Inside EPA's
Risk Policy Report

An exclusive weekly report for scientists interested in environmental policymaking and policymakers interested in science

from Vol. 17, No. 37, September 14, 2010

Guest Perspective

The NRC Silver Book: The Case for Improving Non-Cancer Risk Assessment

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The National Research Council (NRC) published "Science and Decisions: Advancing Risk Assessment" in response to an EPA request for recommendations for near term (2-5 years) and longer term (10-20 years) improvements in how the Agency conducts human health risk assessments. The NRC report, published in December 2009, is a forward-looking analysis that makes recommendations in two broad areas: 1) increasing the utility of risk assessments for decision-makers; 2) technical improvements to the practice of risk assessment. One section of the latter area (improved methodology) has received considerable attention, as the report recommended a new paradigm for dose-response assessment. This commentary is an independent contribution by some committee members regarding Chapter 5 of the report, "Toward a Unified Approach to Dose-Response Assessment."

The chapter's major recommendation calls for reorganizing how chemicals are evaluated. The long-standing method is to treat carcinogens and non-carcinogens with different methodologies, based on the principle that carcinogens (or at least certain kinds) produce a quantifiable risk at low doses, while non-carcinogens have a threshold below which there is presumed to be no risk to the population.

The NRC report takes a different view by giving the distinction over endpoint (cancer vs non-cancer) less importance and instead focusing on possible mechanisms of action and susceptibility factors that may influence the dose-response function at low dose. This stems from a growing set of examples where the dose-response curve for non-carcinogens can appear linear across a broad population even though it might be expected to have a threshold for individuals. This concept is supported by mechanistic considerations in which the toxicant's mode of action (MOA) can interact with background disease processes, or with other chemical exposures, to linearize the lowdose slope. Furthermore, in situations where low-dose linearity can be rejected, the NRC report offers alternative approaches to developing a reference dose (RfD) that makes it a quantitative de minimis risk target. The NRC report reflected a belief that a description of the probability of adverse response at particular exposures was a common goal regardless of the endpoint. This facilitates comparisons between risk management options and is supported by the underlying science.

In this commentary, we briefly describe NRC recommendations with respect to non-cancer endpoints. It is worth clarifying certain aspects of the NRC recommendations at the outset, as there has been substantial misinterpretation of some elements:

1) While the report described how non-carcinogens can have a linear low-dose response relationship in some situations, the committee stated explicitly that not all non-carcinogens would exhibit low-dose linearity.

2) The recommendations are based on both scientific insight (a recognition of the drivers of dose-response relationships at low dose) and risk management needs (the ability to quantify the benefit of reducing exposure for non-cancer endpoints), but they were not based upon the precautionary principle.

3) The report recognizes the inherent differences between cancer and other diseases, and that current cancer and non-cancer approaches contain methodological issues. Therefore, the committee did not recommend harmonization of the existing approaches. Rather, the NRC recommendations focus on a probabilistic expression of risk and provide a framework for unifying the approach for dose-response assessment across chemicals regardless of endpoint. The proposed modeling approaches are prototypical and not intended to represent the final word, but are provided as examples to prompt future work.

4) Although the committee proposed redefinition of the RfD, this does not remove the option for a risk manager to use it as before (e.g., for "bright line" decision-making). But the redefined RfD takes on extra meaning as a risk-specific dose associated with a fraction of the population potentially affected at exposures at the RfD.

5) While the committee's recommendations are substantial, they should not represent a major increase in complexity if default approaches are adopted. The approaches can be phased in as methods and supporting datasets are developed,

beginning with the development and use of default distributions.

6) The approach emphasizes an understanding of toxic mechanism in relation to background disease processes and other relevant exposures. We believe that this puts risk assessment in a better position to interpret and utilize the opportunities emerging from the new technologies for hazard and dose-response assessment (omics, high throughput testing).

The need for probabilistic dose response modeling for non-carcinogens

The RfD and Hazard Quotient (HQ) approach have provided a simple yes/no tool for making risk-based decisions. While this approach has utility in some contexts, it does not provide insight about the level of population risk either above or below the RfD. The current RfD and unitless HQ provide no indication of the benefit of going from a HQ of 20 to 2 or 0.2, and as presently formulated, moving from a HQ of 1.05 to 0.95 would have a greater apparent benefit than moving from a HQ of 10 or even 100 to 2. Furthermore, cost-benefit analyses are increasingly used for regulatory decision-making, requiring estimates of the number of people benefitting from a given intervention. In these assessments, carcinogens are included because their population cancer risk can be estimated, while non-carcinogens are typically left out.

This would be problematic even if the underlying science supported a threshold yes/no approach. However, as recognized by epidemiological evidence for particulate matter, lead and methyl mercury, non-carcinogens can exhibit low-dose linearity (Schwartz 2002; Axelrad et al. 2007). The concern expressed for particulate matter that misclassification of exposure might artifactually linearize the dose response (Brauer et al 2002) is much less relevant for lead and methyl mercury for which the dose response is based upon good biomarkers of exposure, and supported by biological evidence. Further this is unlikely to be artifact where: a) there is considerable inter-individual variability in susceptibility which leads to a distribution of thresholds in the population; b) the endpoint is not rare; and c) the chemical is contributing to processes that are already causing disease in the population.

When Should Low Dose Linear Be The Modeling Choice?

It has been documented for some time that the presence of background processes or exposures can cause a carcinogenic compound that might otherwise exhibit a threshold to be linear at low dose (Crump et al., 1976; Lutz 1990; Lutz 2001). As pointed out by the committee and most recently by Crump et al. (2010a), similar concepts apply to non-cancer endpoints.

It is important to stress that this does not imply that all agents will exhibit linearity at low dose, only those agents which either: 1) do not have a basis for a threshold on an individual level because their MOA involves actions that could readily occur at very low dose (e.g., induce mutations); or 2) have a threshold at the individual level but can augment processes that contribute to background disease such that at the population level a threshold cannot be demonstrated. The committee considered each of these scenarios, which we discuss below.

1) Linear Agents at the Individual Level: Arguments have been made for thresholds even for mutagens because the amount of exposure becomes so small at low dose that host defense mechanisms ought to be able to neutralize the chemical or repair the (DNA) damage. While this article focuses on the RfD, the example of mutagens and cancer risk is illustrative of arguments that might be raised against the low dose linearity of non-mutagenic MOAs. The concept of thresholds for mutagenic carcinogens has not been proven and in fact would be difficult to prove within the constraints of methodological limitations. Several things should be kept in mind:

A) Based upon the huge number of molecules in a mole (Avogadro's number — 6.03×10^{23}), even very low environmental exposures will involve many molecules — for example, one part per trillion of ozone still involves the inhalation of 2×10^{13} molecules in one hour at rest.

B) There are many potential cells and targets within cells that can be attacked.

C) Damage is a probabilistic event as host defenses and repair are not instantaneous or 100 percent efficient; therefore, there is always some probability of an adverse effect, with that probability shrinking in linear fashion as the dose decreases.

D) The slope of that response curve may be different at high dose where there is overwhelming of defenses than at low dose, and so an important challenge is to develop ways to approximate the low dose slope. This is a kinetic question that can be addressed by modeling rates of reactivity, detoxification and repair at low vs. high levels of system utilization and factoring in variability in host defense and repair. These are key areas of evolving research.

2) Linear Agents at the Population Level: These agents would be considered non-linear at the individual level such that each member of the population has a threshold dose that needs to be exceeded for the toxic effect to occur. However, the population has members with background risk factors or disease processes that create the equivalent of a starting level of chemical. Rather than the dose-response starting at zero dose, every molecule is adding, via the intersection of its MOA with the disease etiology or with similarly acting chemicals, to the likelihood for adverse effects to occur in susceptible individuals. For some of these individuals, the disease or adverse effect may already be occurring and so the threshold for effect has been superceded by background processes, with even small doses of chemical agent adding incrementally to this background rate. Therefore, there will be some individuals who will be responsive at low dose and still fewer individuals who will be responsive at extremely low dose, but there will be a probability for some contribution to disease occurrence even at very low dose, given the presence of background exposures and disease processes. This of

course requires commonality between chemical MOA and disease etiology, an area which has received relatively little attention. The slope for this low dose linear response may be different than the high dose slope because the effective dose (percentage that gets past host defense mechanisms) is likely higher at high dose.

There are a variety of examples in which it is difficult to find a threshold for a non-cancer effect in the human population. A case in point is lead. Its neurotoxic effects occur against a backdrop of many risk factors that can affect brain development and learning (e.g., poor diet, poor learning environment, various socioeconomic factors, co-exposure to other neurotoxicants). Further there is a natural distribution of IQ in the population. This leads to a wide range of susceptibility with some members of the population already near the limit of learning disability without lead exposure. For these individuals, even very low doses could increase the probability of their becoming a clinical case and such doses may incrementally shift the entire IQ distribution to lower values. When risk factors are prevalent for a given condition to which the toxicant can add, a population threshold is unlikely.

The linearization of the threshold response when going from the individual to population level is only important for chemicals whose MOA interacts with background conditions that have a high rate. If the disease or background risk factors are uncommon, the size of the population at imminent risk will be small and afford less opportunity for interaction with the chemical under review. When the background rate of exposure or disease is high, these phenomena create a dose equivalent of the chemical that can place all actual exposures to the chemical on the linear part of its dose response function when considering the entire population.

The Unified Framework

Chapter 5 of "Science and Decisions" lays out a unified framework for analyzing three different cases: 1) Threshold at the individual level but linear at the population level; 2) Threshold at the individual and population levels; 3) Linear at both the individual and population levels. The chapter provides suggestions for how to sort chemicals and outcomes into these three bins and how the analysis would differ amongst them while still providing a probabilistic estimate of risk (as opposed to the current RfD).

Most germane to the current article is how to sort between Cases 1 and 2. The key difference is with respect to background interaction with chemical MOA — in Case 2 there is little chance for such an interaction either because there are no shared pathways between toxicant MOA and disease etiology, or the disease is rare. Examples given in Chapter 5 include alachlor induced hemolytic anemia (which occurs rarely in the population due to genetic factors alone) and xenon induced asphyxiation (occurs at high dose but at low dose will not plausibly outcompete oxygen for blood transport. In contrast Case 1 involves a high probability for background interaction as seen with particulate matter induced cardiopulmonary affects (high rate of cardiopulmonary vulnerability and frank disease), ozone's asthma effects (high background rate of oxidant stress in the lungs, high background rate of asthma), and lead's neurotoxic effects. In these examples, theoretical considerations would lead one to conclude that low-dose linearity would be likely, and epidemiological evidence has confirmed these expectations.

The NAS report also provides methodology for quantifying risk where a threshold exists at both the individual and population level — Conceptual Model 2. Several investigators have proposed the use of human variability-based modeling to calculate a probabilistic expression of non-cancer risk (Hattis et al. 2002; Evans et al. 2001). However, Crump et al. (2010b) pointed out issues with the statistical distributions assumed, in particular the assumption of log-normality for human variability distributions. Crump et al. (2010b) argued against the use of such probabilistic approaches for quantifying dose response relationships for Conceptual Model 2 (but supported quantification for Conceptual Models 1 and 3). We acknowledge this analysis and believe that further work in this area to develop default approaches to describe dose-response relationships for the threshold Conceptual Model 2 is preferable over the current uncertainty factor approach.

On theoretical, statistical and practical risk management grounds, a probabilistic version of the RfD is called for in which a low dose linear function is one of the modeling options. At the same time, despite concerns over modeling uncertainty, a default threshold type approach to estimating risk should be considered for either cancer or non-cancer endpoints when the underlying susceptibility, disease processes and mechanisms support the selection of the threshold-based Conceptual Model 2.

Summary and Conclusions

Low dose linearity for certain types of carcinogens and non-carcinogens is plausible and provides opportunities for probabilistic assessment of risk within a common unified risk assessment framework. The current system for non-carcinogens (single bright line RfD) does not allow for quantitative assessment of risk and benefit and does not acknowledge the likelihood of some finite degree of risk below the RfD. Susceptibility varies across the population due to a variety of factors - genetic, lifestyle, co-exposures, aging and disease processes, and can lead to a considerably greater difference in risk among the population than represented by the uncertainty factor of 10 typically utilized. Further as pointed out by the committee and others (Crump et al. 1976; 2010a) a chemical's augmentation of existing processes causing disease in the population leads to low dose linearity. The committee suggested a flexible framework for probabilistic dose response analysis for non-cancer endpoints and set out three different conceptual model examples that could be applied on a case-

by-case basis. Two models involve linearization of the dose—response while a third assumed threshold type dose response relationship. All three approaches would involve the development of default methodologies to facilitate implementation. (Cases with distinct and well understood subpopulations could be modeled separately within the three approaches.) The committee found a probabilistic analysis preferable to the current approach involving semi-quantitative 10 fold intra-human and other uncertainty factors.

The slope of dose-response relationship in the low dose region may be considerably shallower than at high dose, the expression of which presents a challenge to toxicokinetic and toxicodynamic modelers. Therefore, a set of simplified default high dose to low dose slope adjustments based on biologic reasoning (similar to dose effectiveness factor used in radiation biololgy) may be needed in the interim.

The argument against a low-dose linear approach for non-cancer endpoints ignores the examples of lead, particulate matter, ozone, mercury, and others. Appropriate use of low dose linear and other probabilistic models will enable the development of a risk-specific dose for both carcinogens and non-carcinogens, a key step forward for both risk assessment and risk management.