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REVIEW

Species Differences in the Metabolism of Arsenic Compounds

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Humans are exposed via air, water and food to a number of different arsenic compounds, the physical, chemical, and toxicological properties of which may vary considerably. In people eating much fish and shellfish the intake of organic arsenic compounds, mainly arsenobetaine, may exceed 1000 μg As per day, while the average daily intake of inorganic arsenic is in the order of 10–20 μg in most countries. Arsenobetaine, and most other arsenic compounds in food of marine origin, e.g. arsenocholine, trimethylarsine oxide and methylarsenic acids, are rapidly excreted in the urine and there seem to be only minor differences in metabolism between animal species. Trivalent inorganic arsenic (AsIII) is the main form of arsenic interacting with tissue constituents, due to its strong affinity for sulfhydryl groups. However, a substantial part of the absorbed AsIII is methylated in the body to less reactive metabolites, methylarsonic acid (MMA) and dimethylarsinic acid (DMA), which are rapidly excreted in the urine. All the different steps in the arsenic biotransformation in mammals have not yet been elucidated, but it seems likely that the methylation takes place mainly in the liver by transfer of methyl groups from *S*-adenosylmethionine to arsenic in its trivalent oxidation state. A substantial part of absorbed arsenate (AsV) is reduced to AsIII before being methylated in the liver. There are marked species differences in the methylation of inorganic arsenic. In most animal species DMA is the main metabolite. Compared with human subjects, very little MMA is produced. The marmoset monkey is the only species which has been shown unable to methylate inorganic arsenic. In contrast to other species, the rat shows a marked binding of DMA to the hemoglobin, which results in a low rate of urinary excretion of arsenic.

Keywords: Arsenic, methylarsenic, arsenobetaine, arsenocholine, trimethylarsine oxide, methylation, biotransformation, mammals

INTRODUCTION

There are many different chemical forms of arsenic present in the human environment. Some of the more common arsenic compounds to which people can be exposed are shown in Table 1. Arsenic trioxide, which is obtained as a by-product in the smelting of sulfide ores, is used in the production of most other arsenic compounds. The major current uses are as insecticides (lead arsenate, calcium arsenate, sodium arsenite), herbicides [monosodium arsenate, cacodylic acid (dimethylarsinic acid, DMA)], cotton desiccants (arsenic acid), wood preservatives (copper/chromium arsenate), electronic devices (gallium arsenide, indium arsenide), and growth promoters for swine and poultry (substituted phenylarsonic acids). Arsenic is also used in the production of glass (arsenic trioxide), and in alloys to increase hardness and heat resistance (elemental As). Occupational exposure to these arsenic compounds may occur during production and use.

The general population is exposed to arsenic mainly via drinking water and food (Table 2). In water, arsenic occurs mainly as arsenite or arsenate, depending on the pH and the presence of reducing or oxidizing substances. Arsenic in food

Table 1 Formulae of some commonly occurring arsenic compounds

Arsenic trioxide (arsenous oxide)	As_2O_3 (or As_4O_6)
Arsenite	AsO_3^{3-}, AsO_2^-
Arsenate	AsO_4^{3-}, $HAsO_4^{2-}$, $H_2AsO_4^-$
Arsenic trisulfide	As_2S_3
Gallium arsenide	GaAs
Arsine	AsH_3
Methylarsonic acid (MMA)	$CH_3AsO(OH)_2$
Dimethylarsinic acid (DMA)	$(CH_3)_2AsO(OH)$
Trimethylarsine	$(CH_3)_3As$
Trimethylarsine oxide	$(CH_3)_3As{=}O$
Arsenobetaine	$(CH_3)_3As^+CH_2COO^-$
Arsenocholine	$(CH_3)_3As^+CH_2CH_2OHX^-$

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Table 2 Exposure to inorganic and organic arsenic compounds in the general population

Source	Inorganic arsenic compounds (μg As day^{-1})	Organic arsenic compounds (μg As day^{-1})
Air	0.05	—
Food	5–20	5–1000
Water	<1–10	—
Smoking	1–20	—

of marine origin is mainly in the form of arsenobetaine, the arsenic analogue of betaine.[1,2] The concentrations are often in the order of milligrams per kilogram, but values up to 200 mg kg^{-1} have been reported.[1,3] Other arsenic compounds in fish and crustaceans, often present at much lower concentrations than arsenobetaine, include arsenocholine, the arsenic analogue of choline,[4–6] trimethylarsine oxide (TMAO),[1,7] trimethylarsine (TMA)[8] and tetramethylarsonium salts.[9] TMAO and TMA may be formed from arsenobetaine in fish during post-mortem storage, contributing to the garlic-like off-flavor.[7,8] Duplicate diets collected by four Japanese subjects were found to contain 6% inorganic arsenic, 4% methylarsonic acid (MMA), 27% DMA and 48% trimethylarsenic compounds, probably mainly arsenobetaine.[10] It should be noted that certain types of edible seaweed, which are common in the Japanese diet, were reported to contain significant levels of inorganic arsenic, MMA and DMA.[11] However, it has since been reported that the major arsenic compounds in that type of seaweed are inorganic arsenic and dimethylarsenosugars, and that the latter may undergo degradation to DMA.[2] The amounts of these compounds in foods are probably lower in most other countries.

The physical, chemical and toxicological properties of the various arsenic compounds may vary considerably. Following absorption in the lungs or in the gastrointestinal tract, the toxicity of arsenic compounds may also be altered by metabolic transformation, leading to dramatic changes in the toxicity. In order to assess the risk for health effects of arsenic in various exposure situations, it is imporant to have knowledge of the toxicokinetics, the critical organs and the critical concentrations, as well as the mechanisms of toxic action. It is also important to have methods for determining the dose of the bioactive form in relevant indicator media, and if possible, at the site of action. Much of this information is gained from experimental studies using animal models. The animals have to be carefully selected, since there may be pronounced differences in metabolism and toxicity of arsenic betwen animal species.

METABOLISM OF ARSENIC COMPOUNDS OF MARINE ORIGIN IN VARIOUS MAMMALIAN SPECIES

Organic arsenic compounds of marine origin are efficiently absorbed in the gastrointestinal tract.[12–14] Arsenobetaine, the main arsenic compound in seafood, is much less toxic, less reactive with tissue functional groups, and more rapidly excreted in the urine, than is inorganic arsenic. Arsenobetaine is excreted in the urine without being biotransformed. Following administration of a single dose of ^{73}As-labeled arsenobetaine to mice, rats, and rabbits, no radiolabeled arsenic compounds other than arsenobetaine were found in urine or tissues.[13] The tissues with the longest retention of [^{73}As]arsenobetaine were cartilage, epididymis, testes, semen ducts and thymus, and in the rabbit, muscles also.[13] In rats and mice the excretion of arsenobetaine was almost complete within a few days (Fig. 1). In rabbits, only about 75% of the administered arsenobetaine was excreted in the urine in three days, mainly due to a more pronounced retention of arsenobetaine in the muscles. As shown in Fig. 1. the 72 h excretion of arsenobetaine in rabbits is similar to that observed in human subjects following ingestion of fish with high arsenic content. In the human subjects, on average about 70% of the arsenic dose was excreted in the urine within three days,

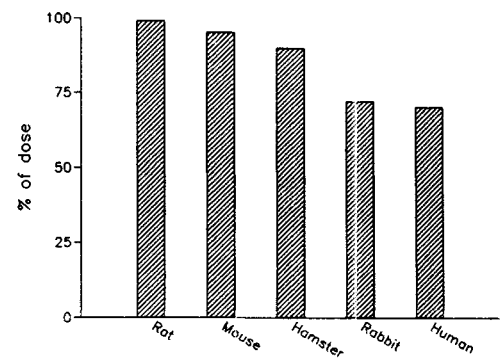

Figure 1 A comparison of the cumulative 72 h urinary excretion of arsenobetaine in rat, mouse, hamster[65], rabbit[13] and human[64] subjects following a single dose of arsenobetaine.

the total range being 52–85% ($N=32$).[12,15–17] In a study in which six volunteers ingested ^{74}As-labeled arsenobetaine with a fish meal, less than 10% of the ^{74}As was retained in the whole body after eight days.[18] After three weeks, less than 1% of the dose remained in the subjects. The distribution pattern of arsenobetaine in human subjects is not known.

The metabolism of arsenocholine in mammals involves oxidation to arsenobetaine, probably by a mechanism similar to that of oxidation of choline.[14] In mice, rats and rabbits, 55–70% of the administered dose of arsenocholine was oxidized and excreted in the urine as arsenobetaine within three days (Fig. 2).[14] Arsenocholine was found in the urine on the first day only, the amount being about 10% of the dose. Studies on the incubation of arsenocholine with rat liver mitochondria *in vitro* indicate that the oxidation to arsenobetaine occurs via arsenobetaine aldehyde.[19] It was suggested that trimethylarsine oxide was formed via a side reaction from arsenobetaine aldehyde. Following incubation with arsenobetaine, no other arsenicals apart from arsenobetaine were found. Administration of [^{73}As]-arsenocholine to mice, rats and rabbits caused higher tissue concentrations and longer tissue retention of ^{73}As than did administration of [^{73}As]arsenobetaine, probably due to incorporation of arsenocholine in phospholipids similarly to choline.[14] ^{73}As was accumulated in muscles and several parenchymatous and endocrine organs, i.e. epididymis, semen ducts, testes, prostate, parathyroid, pancreas, adrenal cortex, liver, lungs, salivary glands and thymus.[14] There were no major differences between species besides those seen with arsenobetaine.

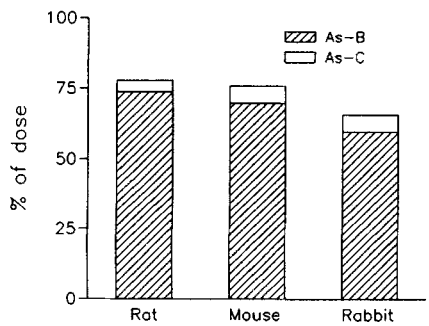

Figure 2 A comparison of the cumulative 72 h urinary excretion of arsenocholine (As-C) and arsenobetaine (As-B) in various animal species following a single dose of arsenocholine. Modified from Marafante *et al.*[14]

The metabolism of the arsenosugars found in various edible seaweeds is not known.

BIOTRANSFORMATION OF INORGANIC ARSENIC

Most mammals are able to methylate inorganic arsenic to MMA and DMA (for review see, for example, ref. 20). All the different steps in the methylation of arsenic are not known, but it seems likely that it takes place mainly in the liver by transfer of methyl groups from *S*-adenosylmethionine to arsenic in its trivalent form.[21,22] Thus, the mechanism of arsenic methylation in mammals (Fig. 3) is very similar to that reported for microorganisms.[23] Basically, it involves alternating reduction of pentavalent arsenic to trivalent, and oxidative methylation by addition of a carbonium ion to the trivalent arsenic. Reduced glutathione (GSH) is believed to be the main reducing agent, and it has been shown that depletion of hepatic GHS decreases the methylation.[22,24,25] A range of other thiols, including cysteine and lipoic acid, as well as SH-containing proteins, are known to react with inorganic arsenic and the methylarsenic compounds.[2] Compounds of the type Me_2AsSR (RSH = cysteine or glutathione) are easily oxidized to dimethylarsinic acid and have never been observed. However, stable Me_2AsSR compounds, e.g. DMA–hemoglobin complex (see below), do exist. The role of protein binding in the biotransformation of arsenic is not clear.

It should be noticed that absorbed arsenate (AsV) is reduced to a large extent in the blood to arsenite (AsIII), which, in contrast to AsV, is present mainly in protonized form at physiological pH. AsIII, but not AsV, is easily taken up by the hepatocytes, where it is methylated to MMA and DMA. The reduction of AsV to AsIII prior to the methylation has been confirmed in experimental animal studies. In rats and rabbits injected with [^{74}As]arsenate, ^{74}AsIII was detected in the

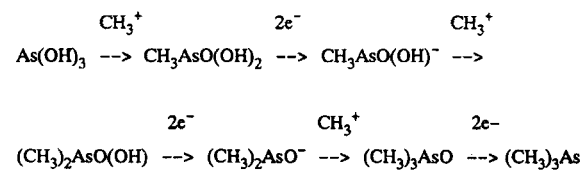

Figure 3 Proposed mechanism for the methylation of inorganic arsenic in mammals.

plasma after only a few minutes, before the appearance of [^{74}As]DMA.[26] In marmoset monkeys, which do not methylate arsenic (see below), only about 20% of an administered dose of AsV was excreted in the urine as unchanged AsV.[27] Another 20% was excreted as AsIII, while the remaining part of the injected arsenic was bound to tissues, mainly as AsIII. The reduction of AsV with subsequent urinary excretion of AsIII has been demonstrated also in human beings.[28] On the basis of the reported data on the reduction of AsV, we have estimated that as much as 50–80% of the absorbed arsenate is reduced to AsIII. Species differences in the reduction of AsV to AsIII have not been reported.

DMA is the main arsenic metabolite in most mammals and it has generally been considered the endpoint of the *in vivo* methylation of inorganic arsenic. However, studies on the fate of DMA administered to man, mouse and hamster have shown that about 5% of the ingested DMA was further methylated and excreted in the urine as TMAO within 48 h.[29] About 80% of the dose was excreted as DMA, part of which (10–15%) was found to be in the form of complexes, not further characterized. There were no major differences between species.

The methylation of inorganic arsenic in mammals is generally considered to be a detoxification mechanism. The methylated metabolites are shown to be much less toxic than inorganic arsenic.[30,31] In most mammals they are less reactive with tissue components than is AsIII,[32,33] and the major part of the absorbed MMA and DMA is rapidly excreted in the urine.[29,33–35] Urinary excretion of MMA and DMA may therefore be used as an indicator of the methylation efficiency. It should be noted that the methylation is influenced by a number of factors, e.g. dose level (decreasing methylation with increasing dose), route of administration (higher rate of methylation following peroral than parenteral administration) and the form of arsenic administered (higher degree of methylation following exposure to AsIII than to AsV).

SPECIES DIFFERENCES IN THE METHYLATION OF INORGANIC ARSENIC

There are major species differences in the urinary excretion of methylated arsenic metabolites following exposure to inorganic arsenic, indicating significant differences in the rate of methylation of inorganic arsenic. Figures 4 and 5 show a comparison of the urinary excretion of arsenic metabolites in various species following exposure to AsIII and AsV, respectively. It can be seen that only human subjects excrete significant amounts of MMA following exposure to in-

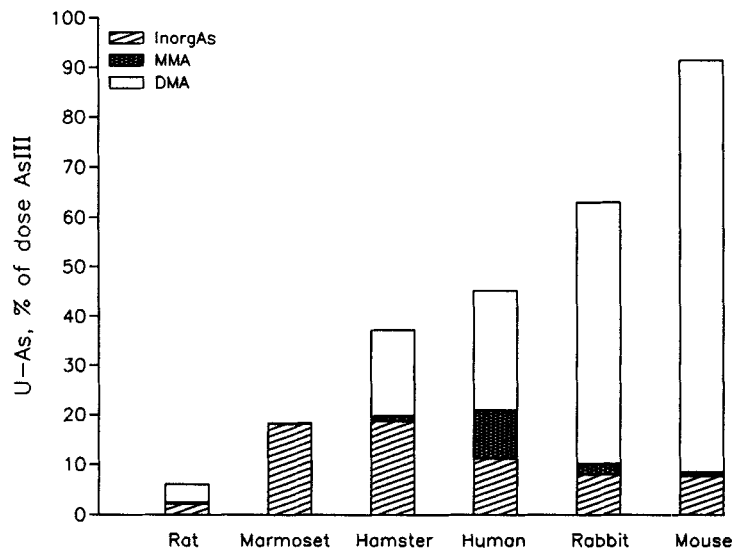

Figure 4 Cumulative urinary excretion of arsenic metabolites in different species 2–4 days after a single dose of arsenite. Dosages (mg As per kg body weight): rat, 0.4, p.o.;[40] marmoset monkey, 0.4 i.p.;[58] man, 0.007, p.o.;[34] hamster, 2, p.o.;[63] rabbit, 0.04, i.v.;[32] mouse, 0.4, p.o.[40]

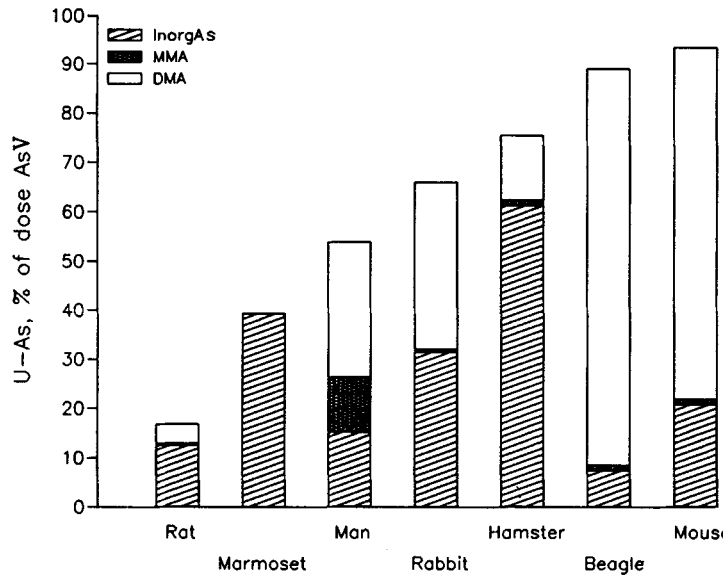

Figure 5 Cumulative urinary excretion of arsenic metabolites in different species 2–4 days after a single dose of arsenate. Dosages (mg As per kg body weight, unless otherwise stated): rat, 0.4, p.o.;[40] marmoset monkey, 0.4;[27] man, 0.01 μg As per person, p.o.;[38] hamster: 2, p.o.;[63] rabbit, 0.04, i.v.;[32] dog: 0.3 μg As per dog;[41,42] mouse: 0.4, p.o.[40]

organic arsenic. In people exposed to 'normal' environmental levels of inorganic arsenic, urinary arsenic consists of 10–20% inorganic arsenic, 10–20% MMA and 60–80% DMA.[35–39]

It is apparent from Figs 4 and 5 that mice and dogs are very good methylators of arsenic. More than 70% of the dose of both AsIII and AsV is methylated and excreted as DMA in the urine within a couple of days.[40–42] Rats are also good methylators for arsenic. The low urinary excretion of methylated arsenic metabolites in the rat is not an indication of a low methylating capacity; it is due to a specific retention of DMA in the erythrocytes. As early as 1942, Hunter and co-workers[43] reported that arsenite, injected in rats, was accumulated in the erythocytes, apparently bound to the hemoglobin. A similar pronounced retention of arsenic in the red blood cells was not seen in guinea-pig, rabbit, chimpanzee, baboon or man. A few years later Ducoff *et al.*[44] and Lanz *et al.*[45] confirmed specific accumulation of arsenic in rat erythrocytes. One interesting finding was that the cat also accumulated arsenic in blood following injection of radiolabeled arsenate, although not to the same extent as the rat. Later it has been demonstrated that more than 95% of the arsenic in erythrocytes of rats exposed to inorganic arsenic is in the form of DMA.[46,47] The accumulation and long-term retention of DMA in the blood of rats has also been demonstrated following exposure to DMA.[33,48] Stevens *et al.*[48] reported that the halflife of DMA in rat blood is about 90 days, which agrees well with the mean life of red blood cells. Interestingly, methylmercury is also accumulated in rat erythrocytes,[49] and it has been proposed that this is due to the higher number of SH-containing cysteinyl residues in rat hemoglobin, compared with that of other species.[50] The mechanism involved in the accumulation of DMA in rat erythrocytes is not known. It would be expected that AsIII, rather than DMA, would be bound to SH groups of cysteinyl residues.

The specific binding of DMA to rat erythrocytes has to be considered when evaluating reports on the metabolism of arsenic rat. For example, it has been shown that depletion of hepatic GSH in rats gives rise to an increased urinary excretion of arsenic.[51] This may be explained by the fact that less DMA is trapped in the red blood cells as a consequence of the decreased production of DMA caused by GSH depletion. This leads to more inorganic arsenic being transported to the kidneys for excretion in the urine. In other species, inhibition of hepatic DMA production, e.g. by inhibition of the transfer of methyl groups from *S*-adenosylmethionine[21] or by a limited access to methyl groups via the diet,[52] leads to an overall decrease in the urinary excretion of arsenic.

The rat differs from other species also with respect to the biliary excretion of arsenic. It has

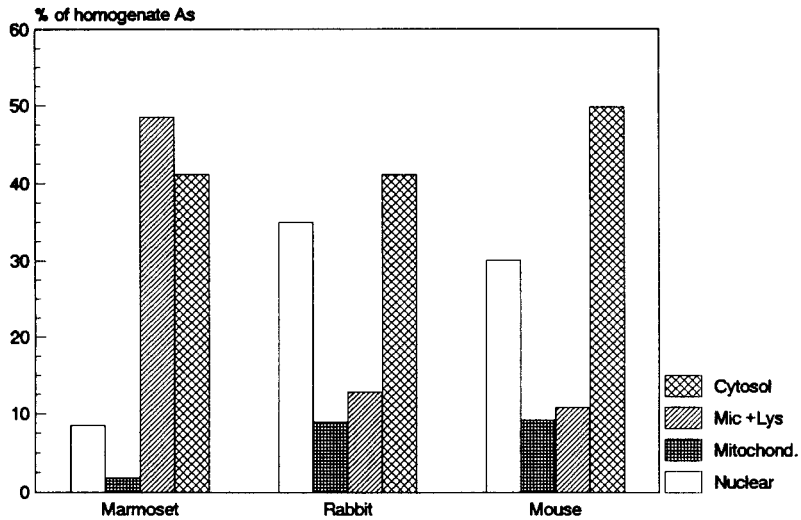

Figure 6 Comparison of the subcellular distribution of arsenic in liver of marmoset monkey, rabbit and mouse, 2–4 days after exposure to arsenite.[21,58,59] Mic + Lys, represent microsomal fraction and lysosomes.

been shown that following injection of AsIII, the rate of biliary excretion of arsenic in rats was 800-fold that in the dog and 37-fold that in the rabbit.[53] Approximately 25% of the arsenic administered to rats was excreted in the bile within 2 h, although most of it was reabsorbed in the gut. Arsenic in bile from isolated rat liver perfused with arsenite was shown by thin-layer chromatography to be associated with glutathione.[54] No MMA or DMA was detected in bile following exposure to arsenite or arsenate.[55] It should be noted that the biliary excretion of GSH and its related thiols and disulfides is considerably higher in rats (more than 10-fold) than in rabbits, for example.[56,57] Furthermore, GSH is the main thiol in rat bile, whereas rabbit bile contains mainly cysteinylglycine and its disulfide, formed from GHS by the action of γ-glutamyl transpeptidase and dipeptidase.

Another animal species with a unique metabolism of inorganic arsenic is the marmoset monkey. It is the only species which, so far, has been shown unable to methylate inorganic arsenic.[27,58] The lack of methylation results in an extensive tissue binding of arsenic and a low rate of excretion (Figs 4 and 5). In marmoset monkeys administered arsenite or arsenate, almost 60% of the dose was retained in the body after three days. About 10% of the dose was retained in the liver, where most of the arsenic was present in the microsomal fraction, almost entirely in the rough microsomes. In mice and rabbits exposed to arsenite, the major part of the cellular arsenic is present in the nuclear and the cytosolic fractions.[21,59] Figure 6 shows a comparison of the subcellular distribution of arsenic in marmoset, rabbit and mouse. It may be of interest to note that in rabbits, in which the methylation of arsenic was decreased by a low dietary intake of methionine, a significant increase in the accumulation of arsenic in the microsomal fraction of the liver was observed.[52] A similar effect was not seen in rabbits in which the arsenic methylation was inhibited by administration of periodate-oxidized adenosine, a potent inhibitor of methyl transfer from *S*-adenosylmethionine.[21]

The rabbit and the hamster seem to be the species most similar to man with regard to the methylation of arsenic, although they excrete somewhat more DMA and less MMA than does man. However, it should be noted that the gastrointestinal absorption of both inorganic arsenic and the methylated metabolites is somewhat lower in the hamster than in most other species,[29,60–63] in which most soluble arsenic compounds are efficiently absorbed.

In conclusion, there are major species differences in the metabolism of inorganic arsenic, while the metabolism of organic arsenic compounds of marine origin seems to be quite similar in different species. Inorganic AsIII is methylated in the liver of most mammals. AsV is reduced in the blood to AsIII, which is then methylated in the liver. DMA is the main metabolite in most mammals. Only human subjects excrete significant amounts of MMA in urine. The marmoset

monkey is the only species known not to methylate inorganic arsenic. In the rat, unlike other species, most DMA produced is bound to the erythrocytes. Furthermore there is pronounced biliary excretion of arsenic in the rat. The rabbit and the hamster seem to be the species most similar to man with regard to the methylation of arsenic.

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