DMA^V Urothelial Carcinogenicity

- Unique to rat; female > male
- Negative 2-year bioassay in mice
- No preneoplastic (proliferative) effects in hamsters (10-week)

Urinary Bladder Carcinogenicity of DMA^{V} in Rats

Mode of Action

- Generation of reactive metabolite, DMA^{III}
- Urothelial cytotoxicity and necrosis
- Persistent increased cell proliferation
- Urothelial hyperplasia
- Urothelial tumors

Dose Response of Dietary DMA^{V}-Induced Bladder Changes

	2 ppm	10 ppm	40 ppm	100 ppm
Cytotoxic urinary DMA^{III} concentration	–	±	+	+
Urothelial cytotoxicity	–	±	+	+
Increased cell proliferation (BrdU labeling index)	–	±	+	+
Hyperplasia	–	–	+	+
Bladder tumors	–	–	–	+

Extrapolation to Humans

- **Non-linear dose response (threshold)**
- **Interspecies extrapolation**
  - **Significant differences in metabolism and disposition compared to other species, especially humans**
  - **Retention in RBCs (binding of DMA^{III} to Hb)**
  - **Conversion of DMA^{V} to TMAO (indicator of significant reduction of DMA^{V} to DMA^{III})**

Mode of Action for DMA-Induced Rat Bladder Cancer

Cytotoxicity → Necrosis → Regenerative Proliferation

Possible Mechanisms (not mutually exclusive)

- **DNA reactivity**
- **Indirect genotoxicity**
- **Reaction with sulfhydryl groups of critical cellular proteins**
- **Oxidative damage**

Oxidative Damage

In Vitro

	Melatonin	Vit. C	N-Acetylcysteine	Tiron	Trolox
Arsenite	+	+	–	–	–
MMA^{III}	–	+	+	–	–
DMA^{III}	–	+	+	–	–

In Vivo

	Melatonin	Vit. C	N-Acetylcysteine
DMA^{V} – 100 ppm	–	±	–

Min *et al.*, 2004

Inorganic Arsenic and Bladder Cancer

- Increased risk at high exposures (generally > 400 µg/L)
- Possible influence of nutritional factors (Se, others)
- No animal model
- Extrapolation from high to low exposure:
  Linear vs. Non-linear

Evidence for Linear

- Genotoxicity
- Micronuclei in urothelial cells in Chilean population (Moore *et al*., 1997)

Evidence for Non-linearity

- **Genotoxicity – indirect**
- **No evidence of increased risk of bladder cancer at lower exposures (Steinmaus *et al.*, 2003; Haque *et al.*, 2003)**
- **Less bladder cancer at low exposures than predicted by linear extrapolation (Steinmaus *et al.*, 2003)**
- **Rare (any?) cases of skin arseniasis at low exposures**