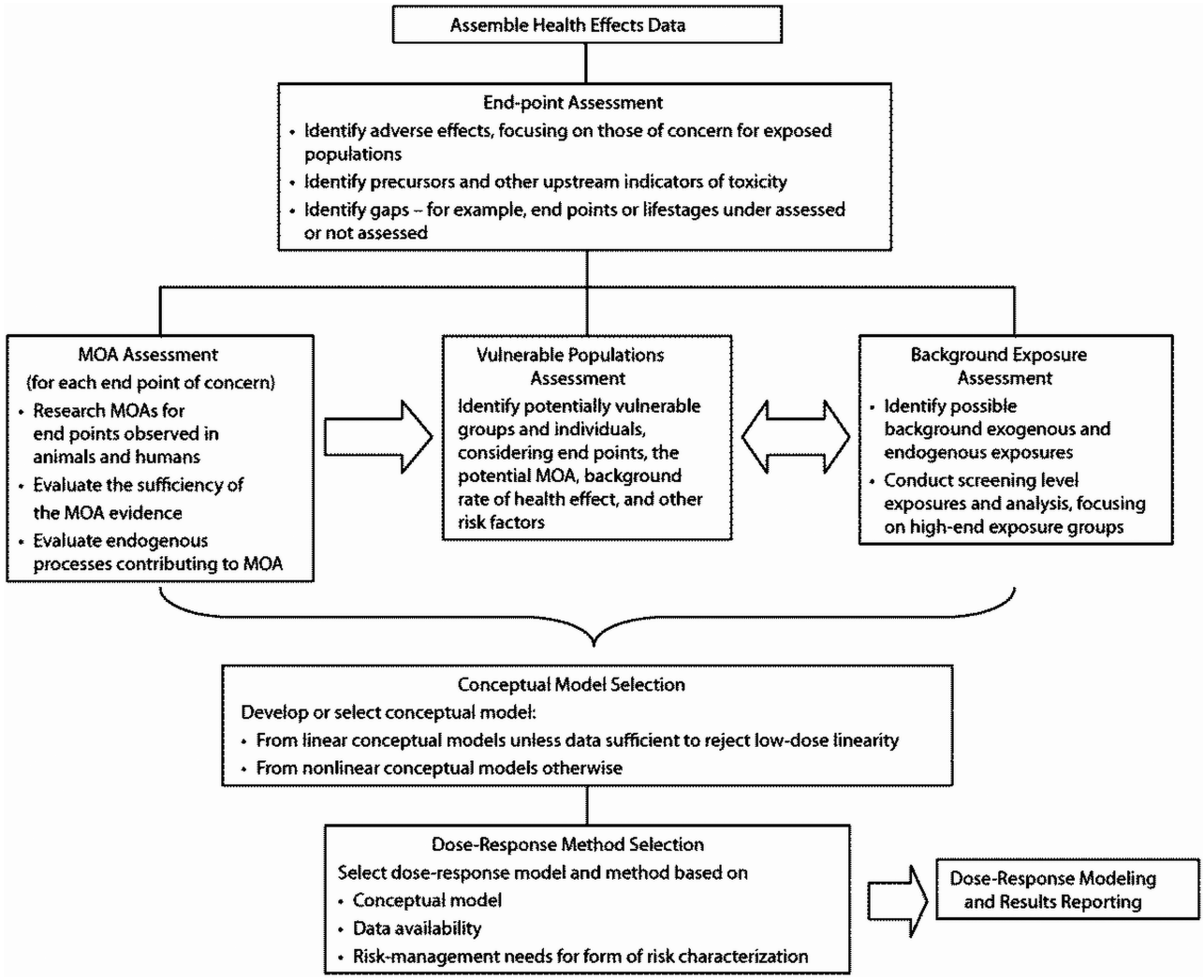

FIG. 2. New unified process for selecting approach and methods for dose-response assessment for cancer and noncancer endpoints. Reprinted with permission from Science and Decisions: Advancing Risk Assessment, © 2009 by the National Academy of Sciences, courtesy of the National Academies Press, Washington, DC.

appropriate and rigorous criteria. This requires an understanding of the scientific basis for the generic defaults under question, the scientific basis for the proposed replacement, and a rigorous means to compare their results and uncertainties.

The default issue presents other challenges for the toxicology community. The report makes recommendations regarding the need periodically to re-examine the scientific basis for the generic defaults (the need for which will remain into the foreseeable future). Advances in basic toxicological knowledge play a central role in such decisions.

The implicit regulatory assumption that compounds for which no significant toxicity data exist carry no risk arises in the report as a kind of hidden default. If a default is required in this area (which is what the report recommends), what toxicological consideration should guide its development? Here is an opportunity for toxicologists to come face-to-face with a long-standing and hidden default in risk assessment.

The issue of defaults stands as a highly uncomfortable but necessary issue for risk assessment. The struggle to strengthen its scientific status is strongly affected by the way in which interim and uncertain toxicological knowledge is used in the risk assessment process and by how we decide that new knowledge needs to be incorporated.

CUMULATIVE RISK

Cumulative risk assessment is an area of emphasis for *Science and Decisions* and a growing topic of interest to EPA. In many ways, it is the culmination of a number of trends at EPA, with a desire to move away from single-chemical single-pathway assessments and toward more holistic considerations of multiple exposures in real-world community contexts. This represents a significant challenge for toxicology along multiple dimensions but also provides opportunities for new and

innovative investigations. Multistressor characterization can be difficult to implement within toxicology, and *in vivo* toxicological studies of apical endpoints rapidly become impractical and uninterpretable as the number of exposures to evaluate increases. *In vitro* high-throughput assays have been proposed as a mechanism to handle chemical mixtures in *Tox21* (Committee on Toxicity Testing and Assessment of Environmental Agents, 2007), resolving some of the limitations of *in vivo* studies but raising other concerns about quantification of decision-relevant health outcomes articulated above.

These well-recognized tensions have been present for some time and have been manifested in various strategies for chemical mixtures risk assessment or cumulative risk assessments strictly oriented around multichemical exposures (e.g., pesticide families under the Food Quality Protection Act). However, *Science and Decisions* emphasizes an additional component of cumulative risk assessment that is quite challenging for toxicology to implement. As described elsewhere (Callahan and Sexton, 2007), EPA's cumulative risk assessment paradigm explicitly calls for the inclusion of nonchemical stressors, potentially including psychosocial stress, access to health care, socioeconomic status, and other factors. This raises obvious challenges for toxicology, especially if toxicology evolves toward using more *in vitro* assessments.

Although there are clearly multiple domains in which toxicology cannot contribute (i.e., the influence of health care access on the effect of a chemical stressor), epidemiology also has significant limitations in determining causal associations with numerous joint exposures. There is, therefore, a significant opportunity for creative applications of toxicological methods to develop insights in the domain of cumulative risk assessment. For example, investigators have developed rat models of stress to evaluate the effect of joint exposures with lead (Cory-Slechta *et al.*, 2010) or particulate matter (Clougherty *et al.*, 2010). PBPK models can include effects of a variety of stressors that influence absorption, distribution, metabolism, or excretion (Tan *et al.*, 2011), which could be used to determine whether the delivered dose or pharmacodynamic outcome is influenced by the presence of relevant nonchemical stressors (Wason *et al.*, 2012). More broadly, any large-scale implementation of cumulative risk assessment requires joint consideration of epidemiological and toxicological evidence, so stronger linkages and more frequent collaborative investigations are warranted. *Science and Decisions* calls for close collaboration between epidemiologists and risk assessors to inform long-term development of cumulative risk assessment, but it is equally important to foster close collaboration between epidemiologists and toxicologists.

IMPROVING THE UTILITY OF RISK ASSESSMENT

One objective of *Science and Decisions* was to improve the utility of risk assessment by developing a decision-making model to make sure risk assessments are undertaken with adequate attention to the decision context (Fig. 3). Specifically, the decision process begins with problem formulation and elaboration of the options available for managing that problem. Risk assessments with a level of complexity appropriate to the problem are then designed, and execution is directed at an examination of the relative merits of the possible interventions. When practicable, especially for well-studied chemicals for which risks are well characterized and routes of exposure understood, risk assessments are used to compare different risk management options. Subsequent to *Science and Decisions*, individual committee members extended this model to further reinforce an orientation around solutions (Finkel, 2011) and to indicate commonalities with long-standing techniques for regulatory impact analysis (Robinson and Levy, 2011).

The new risk-based decision-making model has multiple implications for toxicology. Broadly, the model emphasizes the need for iterative analyses that could include initial screening-level assessments. The ability of toxicology to provide rapid characterization of not just the likelihood but also the magnitude of risk associated with a chemical will be key to the success of the model. Furthermore, with risk assessments conducted in specific decision contexts, toxicology will need to answer questions about the influence of different stressors at different concentrations to determine the appropriate dose-response model. Finally, the model in Figure 3 reinforces the necessity of using risk assessment outputs in conjunction with economic, technological, and societal factors to arrive at risk management decisions, emphasizing the value of quantitative risk information for apical endpoints to which monetary values or other weights can feasibly be assigned.

DYNAMIC RELATIONSHIP BETWEEN TOXICOLOGY AND RISK ASSESSMENT

Implementation of at least the key recommendations of *Science and Decisions* could have profound influences on both the future direction of toxicology and on the quality and effectiveness of regulatory and other types of public health decisions. The report recognizes that scientific research provides the building blocks for reliable risk assessments but also that risk assessment may be required even when scientific understanding and data are incomplete. Assessments of emerging problems such as those associated with cumulative risks from multiple environmental stressors will require the use of assumptions of uncertain scientific standing (e.g., defaults). These applications will, thus, generate uncertainties requiring research in perhaps wholly new areas of toxicology. Applications of risk assessment in other emerging areas, such as product life-cycle analysis, product design ("green chemistry"), and concerns about nontraditional health endpoints arising from novel toxicology testing methods, will similarly require applications of risk assessment that put new demands on toxicology research.

The framework for risk-based decision making (Fig. 3) promotes consideration of a broad set of options for creative problem-solving and risk assessments designed specifically to evaluate the relative merits of those options. Research findings

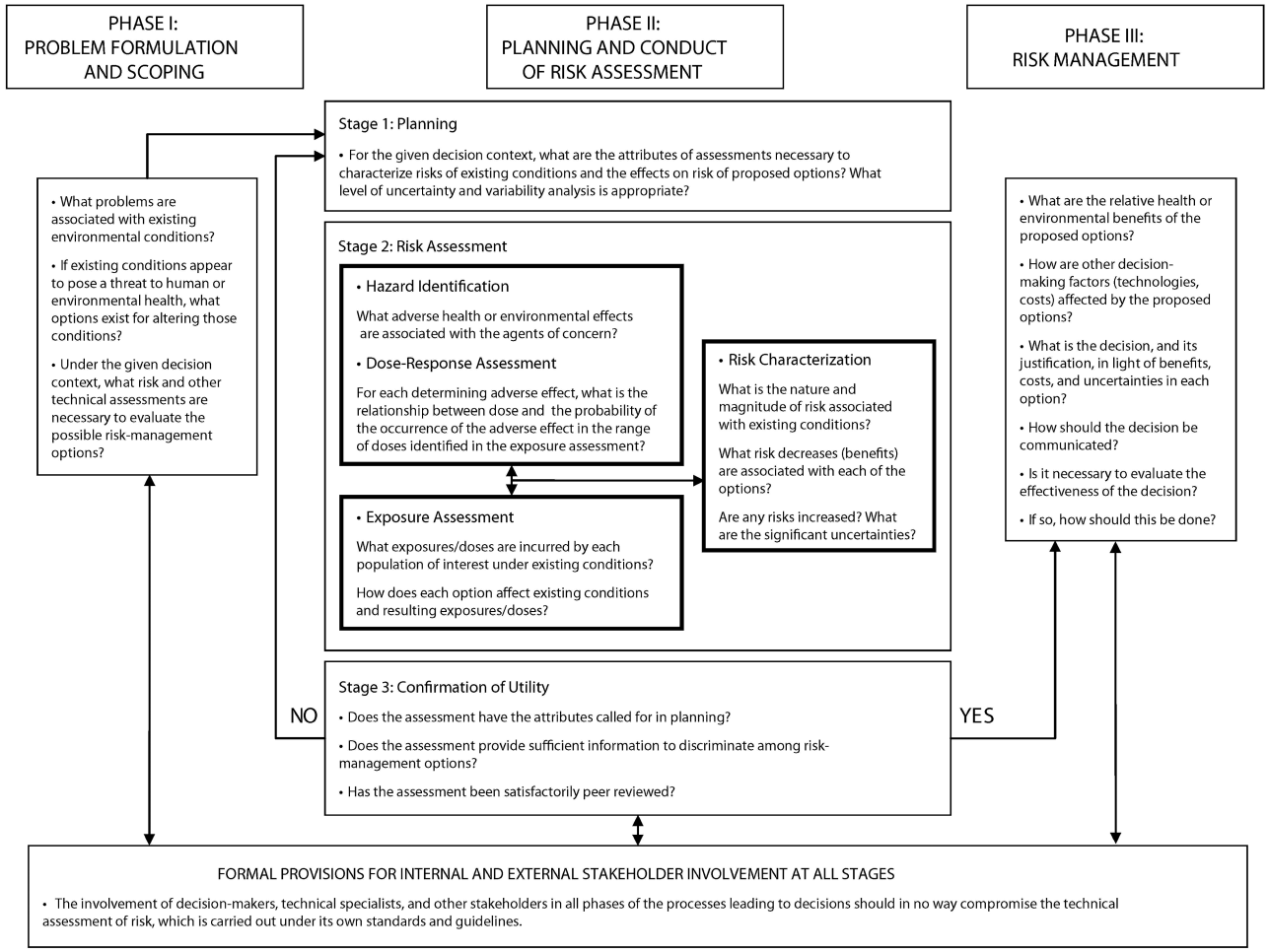

FIG. 3. A framework for risk-based decision making that maximizes the utility of risk assessment. Reprinted with permission from Science and Decisions: Advancing Risk Assessment, © 2009 by the National Academy of Sciences, courtesy of the National Academies Press, Washington, DC.

and the appropriate inferences to be drawn from them are essential to the production of reliable and useful risk assessments. The development of research strategies and protocols to deal with issues raised by application of risk assessment to emerging problems is also necessary to provide those assessments with strong scientific foundations. For both such objectives, involvement of the toxicology community is necessary. Without such involvement, the recommendations of *Science and Decisions* will not have their expected effects. This is not to say that toxicologists are expected to find ways to sustain all of the specific scientific conclusions found in the report; rather, it is to ask that the community offers the best scientific support for moving risk assessment forward.

CONCLUSIONS

Science and Decisions offers a number of recommendations regarding risk assessment practice, some that can be implemented in the short term and some that require significant new research or development of new methods. Both the centrality of risk assessment to decision making at EPA and the centrality of toxicology to risk assessment are emphasized in the report. It is, therefore, important to consider how toxicology can respond to the recommendations and challenges in *Science and Decisions*. Where conflicts exist, the critical question is whether changes in toxicological practice are viable, and if so, what steps are needed to adapt toxicological practice to the evolving needs of risk assessment. Equivalently, it is critical to understand where risk assessment practice, either in its present form or as proposed by *Science and Decisions*, needs to change to reflect the evolving science of toxicology. We are hopeful that toxicologists will use case studies and commentaries to reflect on areas of harmony and of conflict, guiding researchers and decision makers on the best approaches to advance both toxicology and risk assessment.

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