

Comments on US EPA Toxicological
Review of Inorganic Arsenic
on Behalf of the Organic Arsenical
Products Task Force

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Overview

- Emphasis on charge question 2
- Application of Cancer Risk Assessment Guidelines
- Mode of Action (MOA) analysis
- Dose-response recommendations



2005 US EPA Cancer Guidelines and Dose-Response Model Choice

- Biologically plausible alternatives should be allowed, *e.g.*
 - *Where alternative approaches have significant biological support, and no scientific consensus favors a single approach, an assessment may present results using alternative approaches. A nonlinear approach can be used to develop a reference dose or a reference concentration. (U.S. EPA, 2005; Section 1.3.4, p. 1-15)*



2005 US EPA Cancer Guidelines and Dose-Response Model Choice (cont'd)

- Non-linear dose-response models recommended when supported by the MOA, *e.g.*
 - *A nonlinear extrapolation method can be used for cases with sufficient data to ascertain the mode of action and to conclude that it is not linear at low doses but with not enough data to support a toxicodynamic model. (U.S. EPA, 2005; Section 3.3.4, p. 3-23)*



MOA Analysis

- SAB 2007 -- MOA supported non-linear dose-response with possible threshold
- Arsenic review draft
 - Comprehensive in identification of literature through 2007
 - But no integrative analysis

MOA Analysis (cont'd)

- Recent studies provide additional insight on MOA and non-linear dose-response, *e.g.*
 - Critical analysis of 160 studies (Gentry *et al.*, 2010) identifies dose-dependent transitions in transcription from adaptation through proliferation and to apoptosis
 - Cytotoxicity and necrosis of bladder epithelium of rat exposed to InAs (Suzuki *et al.*, 2008)
 - Findings indicative of hormesis (Sykora and Snow, 2008)
- Consistent findings in transcriptional changes in pilot study of humans exposed to InAs



Dose-Response Recommendations

- Weight-of-evidence analysis to assess strength of US EPA proposed dose-response model versus other approaches
- Integrated analysis of MOA studies
- Margin of Exposure analysis using points of departure from current MOA research and from low dose epidemiological studies

