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Guest Perspective

Integrating Cancer And Non-Cancer Dose Response Assessment Approaches To Risk Assessment: The Role of Mode of Action

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The authors appreciate this opportunity to provide a brief perspective on harmonization of cancer and non-cancer assessment, in response to the recent, thoughtful recommendations of the National Academy of Sciences' (NAS) report on *Science and Decisions* in this area.

Risk Assessment at a Crossroads

The NAS committee addressed broad issues in a number of areas related to the substantial challenges faced in the assessment of risks chemical exposures pose to human health . These challenges include the long delays in completing complex risk assessments, some of which take decades, lack of data for many chemicals, and the need to address the many unevaluated chemicals in the marketplace. Deliberations of the committee resulted in a number of recommendations to EPA aimed at improving both the utility of risk assessment application, and the technical analysis that supports risk assessment, as a basis for additional consideration by the broader risk assessment community. Specific recommendations related to:

- The design of risk assessment
- Uncertainty and variability
- Selection and use of defaults
- A unified approach to dose-response
- Combined exposures risk assessment
- Improving the utility of risk assessment
- Problem formulation/Issue Identification
- Stakeholder involvement
- Capacity building

The committee is to be congratulated on its insightful suggestions in relation to this significant range of topics critical to the future direction of chemical risk assessment. The recommendations are helpful in stimulating additional development in critically important areas such as more efficient, fit-for-purpose risk assessment, based on early problem formulation.

This commentary focuses on the recommendation related to "a unified approach to dose-response analysis" for *default* methods for cancer and non-cancer effects. While this was considered "scientifically feasible", the recommendation appeared to be predicated principally on the basis of informing risk benefit analysis, without recognition, perhaps, that this is not always the objective of fit-for-purpose assessment advocated by the committee. Considered to a much more limited extent were scientific advancements relevant to, for example, more efficient and accurate prediction of risk based on understanding of how chemicals induce effects (i.e., mode of action). In this commentary, we consider enhancement of the NAS recommendation for a unified approach to dose-response assessment based on broader integration of additional perspective. This includes other aspects of the *Science and Decisions* report, in particular those related to problem formulation and incorporation of chemical specific data, as well as other NAS reports (such as *Toxicity Testing in the 21st Century*), and the output of previous and ongoing related domestic and international initiatives.

Historical Context and Focus

Traditionally, default assumptions for dose-response assessments adopted by EPA have differed for cancer and non-cancer effects. For non-cancer effects, reference doses or concentrations thought "likely to be without an appreciable risk of deleterious effects" (i.e., "safe doses") are based on the assumption of a threshold, estimated through application of uncertainty factors to no-effect levels observed in animal or human studies. Uncertainty factors applied typically address

variations between species and in the human population but may include others such as the exposure duration of the principal study and comprehensiveness of the database. For cancer, it has generally been assumed that a probability of harm exists at all levels of exposure (i.e., even one molecule has a finite level of risk). This is based principally on considerations for radiation-induced cancer, where unlike chemicals, biological membranes cannot limit the dose. With this assumption of harm at all levels, population risk is estimated for a given magnitude of exposure based on linear extrapolation to zero dose.

Since the introduction of this distinction in the 1970's, evolution of methods to additionally incorporate mechanistic and empirical toxicological data as a basis to better inform dose-response analysis for both cancer and non-cancer effects has contributed to harmonization of these two approaches. For mechanistic data, this includes both categorical default and chemical specific approaches (which are considerably more predictive), to address, for example, susceptible populations as recommended in *Science and Decisions*. In relation to making better use of empirical data, for example, benchmark dose modeling has been introduced to replace no effect levels as points of departure for dose-response analysis of non-cancer effects. Categorical regression contributes as a meta-analytical technique for combining multiple studies, improving duration-concentration-response modeling, evaluating how severity of effect changes with dose and evaluating risk above "safe" doses.

The specific focus in this commentary is on the potential contribution of early, more systematic and transparent consideration of mode of action (MOA) in harmonizing approaches between cancer and non-cancer effects. This includes the important contributions of EPA in this area, such as the introduction of dosimetric adjustments for various categories of agents in inhalation reference concentrations introduced in 1994 and the focus on MOA informed dose-response analysis in the EPA (2005) Cancer Guidelines. The latter drew, in part, on the output of previous initiatives of, for example, scientific societies such as the Society of Toxicology. Consistent with developments in biological understanding, the cancer guidelines include emphasis on analyzing data before invoking default options, understanding underlying mode of action throughout (as a basis, for example, for considering differential risks to children), and a two-step process separating modeling of observed data from extrapolation to lower doses (including both linear and nonlinear extrapolations).

Weight of evidence considerations for MOA in animals consistent with those in these cancer guidelines have been extended to evaluation of human relevance of effects observed in experimental animals, and consideration of the implications for the dose-response analysis. Initiatives of the International Life Sciences Institute Risk Sciences Institute (ILSI RSI) and the International Programme on Chemical Safety (IPCS) have led to the development of international frameworks on MOA/human relevance (HR) for both cancer and non-cancer effects and evaluation of key events for specific endpoints. Robust MOA/HR analysis provides a tool to promote consistent and transparent consideration of the weight of chemical specific evidence on MOA (together with broader understanding of physiology and disease processes). This provides a basis to address another of the Committee's recommendations that: "EPA should develop clear, general standards for the level of evidence needed to justify the use of agent-specific data and not resort to default."

The use of uncertainty factors has also evolved within EPA, and elsewhere to incorporate more predictive information on MOA. For example, in the 1990's, the International Programme on Chemical Safety (IPCS) developed methods to determine Chemical Specific Adjustment Factors (CSAF) to address toxicokinetic or toxicodynamic data for individual chemicals culminating in the publication of guidance in 2005. The same concepts are applied at EPA to develop data-derived extrapolation factors with guidance under development.

Recommendation of the NAS: A Unified Approach to Dose-Response Assessment

To address the dichotomy between default approaches to cancer and non-cancer risk assessments, the committee recommended that EPA implement a phased-in approach to consider chemicals "under a unified dose-response assessment framework that includes a systematic evaluation of background exposures and disease processes, possible vulnerable populations, and *modes of action* that may affect human dose-response relationships." The committee further recommended that the RfD and RfC be redefined to take into account the probability of harm, and emphasized flexibility in developing test cases, applying different conceptual models. The following consideration was seemingly influential in this context: "Because the RfD and RfC do not quantify risk for different magnitudes of exposure but rather provide a bright line between possible harm and safety, their use in risk-risk and risk-benefit comparisons and in risk-management decision making is limited."

It is encouraging that the committee recognized the importance of MOA in increasing the accuracy of prediction and harmonizing the approaches to dose-response analysis between cancer and non-cancer effects. However, this recommendation does not address the fact that the appropriate form of any dose-response analysis is necessarily dependent upon the objectives of a specific risk assessment and the needs of the risk managers as determined in the problem formulation. While these needs might include the evaluation of risk at various levels of exposure, in fact, in many cases, risk managers are seeking a "safe dose," relevant to all potential effects (including cancer). Thus, the NAS recommendation for such harmonization could be perceived to be inconsistent with its emphasis on problem formulation.

Mode of Action — Developments in Harmonizing Cancer/Non-Cancer

As indicated above, evolving advancements in regulatory risk assessment to more meaningfully and accurately predict human health risks have been based on increasing understanding of MOA. This is the fundamental premise underlying recommendations of the NAS panel on *Toxicity Testing in the 21st Century*, in the development of more efficient, MOA-based testing strategies. It is our contention, as well as others previously mentioned,[1] that MOA is also the informed basis by which cancer and non-cancer methods can be meaningfully harmonized and has been the underlying premise for significant advancements in this area at EPA and elsewhere.

Mode of action in this context is defined as a biologically plausible series of key events leading to an adverse effect. *Key events* are those that are critical to the adverse outcome (i.e., necessary but not necessarily sufficient in their own right), and are measurable and repeatable. Perturbations of several cellular processes and toxicity pathways may contribute to each key event. *Mechanism of action,* in contrast, relates to understanding the molecular basis of adverse effects. While there is limited understanding of the mechanisms of toxicity for most adverse effects, identification of key events in a hypothesized MOA, based on robust (but generally incomplete) mechanistic data provides important insight which is critical to effective and efficient prediction and reduction of risk, as a basis to draw inference with less information on hazard.

An important objective of MOA/human relevance analysis, then, is to identify key events that are likely to be the most influential in determining potential qualitative and quantitative differences between test species and humans, and within population subgroups. Consideration of MOA also enables identification of early key events or indicators of susceptibility (termed "modulating factors") that could be measured in humans and contributes to identification of any specific sub-populations (e.g., those with genetic predisposition) who are at increased risk. In fact, this same rationale is apparent in recommendations in a 1991 NAS report on biomarker development, based on fundamental tenets of molecular epidemiology. Specifically, this report noted that focus on early markers could increase the specificity and sensitivity of assessment and intervention endeavors. Thus, if sufficient information exists to support an early key event such as metabolic activation to a reactive metabolite, this directs attention to the relevant parameters in humans, which could be determined. In addition, the kinetic and dynamic data which are considered early in MOA/human relevance analysis are critical to interspecies and intraspecies extrapolations in subsequent dose-response analysis for both cancer and non-cancer endpoints..

As a result, MOA/HR analysis promotes harmonization of approaches to risk assessment for all endpoints through a biologically consistent approach, for which exploration of biological linkages is critical to ensuring maximal use of relevant information. Moreover, it sets the stage for identification of critical precursor, key events for which subsequent quantitation of interspecies differences and interindividual variability in dose response analysis is relevant for either cancer or non-cancer endpoints (see for example EPA's non-linear dose response assessment for the carcinogen perchlorate on the Integrated Risk Information System). In other cases, organ toxicity may be a critical key event in a postulated MOA for induction for tumours at a single site, or a postulated MOA may lead to toxic effects in multiple organs; in both cases, the relevant key events would be considered in the same HRF analysis.

Robust MOA/HR analysis also provides a tool to promote consistent and transparent consideration of the weight of chemical specific evidence on MOA as a basis to address another of the Committee's recommendations that: "EPA should develop clear, general standards for the level of evidence needed to justify the use of agent-specific data and not resort to default."

Summary

Traditional "default" methods involving development of either "safe doses" for non-cancer effects through division of no-effect levels by uncertainty factors, or estimation of population risk by linear extrapolation for cancer are designed to be protective rather than predictive of risk. More meaningful prediction of risk in, for example, potentially susceptible populations, is necessarily dependent upon an understanding of how chemicals induce effects (i.e., mode of action). Indeed, the recent evolution of risk assessment and recommendations for toxicity testing strategies, are based on recognition of the need to develop and incorporate more predictive, mechanistic data. It seems important, then, that additional consideration of the NAS recommendations take into account this broader perspective, based on considerable evolving experience in this area, including that related to mode of action informed predictive methods such as quantitative structure activity modeling which are currently contributing to more efficient assessments, as also advocated in the *Science and Decisions* report.

Objectives of specific risk assessments determined in problem formulation will also require expression of risk in different formats. This includes but is not limited to probability of risk at various levels of exposure; this also seems an important consideration in future deliberation as a basis to reconcile different recommendations of the NAS Committee.

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