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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.

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-

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3 — Unified Approach *continued*

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.

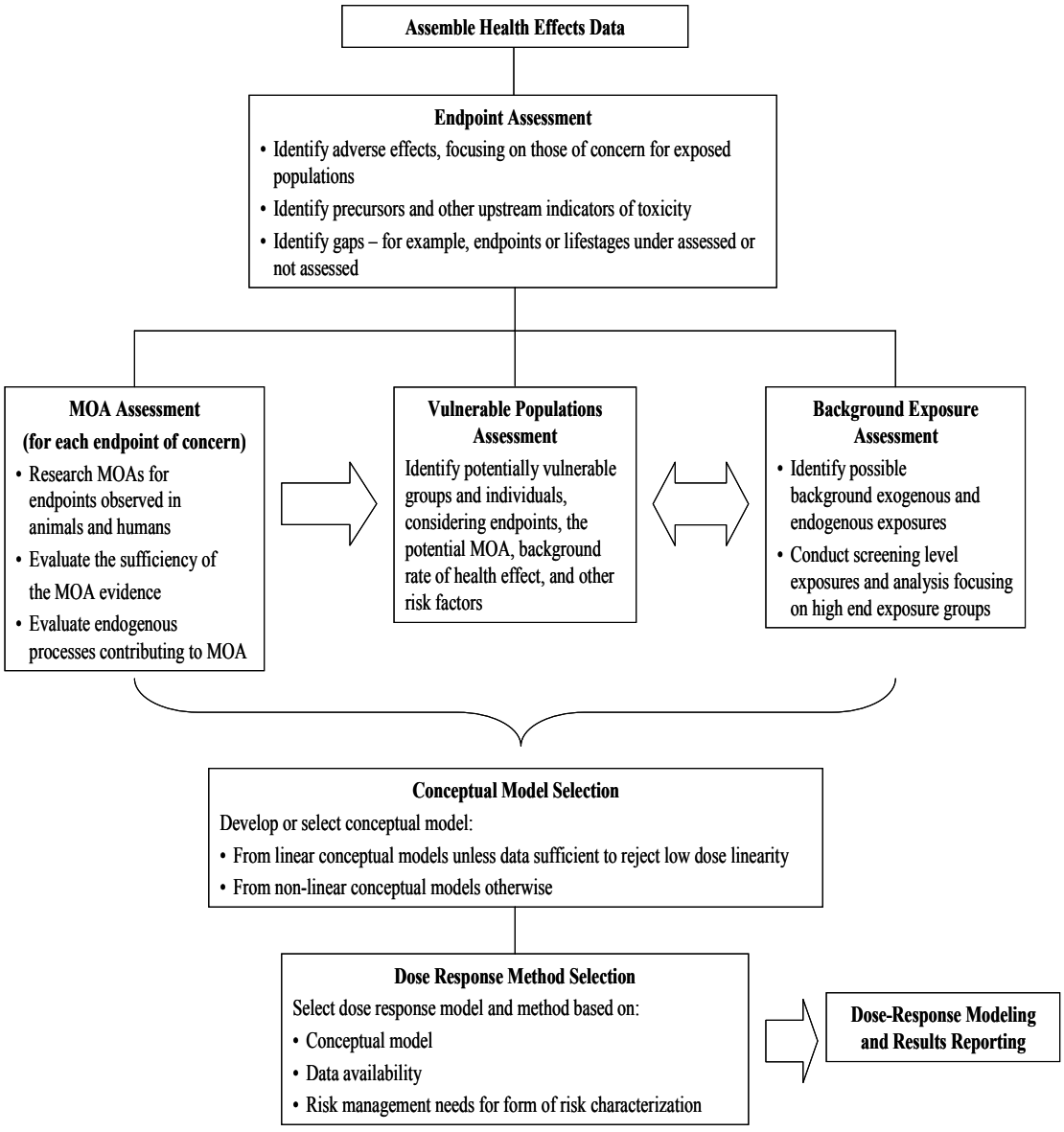

Figure 1. New unified process for selecting approach and methods for dose-response assessment for cancer and non-cancer endpoints involves evaluation of background exposure and population vulnerability to ascertain potential for linearity in dose-response relationship at low doses and to ascertain vulnerable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