



IMPLICATIONS OF RECEPTOR-MEDIATED EVENTS ON DOSE-RESPONSE: A WORKSHOP

The May 3-4, 2007 meeting of the National Research Council's Standing Committee on Risk Analysis Issues and Reviews featured a public workshop on the implications of receptor-mediated processes on dose-response evaluations of toxic chemicals. Often, only high-dose data are available to make predictions about adverse health effects that might occur at much lower environmentally relevant doses. To make those predictions, one must extrapolate from a high-dose region on a dose-response curve to the low-dose region relevant to most human exposures but where data are not available. The U.S. Environmental Protection Agency (EPA) requested a workshop that could explore whether knowledge of a receptor-mediated process could help make

predictions about the shape of the dose-response curve in the low-dose region.

After introductory remarks by Standing Committee Chair Dr. Bernard Goldstein, EPA's Dr. Peter Preuss welcomed the participants and discussed the importance of the topic. EPA has grappled with the issues surrounding receptor-mediated events and wanted to hear from all the points of view around the table to help the agency address complex dose-response questions about receptor-mediated processes relevant to, for example, the agency's draft dioxin risk assessment.

The workshop was composed of three sessions. The first focused on basic receptor biology, translation of receptor-mediated signaling to

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About the Committee. . .

The Standing Committee on Risk Analysis Issues and Reviews was constituted by the National Academies at the request of the Environmental Protection Agency to convene a series of public workshops on key risk assessment issues, including implications of mode-of-action research on dose-response analysis, certain aspects of uncertainty analysis, and the relevance of animal tumors to human health risk assessment, among other topics.

IN THIS ISSUE

1. Implications of Receptor-Mediated Events on Dose-Response: A Workshop
6. Workshop Agenda
7. Roster of Standing Committee on Risk Analysis Issues and Reviews
8. Upcoming Workshop Announcement

organism-level response, and new approaches to evaluate or characterize receptor-mediated processes. The second session focused on how a receptor-mediated mechanism affects the shape of the dose-response curve at different stages of the process (that is, at the molecular, cellular, tissue, and organism level). The figure below illustrates the different assumptions made about the shape of a dose-response curve at low doses. The role of private and public research to answer questions on the implications of receptor-mediated events for risk assessment was also discussed during the second session. In the last session of the workshop, a roundtable discussion was conducted to examine the key considerations for dose-response modeling of receptor-mediated pathways.

On June 5, the Standing Committee on Risk Analysis Issues and Reviews convened a public workshop, “Quantitative Approaches to Characterizing Uncertainty in Human Cancer Risk Assessment Based on Bioassay Results,” which will be summarized in an upcoming newsletter.

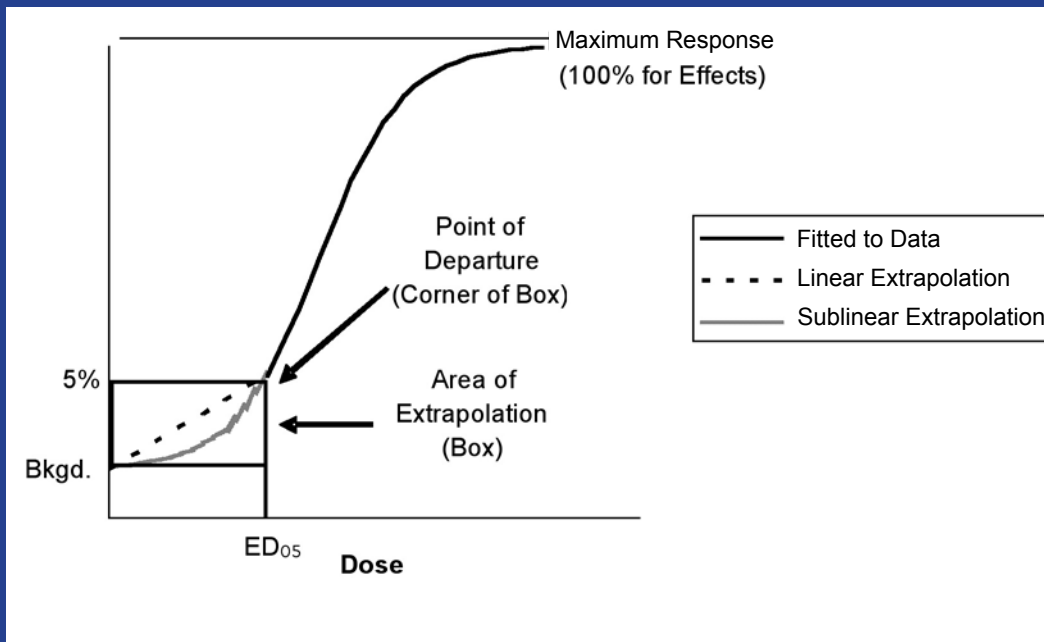


Figure 1. The figure illustrates key aspects of how risk assessors combine data with assumptions to address possible low-dose effects. The doses of a chemical administered to test animals are plotted horizontally and their response, vertically. Because there is no reliable way to observe and measure risks at low doses, assessors must use data outside the “box” in the lower left to estimate what risks may be within the box. NRC 2006.

Session I : Science Presentations

Dr. Jack Vanden Heuvel, Pennsylvania State University, provided an overview in his presentation "Biology of Receptors and Signal Transduction Pathways," and said a model known as the Law of Mass Action is the best approach for understanding how receptors within a cell recognize a distinct chemical entity, such as a ligand, and bind to it. This binding can alter a cell's state, affect signals with other cells, and change gene expression. These changes can initiate a biochemical cascade through cells, tissues, and organs that may lead to overt health effects. With complex receptor-based interactions the linearity of individual processes might not be as critical as the question of how the system as a whole changes under stimulus, according to Vanden Heuvel

In his presentation, "Receptors in Normal Functioning and Disease," Dr. Kevin Gaido, Hamner Institutes for Health Sciences, addressed receptor-mediated pathways in normal function-

ing and disease processes using male androgen-receptor activity and male reproductive system disorders as an example. Sufficient exposure to some pesticides leads to binding with androgen receptors in test animals and diminishes fertility, leading to reproductive tract defects.

Dr. Peter Sorger, Harvard Medical School, presented "Cell-Signaling Networks and Systems Biology Models." Systems biology is a powerful approach that uses computational models and laboratory data to describe and understand the functions of biomolecules from the perspective of interacting systems of components. Sorger said highly-integrated models and better measures of events downstream from receptor-mediated processes would result from a systems biology approach. Ultimately, systems biology of receptor signaling should aid in drug development, in other methods for interrupting disease processes, and in understanding environmental effects on cells.

This newsletter as well as additional information about the committee and its activities can be found at http://dels.nas.edu/best/risk_analysis/. The newsletter of the Standing Committee on Risk Analysis Issues and Reviews is published to keep you informed of committee activities. This is a project of the National Research Council's Board on Environmental Studies and Toxicology. The views expressed in the articles in this newsletter are those of the individual authors and presenters and do not reflect the findings or conclusions of The National Academies.

Invited Speakers for the May 3-4 Workshop

Jack Vanden Heuvel, Pennsylvania State University

Kevin Gaido, The Hamner Institutes for Health Sciences

Peter Sorger, Harvard Medical School

Stephen Safe, Texas A&M

Michael Gallo, Robert Wood Johnson Medical School

Rory Conolly, U.S. EPA

Dale Hattis, Clark University

Alexander Constan, Infinity Pharmaceuticals Inc.

William Farland, Colorado State University

Session 2: Discussion of Key Questions

Dr. Stephen Safe, Texas A&M, presented “Cellular and Molecular Processes in Receptor-Mediated Signaling” and said it is a matter of faith that receptor-mediated responses have linear dose-response relationships at low doses. Safe said there is competition among the Ah and estrogen receptors for the same ligands and that “crosstalk” among receptors and other factors complicate the conclusion that receptor-mediated events are uniformly linear.

Workshop participants discussed the level of biological detail needed to reach conclusions about the shape of dose-response relationships at low doses. Some said that chemical activity at the receptor level tends to have linear dose-response relationships. That could imply that using a linear model for dose-response relationships for overt physiological responses is justifiable. But others said linear relationships at the receptor-level do not necessarily warrant using a linear model for physiological effects downstream of receptor activity as non-linear patterns could be operating.

Dr. Michael Gallo, Robert Wood Johnson Medical School, presented, “Shapes of Dose-Response Relationships at Higher Levels of Organization,” which focused on molecular mechanisms of nuclear-receptors, including Ah receptors. Gallo discussed the interactions of key proteins with the Ah receptor and the results of those interactions. Gallo said analyzing existing data on nutrition and inflammation could illuminate whether receptor-mediated events affect tissues, organs, and other levels of biologic organization in similar ways.

EPA’s Dr. Rory Conolly discussed “Additivity to Background as a Potential Source of Linearity” by focusing on a paper published by Standing Committee member Dr. Kenneth Crump of the Environ Corp. that concluded “if the addition of the test carcinogen merely increases the rates of processes that were occurring anyway, then dose-

response relationships will be linear at low-dose levels.” Conolly noted that because the body can mount adaptive responses to environmental stressors, dose-response curves in the low-dose region may be non-linear and the argument that Crump developed may not have fully considered the biological control and adaptive processes inherent in living systems. Conolly suggested that the question of additivity to background needs to be re-examined in light of those considerations (see Figure 1).

Dr. Dale Hattis, Clark University, focused on variation in biologic resilience to toxic exposures in his talk on “Effect of Robustness of Control Mechanisms to Perturbation.” Hattis examined the variability among species of test animals exposed to doses of chemicals that result in the same level of mortality effects. He concluded that potent classes of chemicals with receptor-based mechanisms of action, such as dioxins and organophosphate pesticides, produce a wider variation in species sensitivities, and that this warranted further examination.

Dr. Alexander Constan, Infinity Pharmaceuticals Incorporated, presented on the role of public and private research in answering key questions and discussed toxicity-testing issues in the development of new pharmaceutical agents. Constan said researchers focus on receptor-mediated events to understand mechanisms of action, observations of animal pathology that might not be relevant to humans, and patterns of possible side effects in preparation for the drug-approval process.

Also speaking on the role of private and public research, Dr. William Farland, Colorado State University, said that accepted protocols for collecting receptor-mediated dose-response data have not been established. Academic researchers are a natural group to pursue such methods, and interdisciplinary teams in universities are now pursuing

challenging low-dose risk assessment questions based on systems-level understanding of receptor-mediated events.

Farland, a former senior scientist and science adviser with the EPA, noted that a review committee had raised concerns about the agency's proposal to rely on a linear model for the cancer dose-response assessment of dioxin. EPA had identified a set of receptor-mediated end points related to both cancer and non-cancer effects in its dioxin risk assessment. Although he acknowledged there was some uncertainty surrounding the selection of the end points and their interpretation, both linear and non-linear dose-response curves were evident. Given EPA's concerns about a relatively small margin of exposure compared to observed effects, and about adding to existing

body-burdens of dioxin exposure, he said using a linear dose-response model for dioxin to describe an upper-bound on cancer risk was warranted. Some participants agreed this was a reasonable interpretation, but others said the uncertainties in extrapolating from animal studies to humans weakened that approach.

Standing Committee Chair Dr. Bernard Goldstein, University of Pittsburgh, asked whether data expected to emerge in the next several years would help with the question of whether dioxin's cancer dose-response relationship is linear at low-dose levels, but workshop participants said they were not certain it would. Farland said the tools to begin to answer that question would be available within two years.

Session 3: Roundtable Discussion

Goldstein said a key question EPA faces is how new research has changed the nature of a risk assessment done today versus an assessment conducted twenty years ago. Workshop participants differed on the issue with some arguing that the new research had done little as stubborn questions persist about the shape of the dose-response curve at low doses and the role of background processes. But others said new understandings of the mechanisms of biochemical processes and tissue response is improving predictions by constraining the range of possible health outcomes that are relevant to risk assessment.

Workshop participants said it is a complex process to scale-up from receptor-binding to overt health effects. Goldstein noted that the group did not appear to be saying that dioxin must have a linear dose-response pattern for overt physiological effects because its activity within biological systems is receptor-based.

In summary remarks, Standing Committee member Dr. Lorenz Rhomberg of Gradient Corp. returned to some of the motivating questions of the workshop: What are the key considerations

for dose-response modeling of receptor-mediated responses? What attributes of a receptor, or a receptor-mediated response, would suggest approximate linearity below the observable range? What attributes would suggest significant non-linearity below the observable range?

Rhomberg said using biologically based models and statistical models are two ways to address those questions. Biological models are made by building up blocks of biological information on the causes of health outcomes of interest. But the statistical models isolate a response and focus on that event and its precursors.

Biological models hold a lot of promise for the future, but in the short-term, agency assessors probably will have to rely on statistical models, according to Rhomberg. In tracing receptor-binding, cell communication, gene expression, and changes in cellular states all the way through to physiological disease, the optimal focus would be on the inputs and outputs of key processes that are the crux of the toxicity response.

WORKSHOP AGENDA

May 3-4, 2007
Keck Center of the National Academies
500 Fifth Street, NW
Room 100
Washington, DC 20001

THURSDAY, MAY 3, 2007

- 8:30 am** Purpose of Workshop
Bernard Goldstein, Committee Chair
Lorenz Rhomberg, Workshop Chair
- 8:40 am** EPA's Expectations for the Workshop; Discussion of the Issues
Peter Preuss, Director EPA's National Center for Environmental Assessment

SCIENCE PRESENTATIONS

- 9:00 am** Biology of Receptors and Signal Transduction Pathways
Jack Vanden Heuvel, Pennsylvania State University
- 9:50 am** Receptors in Normal Functioning and Disease
Kevin Gaído, The Hamner Institutes for Health Sciences
- 10:40 am** Break
- 11:00 am** Cell-Signaling Networks and Systems-Biology Models
Peter Sorger, Harvard Medical School
- 11:50 am** Break for Lunch

DISCUSSION OF KEY QUESTIONS

- 12:45 pm** Cellular and Molecular Processes in Receptor-Mediated Signaling
Stephen Safe, Texas A&M
- 1:30 pm** Shapes of Dose-Response Relationships at Higher Levels of Organization
Michael Gallo, Rutgers University
- 2:15 pm** Additivity to Background as a Potential Source of Linearity
Rory Conolly, EPA
- 3:00 pm** Break
- 3:15 pm** Effect of Robustness of Control Mechanisms to Perturbation
Dale Hattis, Clark University
- 4:00 pm** The Role of Public and Private Research in Answering Key Questions
Alexander Constan, Infinity Pharmaceuticals

5:45 pm

William Farland, Colorado State University

Comments from the Public

6:00 pm

Adjourn

FRIDAY, MAY 4, 2007

8:30 am

**Roundtable discussion; Synthesize previous day of presentations Bernard Goldstein, University of Pittsburgh, Discussion Leader
Lynn Goldman, Johns Hopkins University, Discussion Co-Leader
Rick Corley, PNNL, Discussion Co-Leader**

10:30 am

**Summary Presentation
Lorenz Rhomberg, Gradient Corporation**

11:00 am

Public comment session

11:15 am

Adjourn Workshop

Standing Committee on Risk Analysis Issues and Reviews

Bernard Goldstein (Chair), University of Pittsburgh

Frederic Bois, Institut National de l'Environnement Industriel et des Risques

Michael Brauer, University of British Columbia

Richard Corley, Pacific Northwest National Laboratory

Linda Cowan, University of Oklahoma

Kenneth Crump, Environ Corporation

Lynn Goldman, Johns Hopkins Bloomberg School of Public Health

Philip Landrigan, Mt. Sinai School of Medicine

Thomas Louis, Johns Hopkins Bloomberg School of Public Health

Nu-May Ruby Reed, California EPA

Lorenz Rhomberg, Gradient Corporation

Joyce Tsuji, Exponent Corporation

Workshop Planning Committee

Implications of Receptor-Mediated Events on Dose-Response

Lorenz Rhomberg (Workshop Chair), Gradient Corporation

Frederic Bois, Institut National de l'Environnement Industriel et des Risques

Richard Corley, Pacific Northwest National Laboratory

Lynn Goldman, Johns Hopkins Bloomberg School of Public Health

Bernard Goldstein (Standing Committee Chair), University of Pittsburgh

Philip Landrigan, Mt. Sinai School of Medicine

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THE NATIONAL ACADEMIES
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Washington DC 20001

*Standing Committee on Risk Analysis Issues and Reviews
Board on Environmental Studies and Toxicology*

Workshop Announcement

Mouse Liver Tumors: Benefits and Constraints on Use in Human Health Risk Assessment, Qualitative and Quantitative Aspects

Thursday and Friday, November 8-9, 2007.

Keck Center of the National Academies, 500 Fifth St. Washington DC, 20001.

To register visit: http://dels.nas.edu/best/risk_analysis/evreg.php



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