

2014 ILSI ANNUAL MEETING

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

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- 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 µg/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

NRC Committee on iAs Risk Assessment

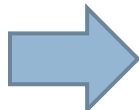
Statement of Task

- 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.

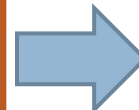
NRC Committee:

Steps of the toxicologic assessment of inorganic arsenic

Step 1
**Hazard
Identification**



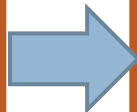
Step 2
**Evidence Evaluation
and
Systematic Reviews**



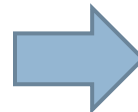
Step 3
**Assessment
Of
Causality**



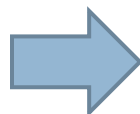
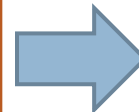
Step 4
**Mode of Action
Analysis**



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

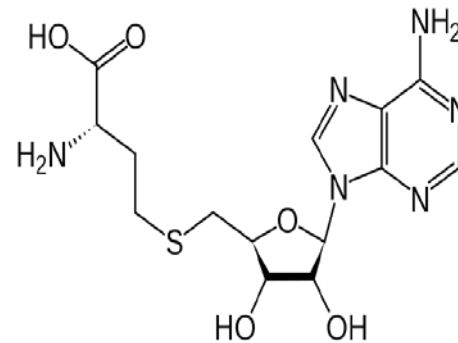
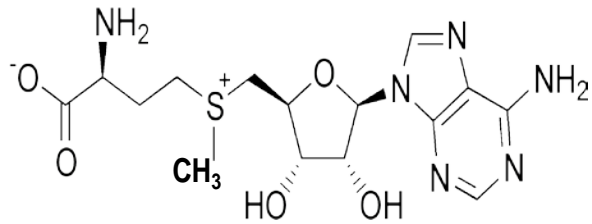
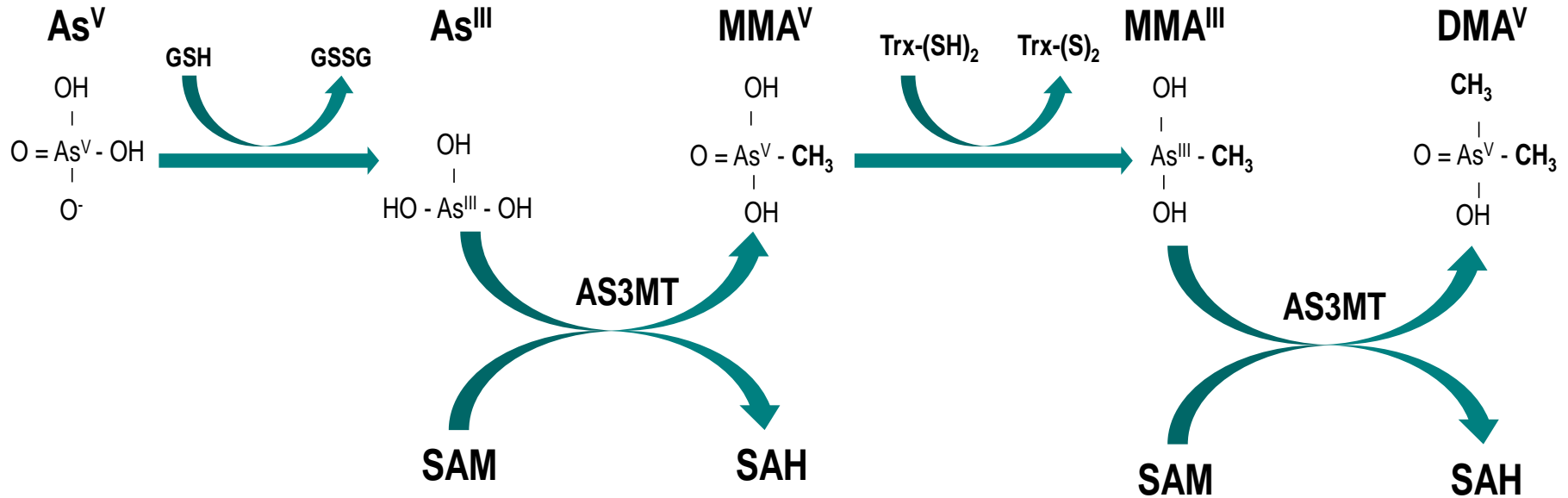
Key Elements

- 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



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

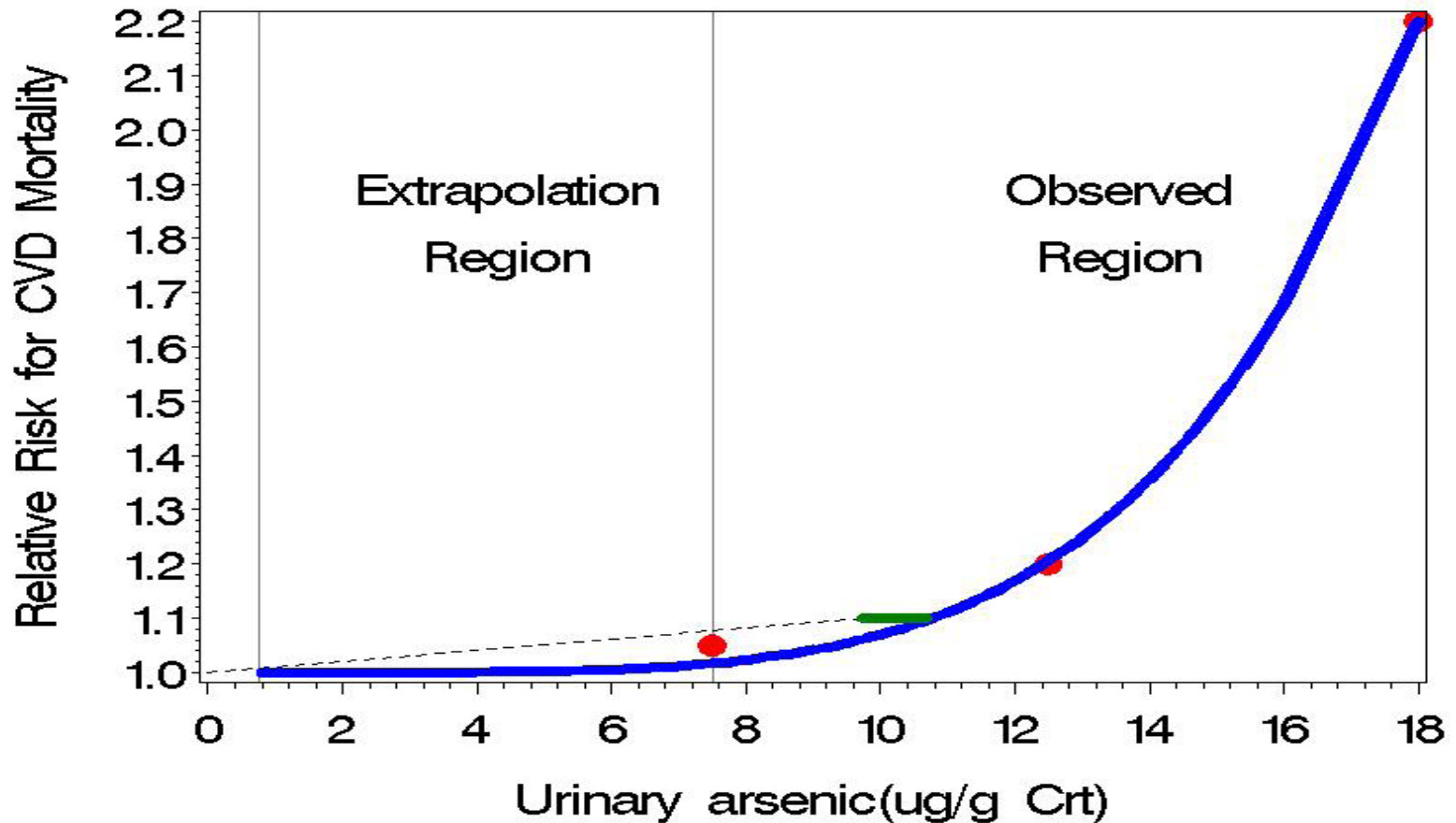


Figure A, Box 7, NRC report; Hypothetical observed and model-predicted mean RR for CVD mortality

NRC Committee on Inorganic Arsenic

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

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

Thank You!

Questions - ??