NATIONAL ACADEMY OF SCIENCES
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WORKSHOP
Inorganic Arsenic: Scientific Considerations for Hazard Identification and Dose-Response Analysis

April 4, 2013

NATIONAL RESEARCH COUNCIL
2101 Constitution Avenue, NW
Lecture Room
Washington, DC

This Event Will Be Webcast

7:30 am	REGISTRATION
7:45 am	**Welcome and Introduction** *Joseph Graziano, Committee Chair*
8:00	**Update on EPA's Inorganic Arsenic Activities** *Kenneth Olden and Vincent Cogliano, U.S. Environmental Protection Agency*

Strengths and Weaknesses of Recent Epidemiologic Studies of Inorganic Arsenic

8:15 am	Cancer Evidence and Dose-Response Relationships *Kenneth Cantor, National Cancer Institute*
8:45 am	Noncancer Evidence and Dose-Response Relationships *Craig Steinmaus, California Environmental Protection Agency, University of California at Berkeley*

Integration of Metabolism and Mode of Action Information in Hazard Identification and Dose-Response Analyses

9:15 am	Metabolism, Its Consequences, and Implications for Low Dose Assessments *David Thomas, U.S. Environmental Protection Agency*
9:40 am	Mode of Action and Mechanism Identification and Implications for Low Dose Assessments *Samuel Cohen, University of Nebraska Medical Center*
10:05 am	Interplay Between One-carbon Metabolism, Arsenic Metabolism and Epigenetics *Mary Gamble, Columbia University*
10:30 am	BREAK
10:45 am	Mode of Action for Lung and Cardiovascular Effects *R. Clark Lantz, University of Arizona*
11:10 am	Impact of In Utero and Whole Life Exposure and Implications for Dose Response *Michael Waalkes, National Institute for Environmental Health Sciences*

11:35 am **Panel Discussion:**
Moderators: *Aaron Barchowsky and Rebecca Fry*

1. Are there data that support low dose mechanisms and modes of action?
2. Is there a continuum of common thread in cancer and noncancer mechanisms and modes of action?
3. Are there gender and species differences in metabolism or modes of action that impact dose response and disease susceptibility?
4. Do the kinetics and dynamics of inorganic arsenic and its metabolites in different organs promote organ-specific disease?

12:30 pm BREAK

Probabilistic Dose-Response and Harmonization Approaches for Cancer and Noncancer Effects

1:30 pm
- Lessons Learned from Lead and Particulate Matter
  Joel Schwartz, Harvard School of Public Health

2:00 pm
- Extrapolation of Mode of Action Data to Dose-Response Modeling of Human Health End Points
  Harvey Clewell, The Hamner Institutes of Health Sciences

2:30 pm **Panel Discussion:**
Moderators: *Gary Ginsberg and Robert Wright*
Discussant: *Daniel Axelrad, U.S. Environmental Protection Agency*

1. Do the available gene expression data define a coherent mechanism for cancer and noncancer effects?
2. Do these data adequately describe the array of effects at low dose?
3. How might the mode of action based dose response be affected by population variability?
4. How would one construct a probabilistic assessment of noncancer dose response from which the probability of an adverse effect can be estimated at any dose?
5. What are the implications of mode of action based and probabilitstic-based assessments for risk-benefit analysis?

3:00 pm BREAK

Risk Assessment Approaches and Application of IRIS Values

3:15 pm
- Systematic Review and Evidence Integration for Literature-Based Environmental Health Assessments
  Andrew Rooney, U.S. National Toxicology Program

3:45 pm
- Perspectives of Risk Assessors and Users of IRIS Values
  Question: Given your experience in risk assessment activities, what aspects of the Toxicological Review of Inorganic Arsenic would be critical for maximizing the utility and credibility of the review for the risk assessments that you undertake?
  Barbara Beck, Gradient Corporation
  Michael Hansen, Consumers Union
  Kate Sande, Minnesota Department of Health
  Joyce Tsuji, Exponent, Inc.

4:10 pm	**Panel Discussion:** Moderators: *Sandra Baird and Hugh Barton* **Question 1:** *Joyce Tsuji and Michael Hansen* **1a.** "Science and Decisions" (NRC 2009) recommended that EPA adopt a unified dose-response assessment framework for cancer and noncancer end points. It has been suggested that an arsenic IRIS assessment might provide: a. Risk estimates for noncancer end points (rather than or in addition to a concentration assumed to be health protective, such as an RfD) b. Nonlinear cancer assessment c. Multiple risk estimates for a single toxicity end point (e.g., alternative mode of action hypotheses, estimates from different studies, multiple dose-response models fitted to the same data) d. Risk estimates for many toxicity end points What recommendations do you have for EPA on use of these approaches? **1b.** If the toxicological review of inorganic arsenic contains risk estimates derived from the dose-response approaches described in Question 1a, how would that impact the practice of risk assessment in the activities you are involved in? **Question 2:** *Barbara Beck and Kate Sande* **2a.** EPA has been asked by stakeholders to explicitly include consideration of populations that may have increased susceptibility to the adverse effects from arsenic (e.g., life stages, genetics, pre-existing disease, and environmental stressors such as co-exposures and nutritional deficiencies). What type of quantitative estimates of susceptibility would be useful in your risk assessment activities? If quantitative estimates cannot be derived, how do you recommend EPA provide information on susceptibility so that it can be used to inform your risk assessment activities? **2b.** What types of documentation (and level of detail) are necessary to assist you and other users of an IRIS assessment if one of these approaches (which are not currently standard methods) were used?
5:00 pm	**Additional Questions for Workshop Speakers and Panelists from Committee**
5:20 pm	OPEN MICROPHONE *Each speaker has a maximum time limit of 5 minutes. Accompanying written materials are encouraged.*
6:00 pm	ADJOURN