Critical Scientific Issues
In
Assessing Health Risk
From
Oral Exposure To Inorganic Arsenic
National Research Council Update

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INORGANIC ARSENIC HEALTH RISK ASSESSMENT

Focus of Discussion

- Historical perspective of EPA activities
- NAS/NRC Committee process
- Critical issues identified for IRIS assessment
  - Potential health outcomes
  - Metabolism/disposition/exposure issues
  - Mode-of-action analyses
  - Dose-response considerations
  - Susceptible populations considerations
- Next steps for health risk assessment
INORGANIC ARSENIC HEALTH RISK ASSESSMENT

**DISCLAIMER**

- ~ 35 years in pharmaceutical industry did not make me an expert on arsenic toxicity!
  - One of few members on NRC Committee with little arsenic/metal experience
- Views to be expressed are those of JSMacDonald not necessarily those of the NRC Committee
  - Slides shared with Committee officials and comments incorporated – but not an “official” report
- No affiliations with any organizations potentially impacted by outcome of EPA IRIS assessment
NRC Committee

Membership

- JOSEPH H. GRAZIANO (Chair), Columbia University Mailman School of Public Health, New York, NY
- HABIBUL AHSAN, University of Chicago, Chicago, IL
- SANDRA J.S. BAIRD, Massachusetts Department of Environmental Protection, Boston, MA
- AARON BARCHOWSKY, University of Pittsburgh, Pittsburgh, PA
- HUGH A. BARTON, Pfizer, Inc., Groton, CT
- GARY P. CARLSON, Purdue University, West Lafayette, IN
- MARY E. DAVIS, West Virginia University, Morgantown, WV
- YVONNE P. DRAGAN, AstraZeneca Pharmaceuticals, Waltham, MA
NRC Committee - Membership

- REBECCA C. FRY, University of North Carolina, Chapel Hill, NC
- CHRIS GENNINGS, Virginia Commonwealth University, Richmond, VA
- GARY L. GINSBERG, Connecticut Department of Public Health, Hartford, CT
- MARGARET KARAGAS, Dartmouth Geisel School of Medicine, Lebanon, NH
- JAMES S. MACDONALD, Chrysalis Pharma Consulting, LLC, Chester, NJ
- ANA NAVAS-ACIEN, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
- MARIE E. VAHTER, Karolinska Institute, Stockholm, Sweden
- ROBERT O. WRIGHT, Mount Sinai School of Medicine, New York, NY
Historical Perspective on EPA efforts to Assess iAs Health Risk

**Timetable of events**

- 1999: NRC reviews 1988 IRIS assessment
- 2001: NRC updates 1999 report; recommends use of epidemiology data in assessment
  - EPA uses NRC reports to establish 10 $\mu$g/L as the maximum permissible level
- 2003: EPA starts reassessment of iAS drinking water standards
- 2005: EPA recommendations submitted to EPA SAB for review
- 2007: EPA SAB released comments on draft report
- 2010: EPA release of draft updated iAs IRIS report
  - Focus on cancer endpoints only
- 2011: EPA SAB releases comments on draft IRIS report
- 2011: US Congress mandated NRC review of draft IRIS report before final version issued
Statement of Task

- ad hoc NRC committee to conduct workshop to review critical scientific aspects of iAs toxicity (cancer and non-cancer) with broad spectrum of stakeholders
  - Workshop held April 4, 2013
- NRC committee will issue interim report detailing how issues can best be addressed in EPA’s IRIS assessment
  - Report issued November 7, 2013
- NRC Committee will review EPA’s revised draft IRIS assessment to assure all issues are appropriately addressed
  - Including addressing recommendations from previous NRC reports on how to conduct risk assessments
    - Particularly focus on NRC 2011 Chapter 7 recommendations on formaldehyde on criteria and justification of chosen methods for assessment, modeling approaches, etc.
NRC Committee:
Steps of the toxicologic assessment of inorganic arsenic

Step 1: Hazard Identification
Step 2: Evidence Evaluation and Systematic Reviews
Step 3: Assessment Of Causality
Step 4: Mode of Action Analysis
Step 5: Susceptible Subpopulations
Step 6: Dose Response Analysis

Final Arsenic Assessment
Hazard Identification:
Health Endpoints to Consider

- **Tier 1:** Evidence of a causal association determined by other agencies and in published systematic reviews
  - Lung, skin, and bladder cancer
  - Ischemic heart disease
  - Skin lesions
Hazard Identification: Health Endpoints to Consider

- **Tier 2: Other priority outcomes**
  - Prostate, and renal cancer
  - Diabetes
  - Non-malignant respiratory disease
  - Pregnancy outcomes (neonatal mortality)
  - Neurodevelopmental toxicity
  - Immune effects
Hazard Identification: Health Endpoints to Consider

- **Tier 3: Other endpoints to consider**
  - Liver, pancreatic cancer
  - Renal disease
  - Hypertension
  - Stroke
  - Pregnancy outcomes (fetal loss, stillbirth, neonatal mortality)
Assessment of Causality

**Key Elements**

- Categorization of evidence on various health endpoints
  - EPA criteria: 5 categories from clearly causally associated to not associated
- Derived from systematic and comprehensive evaluation of available literature
- Need to characterize judgments according to modified Bradford-Hill criteria
- Identify data gaps and prioritize for subsequent analysis for mode-of-action and dose-response
Mode of Action Analysis

**Key Elements**

- To be performed for those endpoints determined to have a *causal* or *likely to be causal* relationship to iAs
  - May also be used for endpoints with suggestive evidence to assist in calibrating causality
- Exposure-response relationship essential component of process
  - Likely to be data gaps at low end of dose-response curve
- Comprehensive assessment of global body of data
  - In vitro, in vivo (animal), epidemiologic

*Are exposures sufficient to trigger key biological event(s) underlying adverse health outcome?*
Dose response analysis

**Key Elements**

- **Basis of analyses for most health endpoints will be epidemiologic data**
  - Dose-response meta-analyses may be possible for some endpoints
- **Mode of action data should be used to extrapolate below the observed range when epi data are inadequate**
- **Analyses should be performed even in the absence of definitive MoA**
  - For endpoints likely to be causally or likely associated with iAs exposure
- **In the absence of MoA data, alternative statistical approaches may be used**
Important Considerations in iAs toxicity assessment

- Adequacy of data on exposure
  - Parent compound (iAs); appropriate endpoint
  - Metabolites
  - Low exposures
- Concomitant exposures
  - Pb, Se, other metals
  - Cigarette smoke
- Nutritional status of exposed population
  - Folate status particularly important
- Measures of outcome for non-cancer endpoints
  - BP, neurodevelopment, pregnancy outcomes
- Sensitive populations
Complex metabolic profile

\[
\begin{align*}
\text{As}^V & \xrightarrow{\text{GSH}} \text{As}^{III} \\
\text{MMA}^V & \xrightarrow{\text{Trx-(S)2}} \text{MMA}^{III} \\
\text{DMA}^V & \xrightarrow{\text{AS3MT}} \text{SAM} \\
\end{align*}
\]
Complex metabolism complicates the risk assessment process

*Some of the metabolic factors affecting As toxicity*

- Methylation efficiency
  - females more effective than males
    - pregnancy enhances ability to convert iAs to MMA and DMA
- Methylation to DMA appears to detoxify
  - poor methylators seem to show more adverse events
- As3MT activity
  - dietary influence
  - tissue variability
  - population genotype variability
Susceptibility factors

- **Nutritional status**
  - Synthesis of SAM influenced by nutritional status
    - Folate, choline, betaine, B-vitamins
  - Selenium – antagonist with As

- **Pre-existing disease, cigarette smoking, alcohol consumption**

- **Co-exposures**
  - Other metals: Cd, Pb, Hg, Ni, Cr, Co
  - PAH’s

- **Sex-related differences, life stages**
  - Susceptibility in pre- and perinatal stages
Exposure considerations - a critical component of risk assessment

- Causality at high exposure for many end-points not questionable
- Key issue is effects at low exposures
- Appropriate measure of exposure
  - Food, well water concentration
    - Reliable measures difficult to obtain particularly at low levels
  - Biomarkers
    - Hair, nail levels
      - No good detail on metabolite exposure
    - Urine, blood
      - Best – but very difficult to obtain on population basis
Critical consideration: method of extrapolation from observed data

Figure A, Box 7, NRC report; Hypothetical observed and model-predicted mean RR for CVD mortality
**Next Steps**

- EPA review of available data in progress
- Draft of IRIS Risk Assessment expected from EPA end 2014/early 2015
- NRC Committee to review and comment on draft before finalization
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Thank You!

Questions - ??