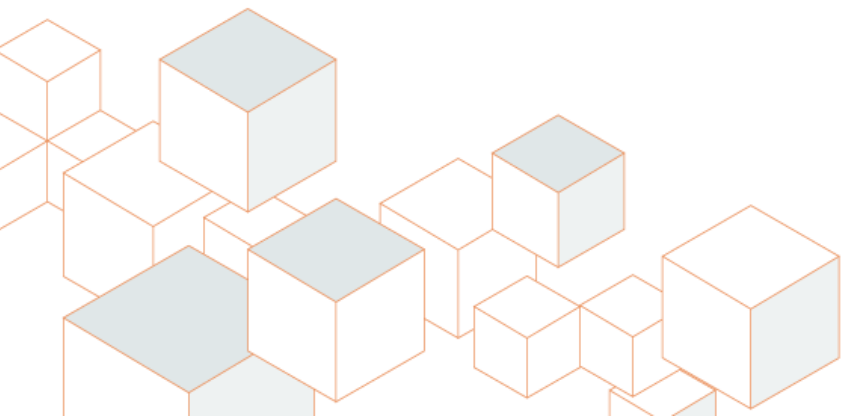




THE EPA BI-MONTHLY MEETING INORGANIC ARSENIC SCIENCE DISCUSSION

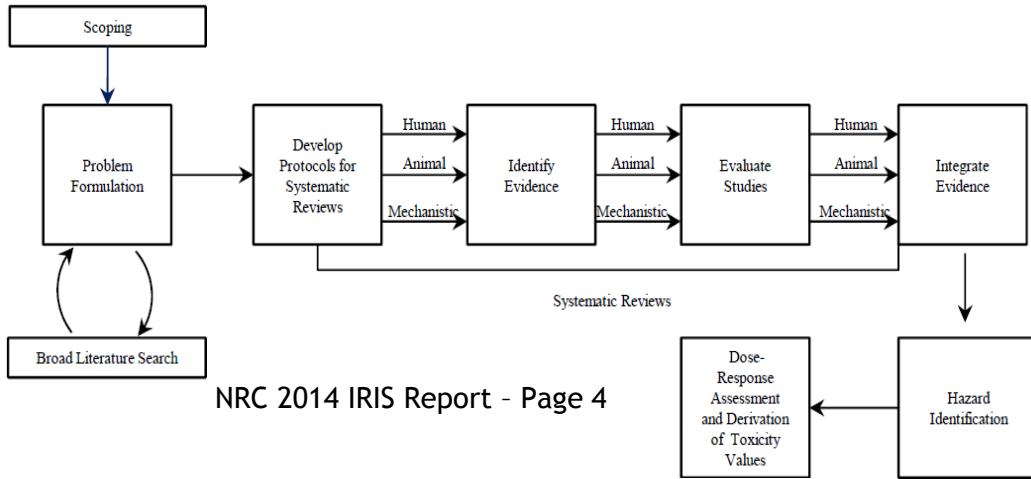
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JUNE 26 – 27, 2014**



SCIENCE ISSUE 6: MODE-OF-ACTION AND ADVERSE OUTCOME PATHWAYS



MOA Hypothesis Summaries



NRC 2014 IRIS Report - Page 4

- Hypothesized MOA
- Experimental support:
 - Dose-response concordance
 - Strength, consistency, specificity of association
 - Temporal relationship
 - Biological plausibility and coherence
- Consideration of alternative MOAs

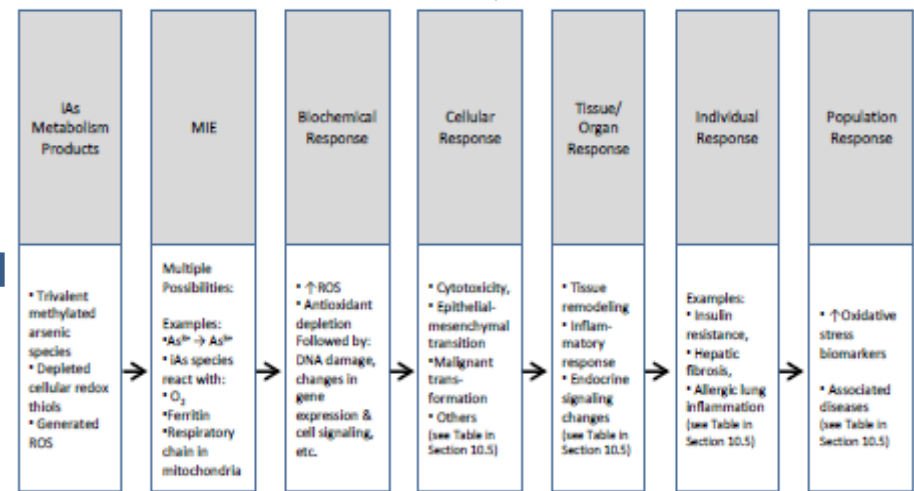


Figure 9-6, Page 1-47; Hypothesized MOA for Oxidative Stress

Key Events	Observations	Organ system	Test System	Dose (Exposure Duration)	References
Molecular Initiating Events					
Reaction with O ₂ (intermediate arsenic species; e.g., dimethylarsine)	↑ free radicals (e.g., Dimethylarsenic peroxy radical [(CH ₃) ₂ AsOO], superoxide anion)	Multiple (See Review Article)	Multiple (See Review Article)	Multiple (See Review Article)	Reviewed in (Flora, 2011)
Reaction with ferritin (Methylated-As)	Redox-active Fe release	Multiple (See Review Article)	Multiple (See Review Article)	Multiple (See Review Article)	Reviewed in (Flora, 2011)
Oxidation of As(III) to As(V)	H ₂ O ₂ formation followed by Fenton reaction (hydroxyl radical formation)	Multiple (See Review Article)	Multiple (See Review Article)	Multiple (See Review Article)	Reviewed in (Flora, 2011; Jomova and Valko, 2011)
Reactions with NADPH oxidase	↓ ROS with NADPH inhibitor	Liver (Human)	Human immortalized liver cell line HL-7702	Diphenyleneiodonium chloride (DPI) (30 min pretreatment) + 5 μM arsenite (2 hr)	(Li et al., 2014); Reviewed in (Flora, 2011)
Reactions with mitochondrial respiratory chain	↓ ROS with mitochondrial respiratory chain inhibitor	Liver (Human)	Human immortalized liver cell line HL-7702	Rotenone (30 min pretreatment) + 5 μM arsenite (2 hr)	(Li et al., 2014); Reviewed in (Flora, 2011)
Biochemical Responses					
Generation of reactive oxygen species	↓ dichlorofluorescein diacetate (peroxides)	Skin (Human)	HaCaT transformed keratinocytes	0.5 μM trivalent arsenic (As(III)) (24 hr)	(Snow et al., 2005)

Page 10-47; Prelim Data for Effects mediated Oxidative Stress

- Missing Considerations**
- GSH Role
 - Adaptive Responses
 - In vivo/In vitro Differences