

DSRG Teleconference, March 3, 2009

First in a series of discussions on the National Academy of Sciences (NAS) report, "Science and Decisions: Advancing Risk Assessment"

Jeff Gift, Moderator
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Michael Dourson, Presenter
Toxicology Excellence for Risk Assessment

Members were asked to submit questions and issues for discussion prior to and after the Teleconference to: NAS08report@yahoogroups.com

Paul Feder, DSRG Chair, welcomed members of both the SRA's DSRG and SOT's RASS.

Jeff Gift indicated that the Teleconference will be recorded so that we can use the discussion to develop topics for future Teleconferences.

Michael Dourson presented slides prepared by Lynn Haber as an overview for TERA staff. The slides reviewed the evolution of risk assessment and recommendations for improvement of risk assessment at EPA. The recommendations included that EPA should formalized risk assessment planning and place increased emphasis on the value of information so as to determine clear decision rules. Additionally, uncertainty and variability need more attention and should be approached with a tiered approach. With respect to defaults the agency should develop alternative assumptions in place of defaults when it determines the alternative is clearly superior.

Chapter 5 of the report addresses dose-response. Specifically Pages 165 – 167 include the recommendations. Background processes should be incorporated into the dose-response assessment similar to publications of Kenny Crump for non-threshold carcinogens. The RfD should be redefined as a risk specific dose. Dr. Dourson reviewed the low-dose linearity issue for noncancer conceptual models as shown in Figures 5-4, 5-5, and 5-6 of the report. Cancer dose response should explicitly address human variability and should address cumulative risk assessment including incorporation of non chemical stressors.

Dr. Dourson requested comments from NAS Panel Members – no comments were offered.

Seven questions and a comment were received prior to the Teleconference.

Comment

1. The Report often has been incorrectly criticized as adopting low-dose linear extrapolation for all cases. The Report clearly suggests the use of nonlinear low-dose extrapolation for cancer and noncancer endpoints when the MOA of a chemical supports a nonlinear dose-response that is independent of any background MOA. Even when linear extrapolation is indicated, the Report does not endorse linear extrapolation from high doses. Rather, the Report recommends a probabilistic

approach for estimating a low-dose cancer or noncancer risk followed by linear extrapolation to even lower doses.

Commented by Dave Gaylord who indicated that many people have been missing the point of Chapter 5 and he sees the report calling for a process to follow for cancer and noncancer endpoints and the process will direct linear or nonlinear extrapolation. Chapter 5 recommends estimation of risk for both noncancer and cancer. Significant discussion ensued on issues of risk cost benefit analysis, criticisms toward linear extrapolation, individual versus population thresholds, and non-linear dose response that is curvilinear at low doses (fig 5-6 of the NAS report). There was considerable discussion concerning the terms “threshold” and “non-linear.” It was pointed out that some linear models can have thresholds and some non-linear models may lack thresholds. A question was posed relative to this comment regarding the degree to which the NAS distinguishes between dose-response shape and threshold in their report?

Questions

5. What does the NAS mean when they state that replacement of default should have an evidentiary standard that is “clearly superior” to the default, when the default itself is seldom based on chemical-specific data? At face value, this “evidentiary standard” would seem to be an easy hurdle to overcome, since some chemical-specific data is “more evidence” than no chemical-specific data. If this is what the NAS intended, why call this out as an issue?

The question presumes that defaults are not based on science. There are clear basis for some defaults and the report urges the development of better defaults. The comment was made that the question should clarify that the defaults are based on science, when defaults are not based on chemical specific information they should be revised based on the chemical specific data. Michael Dourson indicated that the question will be revised to address the discussion including how much chemical specific data is necessary to modify a default.

4. The stochastic assumption underlies the dose response assessment for chemical carcinogenicity based on data from radiation carcinogenesis. However, chemical exposures are known to differ from radiation exposures in ways that allow individual variability in toxicokinetics and toxicodynamics to affect the outcome. This evidence for inter-strain, inter-species, or inter-individual differences is overwhelmingly found in experimental animal studies and in human epidemiology studies. Should this stochastic assumption then be applied to chemical dose response assessment? Should its use be mollified?

Kenny Crump indicated that stochastically should be applied equally to chemicals and radiation. After discussion Lynn Haber rephrased the question: Is there a stochastic component and if so how would it be combined with the other chemical factors of toxicokinetics and toxicodynamics to inform the shape of the dose response curve? Clark Carington indicated that part of the problem is with using stochasticity as if it were something different than variability; a cancer bioassay can't tell what the source of the variability is. Rick Hertzberg indicated that the issue results from the original one hit models for radiation risk versus the processes that a chemical must go through in the body before it can act on the target tissue. Lynn Haber offered to revise the question taking into account issues raised in the discussion.

3. *Cummulative risk is addressed by assessment scientists by reference to mixtures guidelines from a number of organizations (e.g., ACGIH, 2008; EPA, 1986, 2000). What is it about these guideline that the NAS thought was deficient?*

Question was withdrawn by Mike Dourson.

1. *How do experimentally and theoretically evident biological thresholds for adverse effect weigh in on the suggested NAS way forward? What is the impact of individual variability on these thresholds and on determining "safe" doses, such as RfDs and RfCs?*

Question not discussed due to time limitations and owing to the earlier discussions on non-linearity and thresholds.

2. *Risk assessment scientists routinely incorporate background exposures into a dose response assessment of an individual chemical by reference to use of concurrent controls (e.g., BMD methods use either extra risk or added risk). What about this process does the NAS feel is insufficient for understanding individual chemical dose response? If the NAS is concerned with background exposures to other chemicals evoking similar critical effects, then is this not a chemical mixtures (or cummulative risk) issue addressed with appropriate guidelines? See question 3.*

Mike Dourson clarified that the issue is generally addressed by using a background with same stressors. Kenny Crump indicated that background has to do with background in human populations; the higher the background in human population the more likely the response might be linear. Mike Dourson indicated that background assessment is really a mixtures risk assessment issue.

Ila Cody offered to send some refinements to the questions to make them more robust.

6. *This is a two part question having to do with the need for endpoint site concordance between humans and laboratory animals, which is discussed in the section on "Data Assembly and End-Point Assessment" (pages 133-134 of the draft report).*

a. *The report states that "In some cases, the target organ in a rodent species, such as the forestomach or Zymbal gland, may not have an exact human counterpart. However, the presence of carcinogenic action in tissues for which there is no correspondence in humans or that may be regulated differently in humans does not mean that the toxicity or tumor finding in animals is irrelevant." Is this meant to apply only to "carcinogenic action" as is suggested by the text, or does it apply to any adverse effect (e.g., irritation of the forestomach)?*

See Page 133 – Do they really mean carcinogenic action or more generally any adverse effect? Harmonizing issues relative to non-cancer and cancer risk assessment. Degree to which it is adverse is a dose/response function. When do we need concordance between human and animal tissue changes?

b. The report goes on to state that "...Because epidemiologic studies are often limited in their ability to explore outcomes related to workplace or environmental exposures, it is typically impossible to rule out the relevance of an effect seen in a particular rodent tissue unless there is detailed mechanistic information on why humans would not be affected (IARC 2006)." What is meant by "detailed mechanistic information?" Is knowledge of an individual, required step in the process that is lacking in humans adequate?

Steve Lewis questioned to what degree this report changes the science policy. Mode of action issues – mice/rats and humans – were discussed. Question on what is considered adverse for non-cancer or cancer. A discussion of the Toxicity in the 21st Century document would make much of this report irrelevant.

7. My question to presenters and others on the call relates to whether chemical effects on hormone levels might be non-cancer effects that could demonstrate a linear dose-response. For example, a recent paper about thyroid hormone disrupting chemicals <http://www.ehponline.org/members/2009/0800247/0800247.pdf> indicates that adverse outcomes related to thyroid hormone suppression (neurodevelopmental and cardiovascular) are observed within the normal range of thyroid hormone levels in the population. Thus, the authors conclude that thyroid disruption observed on a population basis should be considered a biomarker of adverse outcomes. While some might suggest that homeostatic mechanisms would cause a threshold-type dose-response for effects on thyroid hormones, on a population basis this may not be the case, since a significant portion of the population is already within a region of the dose-response where hormone levels are associated with effects. In a different example, some researchers have looked for thresholds in dose-response for developmental exposure to antiandrogens and organ weight, and seen no threshold in dose response.

Due to time constraints this question was not addressed.

The group agreed to continue to accept questions through the SOT meeting at NAS08report@yahoo.com after which DRSG would meet to prioritize the questions to be discussed in future teleconferences.

Submitted by Julie Fitzpatrick