

**A Speciation Study focused on the Identification of
Proximate Toxic Arsenic Metabolites**

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**Chemical species of arsenic
taken by humans and excreted into urine**

Ingested forms

- | | |
|------------------|--|
| Inorganic | arsenite
arsenate |
| Organic | arsenosugars
arsenocholine
arsenobetaines |

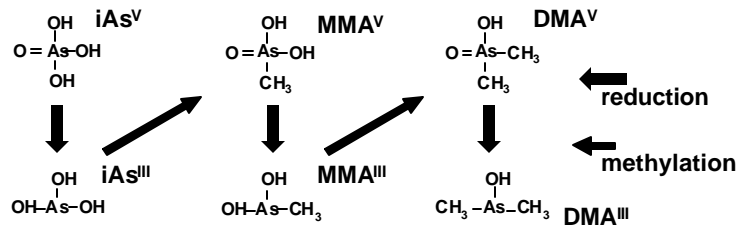
Excreted forms (urinary metabolites)

**dimethylated arsenic (DMA)
(dimethylarsinic acid (DMA^V))**

**Most probable pattern in the toxification of
arsenic in humans**

<i>Ingested forms</i> Arsenite or Arsenate	<i>Urinary metabolites</i> DMA (DMA ^V)
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**Reduction and methylation reactions
in the metabolism of arsenic**



iAs^V arsenate	iAs^{III} arsenite
MMA^V monomethylarsonic acid	MMA^{III} monomethylarsonous acid
DMA^V dimethylarsinic acid	DMA^{III} dimethylarsinous acid

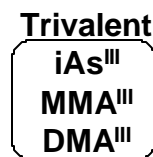
**Reduction and methylation reactions
in the metabolism of arsenic**

**Detoxification pathway
or
Toxification pathway?**

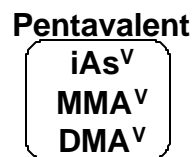
**Which arsenic metabolites do cause
the arsenic toxicity?**

**What are the proximate toxic
arsenic metabolites?**

Tri- and pentavalent forms of arsenic

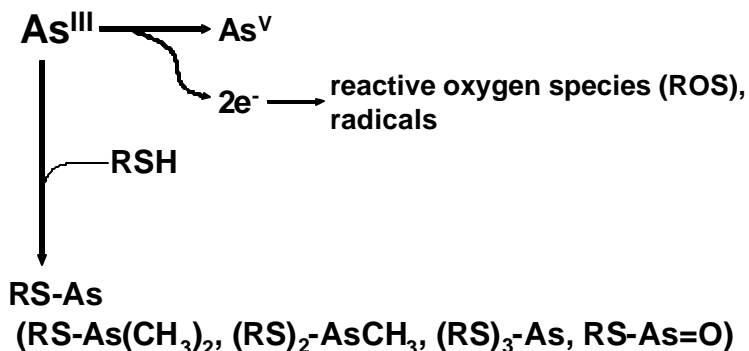


More reactive



less reactive

Possible reactions for trivalent forms of arsenic



Separation and subsequent analytical procedures for arsenic in the body

Soluble

Free

Pentavalent arsenic **A**
(iAs^V , MMA^V , DMA^V)

Trivalent arsenic **B**
(iAs^{III} , MMA^{III} , DMA^{III})

Conjugated

Trivalent arsenic – GSH **C**
($iAs^{III}(GS)_3$, $CH_3As^{III}(GS)_2$, $(CH_3)_2As^{III}(GS)$)

Trivalent arsenic - soluble proteins **D**

Non-soluble

Conjugated

Trivalent arsenic - non-soluble proteins **E**

Separation and subsequent analytical procedures for arsenic in the body

Soluble	Free	Pentavalent arsenic	A
		Trivalent arsenic	B
	Conjugated	Trivalent arsenic – GSH	C
		Trivalent arsenic - soluble proteins	D
Non-soluble	Conjugated	Trivalent arsenic - non-soluble proteins	E

A, B: Free arsenic can be speciated simultaneously on an anion or cation exchange column by HPLC-ICPMS.

C: Trivalent arsenic conjugated with GSH can be speciated simultaneously on an anion exchange column by HPLC-ICPMS.

D: Trivalent arsenic conjugated with thiol groups of soluble proteins can be characterized on a gel filtration column by HPLC-ICP MS. However, the arsenic species and the corresponding protein have to be identified separately.

E: Trivalent arsenic conjugated with non-soluble proteins is not applicable to HPLC separation. The arsenic species can be identified after separation to free arsenic.

Why rats are less toxic to arsenic than other mammals?

What is the significant difference in the metabolism of arsenic in rats compared with other animals?

What are the difference in the toxicity and hence metabolism of arsenic between sensitive and tolerant animal species?

Characteristics of arsenic metabolism in rats

Longer biological half time in rats than in humans.

➡ **Why arsenic is more toxic in humans despite of its shorter biological half time?**

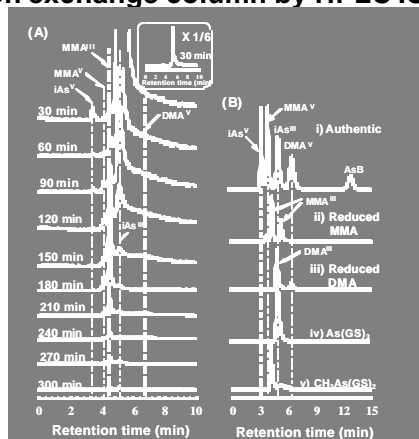
Specific accumulation of arsenic in red blood cells in rats.

➡ **Why does arsenic accumulate in RBCs in rats?**

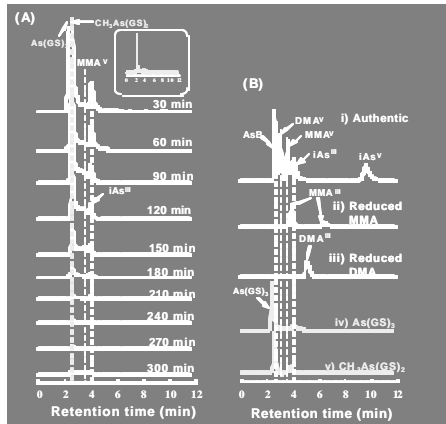
The major urinary metabolite in rats and humans is believed to be DMA(DMA^V).

➡ **Is it true?**

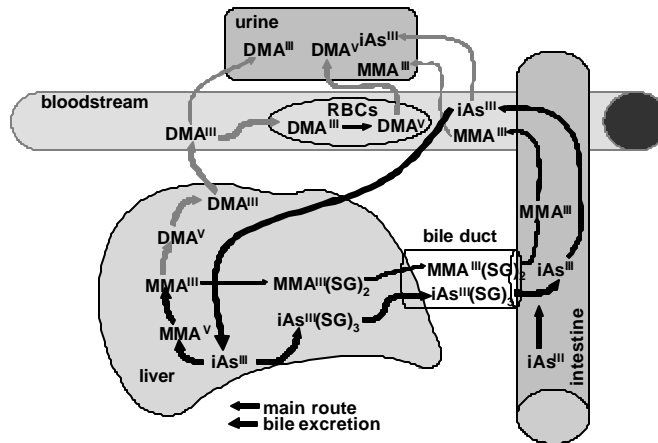
Speciation of arsenic in the bile of rats after an intravenous injection of arsenite on a cation exchange column by HPLC-ICP MS



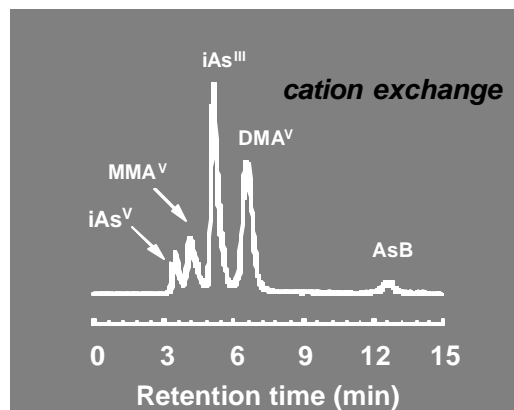
Speciation of arsenic in the bile of rats after an intravenous injection of arsenite on an anion exchange column by HPLC-ICP MS



Proposed metabolic pathway for arsenic after an intravenous injection of arsenite in rats

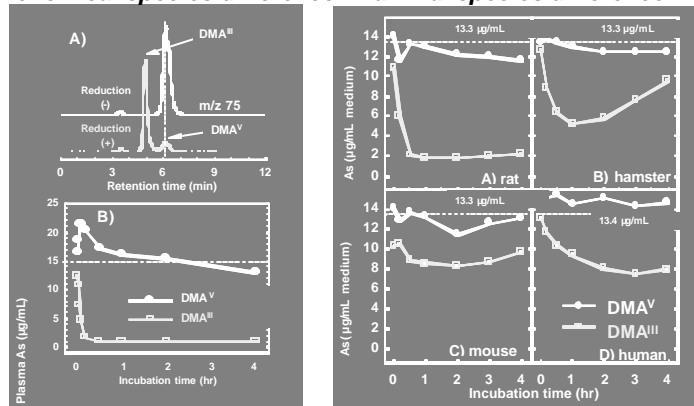


Speciation of arsenic in the urine of rats after an intravenous injection of arsenite



Selective uptake of DMA^{III} by red blood cells (RBCs)

chemical species difference **animal species difference**



Co-authors

Y. Shiobara, Y. Ogra and K. T. Suzuki

Animal species difference in the uptake of dimethylarsinous acid (DMA^{III}) by red blood cells.

Chem. Res. Toxicol. 14, 1446-1452 (2001).

B.K. Mandal, Yasumi. Ogra and K.T. Suzuki

Identification of dimethylarsinous and monomethylarsonous acids in human urine of the arsenic affected areas in West Bengal, India.

Chem. Res. Toxicol. 14, 371-378 (2001).

K.T. Suzuki, T. Tomita, Y. Ogra and M. Ohmichi

Glutathione-conjugated arsenics in the potential hepato-enteric circulation in rats

Chem. Res. Toxicol. 14, 1604-1611 (2001)

