

# **Cancer Risk Assessment Issues for Organic and Inorganic Arsenic**

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# Overview

Two draft documents brought forth for your review: inorganic arsenic (iAs); and an organic arsenical, dimethylarsinic acid (DMA<sup>V</sup>).

- The inorganic arsenic document is a cancer health assessment.
- The organic arsenic document is primarily an MOA analysis, a full cancer health assessment will be completed based on feedback from this committee.
- The SAB's advice on DMA<sup>V</sup> will also shape risk assessments for several other organic arsenicals.
- These assessments embody principles discussed in the 2005 Cancer Guidelines; and as a consequence are precedent setting.



# OPP Key Points

For DMA<sup>V</sup> exposure:

- In rats, metabolic/kinetic differences seen following direct exposure to iAs versus DMA<sup>V</sup>
- In rats, carcinogenic properties of exogenous inorganic arsenic, MMA<sup>V</sup>, & DMA<sup>V</sup> are distinct
- Only complete data set that describes cancer development is in the rodent (rat bladder tumors)
- Convincing MOA based on scientifically defensible key events
- Animal MOA is considered relevant to humans
- Bladder cancer is the only cancer endpoint of concern in humans
- Dose response extrapolation proposed to be nonlinear based on MOA considerations



# OW Key Points

For iAs exposure:

- Several plausible modes of action for cancer have been suggested, different factors affect metabolite production, metabolites vary in modes of action, and each metabolite has distinct toxicity. Therefore, EPA retains linear extrapolation at low doses.
- The Southwestern Taiwanese ecological studies are the strongest sources of dose-response information for cancer endpoints. EPA will focus cancer assessment on arsenic-induced bladder and lung cancers.
- Because the Southwestern Taiwan study is selected for the risk assessment, with newly available information, EPA needed to decide the drinking water rate and dietary intake of inorganic arsenic from food for the Southwestern Taiwanese population.
- EPA decided to use Additive Poisson model, with age adjustment, mortality adjustment, and background population to estimate the potency of inorganic arsenic.



# *Risk Assessment Issues*

- Evaluating human carcinogenesis for iAs and DMA<sup>V</sup> using the rat model?
- Sufficient evidence to establish a MOA for DMA<sup>V</sup> in humans?
- MOA and implications for dose response assessment of:
  - **DMA<sup>V</sup>?**
  - **iAs?**
- Considerations for low-dose extrapolation for DMA<sup>V</sup> and/or iAs in humans?



# *Evaluating Human Carcinogenesis Using the Rat Model*

- iAs is a potent carcinogen in humans and induces tumors in a variety of tissues.
- Rats are a poor model of human iAs carcinogenicity: different sensitivity and profile of tumors.
- Only rat data available for DMA:
  - Qualitatively the MOA appears plausible for bladder cancer in rats & humans;
  - Quantitatively it is less clear for human bladder cancer and for other sites.



# Evaluating Human Carcinogenesis Using the Rat Model

Exposure	Urinary DMA	Species	Response
iAs 10 ppb in drinking water	~8 ppb	Human	~ 1/1000 Tumors, including bladder (NRC, 2001)
DMA @ Proposed RfD 0.07 ug/kg/day	~3 ppb	Human (Buchet et al., 1981)	0 probability to ?
DMA 10 ppm in drinking water	~3 ppm	Rat (Wanibuchi, et al., 1996)	Bladder cell proliferation
DMA 50 ppm in drinking water	~20 ppm	Rat (Wei et al., 1999)	Bladder tumors



# Evaluating Human Carcinogenesis of DMA<sup>V</sup> Using the Rat Model

Considering the previous presentations and the comparison in the previous slide, one might conclude:

- Exogenous DMA<sup>V</sup> is not a bladder carcinogen in humans below the RfD nor does it contribute significantly to the human carcinogenicity of iAs because:
  - For direct DMA exposure, DMA<sup>V</sup> is excreted before it is metabolized to DMA<sup>III</sup>, and it's DMA<sup>III</sup> that significantly contributes to DMA carcinogenicity;
  - iAs and metabolites preceding DMA are contributing significantly to human carcinogenicity;

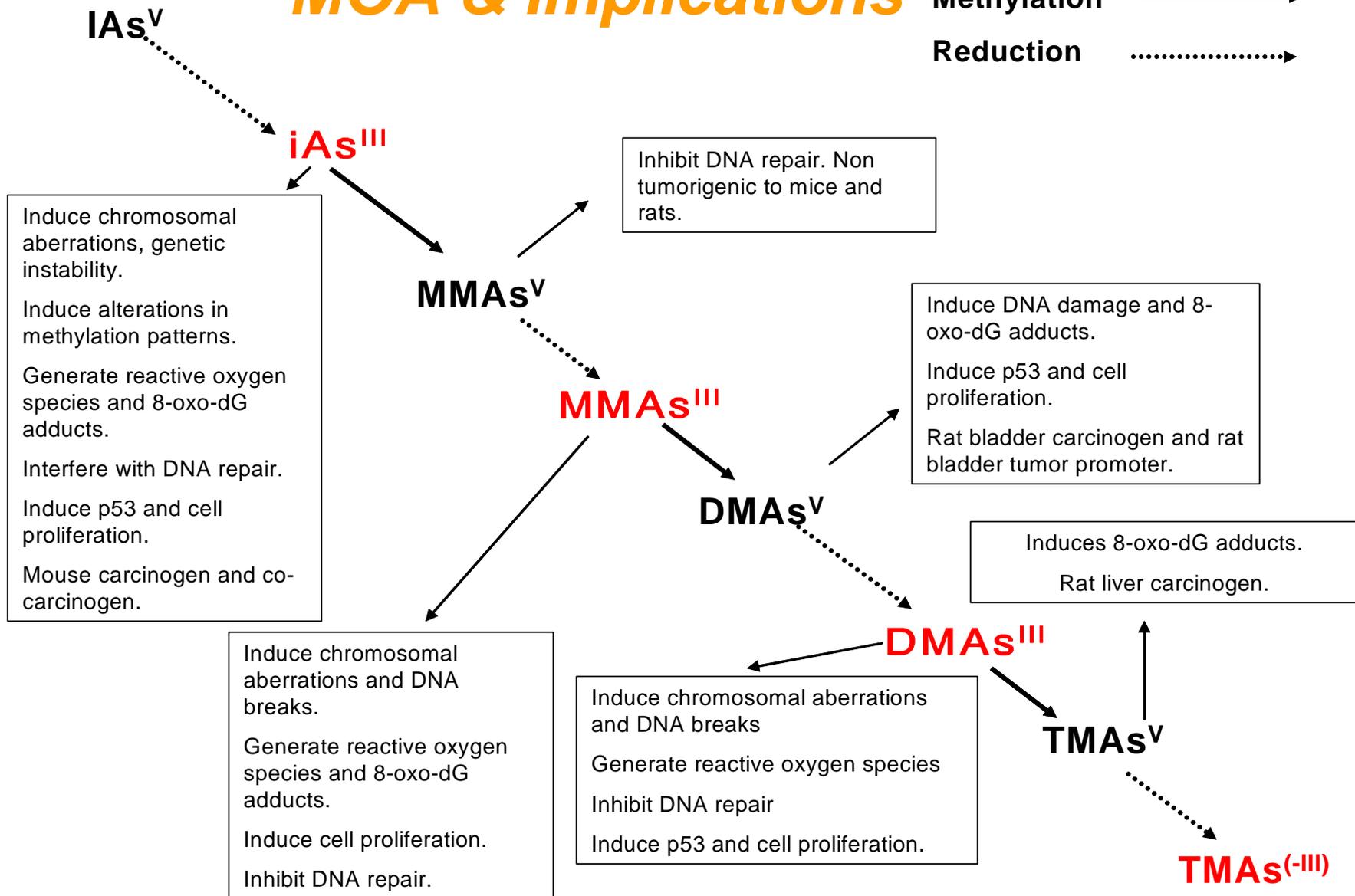
or

- Rats are less sensitive than people to DMA and/or to iAs and metabolites preceding DMA. Cytotoxic may be needed to see any response in rodents.



# MOA & Implications

Methylation  $\longrightarrow$   
 Reduction  $\cdots\cdots\cdots\longrightarrow$



Exogen.  
iAs<sup>v</sup>

# MOA & Implications

Methylation  $\longrightarrow$   
Reduction  $\cdots\cdots\cdots\longrightarrow$

iAs<sup>III</sup>

MMAs<sup>v</sup>

MMAs<sup>II</sup> DMA<sup>v</sup>

DMA<sup>v</sup>

DMA<sup>III</sup>

TMA<sup>v</sup>

TMA<sup>(-III)</sup>

Induce chromosomal aberrations, genetic instability.  
Induce alterations in methylation patterns.  
Generate reactive oxygen species and 8-oxo-dG adducts.  
Interfere with DNA repair.  
Induce p53 and cell proliferation.  
Mouse carcinogen and co-carcinogen.

Inhibit DNA repair. Non tumorigenic to mice and rats.

Induce DNA damage and 8-oxo-dG adducts.  
Induce p53 and cell proliferation.  
Rat bladder carcinogen and rat bladder tumor promoter.

Induces 8-oxo-dG adducts.  
Rat liver carcinogen.

Induce chromosomal aberrations and DNA breaks.  
Generate reactive oxygen species and 8-oxo-dG adducts.  
Induce cell proliferation.  
Inhibit DNA repair.

Induce chromosomal aberrations and DNA breaks  
Generate reactive oxygen species  
Inhibit DNA repair  
Induce p53 and cell proliferation.



# MOA & Implications

- **iAs**

- Risks are evaluated based on human epidemiological data.
- Variety of MOAs seem likely for iAs and metabolites; it is a mixtures issue.
- Insufficient data in humans or animals to establish presumably complex MOA(s).

- **DMA**

- Fewer metabolites simplifies evaluation.
- Set of key events established in animals.
- Lack of direct empirical evidence for DMA's MOA in humans. and/or in vivo in animals on some aspects of proposed MOA
- Conclusion based on inference from related data.



# MOA & Implications

## DMA (cont.)

- There is general agreement on the key biologic events in the bladder, including:
  - ROS-induced DNA damage;
  - Cellular cytotoxicity at high dose in the rat;
  - Regenerative cellular proliferation at high dose in the rat;
  - Cell proliferation is required for fixation of chromosomal mutations.
- Frequency of conversion of DNA damage to chromosomal mutations is likely to be substantially influenced by cell replication rates; cytotoxicity will impact dose/response.
- Scientific opinions diverge on whether or not cytotoxicity and regenerative cell proliferation are both necessary and sufficient to induce bladder tumors in humans, particularly given a background of iAs exposure.



# MOA & Implications

- If cytotoxicity/regenerative proliferation are essential to tumor formation for DMA<sup>V</sup>, then there is no risk in the absence of cytotoxicity/regenerative cell proliferation, and an RfD would be appropriate.
- Since cell proliferation is a key event in tumor formation with or without cytotoxicity/regenerative proliferation, then risk is dependent on the rate of cell proliferation, either background or induced; additivity to background suggests linear low dose term for both DMA<sup>V</sup> and iAs.
- Data for a complete biologically based model is currently inadequate for both DMA<sup>V</sup> and iAs, although the MOA suggests linear quadratic equation; the range of human susceptibility is unknown.



# *Considerations for Low Dose Extrapolation*

Additivity phenomena may occur with:

- Tissue doses from multiple external sources of exposures and/or metabolic production;
- Exposures to multiple agents or background processes that produce the same biological effect, e.g., “background” DNA damage;
- Additivity with background disease processes, i.e., a carcinogen may be anticipated to have an effect on probability of disease if it increases the transition probability for one stage in a system where this multistage process is complete.



# *Considerations for Low Dose Extrapolation*

- Where thresholds exist for responses in individual members of a population, a distribution of susceptibility between individuals can lead to a non-threshold population dose response model.
- When a carcinogen acts additively with ongoing processes of carcinogenesis, the dose response pattern is expected to be linear at low dose under very broad range of modeling assumptions.
- The incremental risk of adding to a background response is dependent on where you are on the dose/response curve.



# Considerations for DMA<sup>V</sup> Low Dose Extrapolation

- Background or exogenous contributions to risk:
  - Exposures to iAs are known to occur and will contribute to body burden of DMA;
  - Exposure to ROS is common within the human population and the distribution of such exposures in the population, or for dose-response is unknown;
  - Other mechanisms of action may be contributing to components of the proposed MOA
- Not accounting for these factors may result in underestimation of risks for populations affected by these factors.
- How should they be accounted for in the **DMA<sup>V</sup> assessment?**



# Summary of Risk Assessment Issues

- Evaluating human carcinogenesis for iAs and DMA<sup>V</sup> using the rat model?
- Sufficient evidence to establish a MOA for DMA<sup>V</sup> in humans?
- MOA and implications for dose response assessment of:
  - DMA<sup>V</sup>?
  - iAs?
- Considerations for low-dose extrapolation for DMA<sup>V</sup> and/or iAs in humans?



The background of the slide features a large, faint watermark of the United States Environmental Protection Agency (EPA) logo. The logo is circular and contains a stylized flower with three leaves and a central globe. The text "ENVIRONMENTAL PROTECTION AGENCY" is written around the perimeter of the circle, and "U.S." is at the top.

Thank you.