Comments on Inorganic Arsenic Key Science Issue 6: Mode of Action and Adverse Outcome Pathways

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Science Issue 6: Mode of Action and Adverse Outcome Pathways

- Need to clearly articulate linkage between proposed steps in terms of biological relevance
- Many studies listed for support for key events, but not all of comparable reliability and relevance, *e.g.:*
  - Concentrations, doses
  - Transformed *versus* primary cell lines
  - Relationship to indicators to adverse outcomes in at-risk human populations
  - Demonstrated relevance to adverse effects in animal models

Science Issue 6: Mode of Action and Adverse Outcome Pathways (cont.)

Oxidative damage – an example of importance of linkage to more apical endpoints

- Co-administration of antioxidants to rats and mice – inconsistent evidence for prevention of urothelial damage (Cohen *et al.,* 2006)
- No association of biomarkers of oxidative damage in serum and elevated arsenic in water in Bangladesh (up to 700 iAs µg/L in water) (Harper *et al.,* 2014)