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Two Years On, Assessors Urge NAS To Clarify Advice On Linear Risk Method

Two years after a landmark National Academy of Sciences' (NAS') report recommended changes to EPA's risk assessment practices, many risk assessors are still seeking clarification on what the report means when it recommends the use of "linear" cancer risk assessments in various scenarios.

At an Oct. 11-13 workshop on the NAS report, *Science and Decisions*, risk assessors and other attendees urged one member of the NAS panel to further clarify it, saying that the report as currently written is confusing.

The workshop was the second in a series of three, called "Beyond Science and Decisions: From Issue Identification to Dose-Response Assessment," held in Arlington, VA. The agenda included presentations of some 18 case studies intended to provide risk assessment methodologies for various scenarios, including cancer and non-cancer assessments, and assessments of chemicals for which there is limited toxicological data.

"I think the use of linear and non-linear in *Science and Decisions* is very confusing. Hopefully we can all get past that," said Kate Sandy of Minnesota's Department of Health. And Michael Dourson, one of the organizers of the workshop, added, "Additional clarification is needed."

The workshop, organized by The Alliance for Risk Assessment (ARA) and cosponsored by a host of states, consultants, industry and non-governmental organizations, was focused on recommendations in the December 2008 NAS report, *Science and Decisions: Advancing Risk Assessment*, known as the "Silver Book."

The goal of the conferences is to publish a peer-reviewed handbook of risk assessment methods for various situations, such as limited data, acute exposures, probabilistic methods and using available human data, as exemplified in the case studies, Dourson said.

Development of the handbook comes as EPA is also working to craft its own response to the NAS. Scientists and assessors from across the agency are meeting Oct. 25-28 in Arlington, VA, to discuss recommendations in the Silver Book's as well as two other NAS reports, *Toxicity Testing in the 21st Century* and *Phthalates and Cumulative Risk* (*Risk Policy Report*, July 6).

The response is led by EPA's Risk Assessment Forum, and its chairman, Ed Ohanian, described the colloquium's goals at the ARA conference as creating an "action plan for future directions in human health risk assessment at EPA." Ohanian emphasized that the plan will consider both the NAS recommendations and Administrator Lisa Jackson's priorities, particularly those regarding children's health and environmental justice.

Linear extrapolation is generally a conservative method of modeling dose-response, the basis of risk assessment, at the low doses of exposure found in the environment. The approach generally assumes no safe level of exposure and results in harms proportional to the dose. Non-linear modeling assumes there is a threshold dose level below which exposure is not reasonably anticipated to be harmful. The linear modeling, which generally produces conservative assessments of cancer risk, is often opposed by industry and other regulated entities, including other federal agencies.

Existing EPA guidelines apply conservative linear assessment to cancer risk assessments of chemicals that are mutagenic, or those whose biological mechanism for causing cancer is unknown, because it is considered health-protective in the face of uncertainty. The approach is not applied to non-cancer estimates of risk, where a threshold is assumed.

But *Science and Decisions* recommends performing cancer and non-cancer assessments similarly, by a "unified approach to dose-response assessment." The report recommends three different "conceptual models" of how to perform risk assessments, depending on whether the chemical or environmental contaminant exhibits non-linear or linear responses in individuals or the population at low doses or generally, and whether the response is dependent or independent of background exposure.

Since its December 2008 publication, members of the NAS committee that wrote the report have indicated that their recommendations regarding how best to perform dose-response analyses have been misunderstood. Four of the panelists highlighted these issues in a recent guest perspective in *Risk Policy Report* (*Risk Policy Report*, Sept. 14).

The panelists note that the report recommends harmonizing cancer and non-cancer risk assessment approaches — but not toward an existing model. Instead, they propose a new, mode of action-based model for assessment. "Rather, the

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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 authors note that "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." They argue that their recommendations are based on "both scientific insight . . . and risk management needs . . . but were not based on the precautionary principle."

Misunderstandings continued during the ARA conference, where attendees asked Greg Paoli, one of the *Science and Decisions* authors, to explain again the committee's recommendation regarding the use of linear modeling. "It's very important to understand what the committee meant by linear," Paoli replied. "Particularly because we talk about harmonizing [cancer and non-cancer assessments] they assume it's the same as cancer [assessment.] That's not what we meant. [We meant], harmonize so that both are different from what they are now."

To clarify, Paoli quoted from the Silver Book's fifth chapter, where it recommends changes to dose-response practice: "Note that low-dose linear means that at low doses "added risk" (above background) increases linearly with increasing dose; it does not mean that the dose-response relationship is linear throughout the dose range between zero dose and high doses."

Paoli continued, "It does not mean dose response is linear at zero [to high doses] . . . Linear refers to a positive slope at the origin. No threshold at the origin doesn't mean you draw a line at the point of departure."

But others at the conference continued to express some confusion. One attendee, EPA scientist Ohanian, said, "I don't think that explanation will work with risk managers."

After the conference, Paoli explained that the committee's report differentiates between individual and population dose-response curves. Individual dose-response curves can be non-linear, with thresholds, yet yield a dose-response curve that has no threshold at the population level, Paoli said. This is because some individuals in the population are already experiencing the adverse effect given background exposures and disease. So, with even a small increment of the dose above background, additional people will become included in the fraction of the population affected. That slight increase in the fraction of the population affected with increased dose above the background can make the low-dose region of the dose-response curve linear for the population.

Paoli added that the committee's intent was to recommend a unified assessment method for cancer and non-cancer risk assessments where assessors should "begin the process of considering the dose-response curve the same way and let mode of action be the difference between them. The committee is saying there's no global default for either. Mode of action is the unifying part."

Paoli pointed out that mode of action assessment — for each endpoint of concern, not just cancer — is among the first steps of the unified framework the committee recommends for risk assessment. It is also an interpretation called for in another recent guest perspective, by organizers of the ARA conferences (*Risk Policy Report*, Sept. 28). — *Maria Hegstad*

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