

## **Rethinking Approaches To Low Dose Extrapolation for Environmental Health Risk Assessment**

### Introduction

Over the past half-century, methods for quantitatively assessing the human health risks from exposures to environmental contaminants have become increasingly sophisticated in the treatment of the key risk assessment components that ultimately provide projections of the public health risks from these exposures. Estimation of the dose-response function is one of four critical elements of the now paradigmatic approach to health risk assessment developed in 1983 by the National Research Council (NRC 1983).

Establishing dose-response functions frequently requires extrapolating limited amounts of data from high-concentration animal toxicological studies to the relatively lower concentrations typically experienced by humans. Statistical methods, known as “low-dose extrapolation” models, have been developed for this purpose, and their merits and limitations have been debated since the earliest efforts in environmental contaminant risk assessment.

Historically, noncancer health outcomes related to exposure to environmental pollutants were generally considered to have a nonlinear dose-response relationship with identifiable thresholds (i.e., an exposure concentration below which no response or no significant response occurs in the population, including sensitive subpopulations). A no-threshold approach to extrapolation of dose-response (or in some instances, exposure-response) relationships for relatively low levels of toxic chemical exposure has been the generally accepted model for most cancer outcomes from chemical exposures since the earliest uses of risk assessment for cancer outcomes. Recent advancements in statistical methods have allowed for more robust epidemiologic evaluation of very large populations exposed to environmental pollutants at ambient concentrations, thus providing information that informs low-dose extrapolation issues. In studied populations,

thresholds have not generally been observed for cancer or, more notably, noncancer outcomes. This observation derives primarily from studies of radiation (NRC 1999, 2005), second-hand tobacco smoke (US DHSS 2004), nitrogen and sulfur oxides (U.S. EPA 2008a, 2008b), particulate matter (U.S. EPA 2006b), ozone (U.S. EPA 2006a) and lead (U.S. EPA 2006c). These studies have spurred reconsideration of the cancer and noncancer paradigms utilized to extrapolate dose-response relationships for the relatively low doses of environmental toxicants typically encountered in the ambient environment.

To further address this issue, the U.S. Environmental Protection Agency (U.S. EPA) and the Johns Hopkins Risk Sciences and Public Policy Institute (RSPPI) organized a workshop, entitled “State-of-the-Science Workshop: Issues and Approaches in Low Dose – Response Extrapolation for Environmental Health Risk Assessment,” which was held April 23–24, 2007 in Baltimore, Maryland. Participants included experts from diverse disciplines, including toxicology, biostatistics, human biology, epidemiology, and risk assessment. A summary of the issues discussed and key findings and recommendations from this workshop follows below

### Key Issues

Two key issues specifically related to the application of low-dose extrapolation methods in risk assessments of environmental pollutants were identified during workshop discussions: (1) defining the concept of mode of action (MOA) with sufficient specificity that it can be utilized consistently for risk assessments and determining sufficiency of data to determine MOA, and (2) the implications for dose-response model selection of interindividual variability and risk additivity from background disease processes and exposures for both cancer and non-cancer outcomes.

#### *Mode of Action*

The U.S. EPA defines mode of action with respect to cancer outcomes as “a sequence of key events and processes, starting with interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in cancer formation” (U.S.

EPA 2005). Utilizing MOA information has become increasingly prominent in state-of-the-science approaches to assessing the risks of environmental exposures to chemicals. Recent U.S. EPA documents on human health risk assessment and selection of low-dose extrapolation approaches emphasize the use of MOA data in characterizing dose-response relationships for both cancer and noncancer outcomes (U.S. EPA 2005, 2004). In these documents, *mode* of action is contrasted with *mechanism* of action, with the latter term implying a more detailed understanding of key biological events, typically at the molecular level. However, a more detailed definition of mode of action that can be applied in a consistent manner to inform the choice of models for low dose extrapolation in chemical/pollutant risk assessments is currently lacking. Further, comprehensive approaches for evaluating the evidence to support selection of any particular MOA for use in risk assessments have yet to be fully developed.

#### *Individual Variability, Background Disease and Exposures*

A common assumption when extrapolating experimental animal data to estimated human responses at low doses is that if nonlinear or dose-transitional key events in an MOA are identified, then an actual or practical threshold exists. While this may be true for individuals, its applicability to large population is less certain. Population variability, as well as the potential for additivity with other preexisting background disease processes or exposures, is an inherent component of large-population dose-response relationships that influences consideration of no-threshold low dose–response models. Therefore, it is difficult to draw conclusions about the shape of the dose-response function for the general population from MOA information alone. As noted above, well-researched, data-rich examples from the epidemiologic literature regarding, for example, particulate matter, ozone, lead, secondhand tobacco smoke, and radon, reinforce the need for updating dose-response assessment procedures for extrapolating dose-response models to low-dose exposures, particularly with regard to continued application of the threshold dose-response as an inference-based model for noncancer outcomes.

Often the choice of how the additional risk of exposure to an environmental toxicant should be combined with the factors that influence background risk levels is uncertain. Sufficient confidence in the understanding of MOA for both the background determinants and the agent of interest are needed to address this issue with any certainty. Absent such knowledge, risk assessors often default to a multiplicative effect of the exposure of interest on background risk, in part for computational convenience. Sensitivity analyses may be used to explore the consequences of assuming additivity to background risk or other alternatives.

Because of the paucity of mechanistic information to inform selection of disease categories, it was noted that many mechanistically dissimilar diseases may be added incorrectly to background risks. In some situations, the additivity assumption may not be useful, e.g., when toxicity is associated with high doses of essential elements or when adaptive capabilities at various levels of biological organization are sufficient to modulate responses to environmental stressors at the population level.

#### Workshop Findings and Recommendations

- The historical dichotomy between low dose-response extrapolation methods typically applied to cancer and noncancer outcomes should be set aside, and selection of low-dose extrapolation models should be informed by categorization of mechanisms of toxicity, such as genotoxic, epigenetic, or cytotoxic processes, and by population level factors (e.g., susceptibility).
- Almost all workshop participants preferred a linear, no-threshold approach to low-dose extrapolation, combined with modeled estimates of the low range of the observed data (e.g. benchmark dose modeling), for both cancer and noncancer outcomes unless there is sufficient data to select an alternative model. A small minority of participants expressed some reservation regarding selection of a linear non-threshold dose-response function as the default model assumption for cancer and noncancer outcomes given information on human biologic processes such as reversibility and repair.

- Using MOA information to inform dose-response modeling holds substantial promise and there are potentially numerous ways to conceptualize MOAs. However, the improvements are needed to both specifically defining the concept of MOA for application to risk assessment models, as well as the basis for assessing the scientific evidence to support Extensive multidisciplinary collaboration among biologists, toxicologists, epidemiologists, and statisticians will be needed to identify MOAs that describe the biological dose-response process in a manner that is informative for modeling. Participants recognized that successful development of this approach will likely extend beyond the near-term (i.e., >3-5 years).
- Integrating information from human and animal data into risk models holds the potential for improving the precision of low-dose extrapolation models.
- Utilize statistical approaches such as model averaging to inform model selection, which allows for incorporation of any prior information that would lead to particular weights for a suitable, usually large, specified set of models that are often weighted equally a priori. Posterior model probabilities are then computed for the individual models, reflecting the likelihood that a model fits the given the observed data. Model results are then averaged with respect to the posterior probabilities, giving greater weight to those models that best fit the data.

Note: This article has been excerpted and modified from a more detailed workshop report published in *Environmental Health Perspectives*, February 2009 (White, RH et al. 2009. State-of-the-Science Workshop Report: Issues and Approaches in Low-Dose–Response Extrapolation for Environmental Health Risk Assessment. *Environ Health Perspect* 117:283–287).

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