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UPTAKE, DISTRIBUTION, AND METABOLISM OF TRIVALENT ARSENIC IN THE PREGNANT MOUSE

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To investigate the distribution of trivalent arsenic (arsenite) in the pregnant rodent, CD-1 mice were dosed with sodium arsenite by ip injection or by gavage on gestation d 18 (copulation plug day = d 1). Doses were 8 (ip) or 25 (po) mg/kg, and samples of maternal blood, liver, and kidneys, as well as fetuses and pooled placentas, were analyzed for total arsenic at intervals of up to 24 h. Fetal tissue was also analyzed for relative proportions of inorganic arsenic and methylated metabolites. Arsenic uptake was significantly greater in the injected mice and their fetuses (as a proportion of the administered dose), with levels highest at 10 min to 4 h in maternal tissues and 24 h in fetuses. Peak maternal arsenic levels (as μg/g or μg/ml) ranged from 2.36 (blood) to 26.15 (liver) for the ip injected and 1.25 (blood) to 17.64 (liver) for the gavaged treatment group. The rate of arsenic elimination from maternal samples was not significantly influenced by administration route, with first-order elimination rate constants (k) of 0.215 and 0.234 h^{-1} for the po and ip dosed mice, respectively. Fetal tissue arsenic peaks were 2.10 and 0.77 μg/g for the ip and po treatment groups, respectively. The proportion of methylated arsenic in fetuses increased to 79% in the ip treatment group and 88% in the po group by 24 h. Such results show that much of the arsenic reaching the mouse fetus has been methylated to less toxic metabolites. They also confirm that assumptions made regarding hazard to the fetus must reflect the likelihood that a portion of any maternal dose of inorganic arsenite reaching a fetus may have been methylated, and they support previous findings that arsenite is toxic to the conceptus at lower doses when given by injection than by gavage.

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INTRODUCTION

Inorganic arsenic typically occurs in the environment as either the trivalent (arsenite) or pentavalent (arsenate) form. Arsenate has been known as a teratogen in the chick embryo since the work of Ancel and Lallemand (1941), and was identified as a developmental toxicant in mammals by Ferm and Carpenter (1968). Their work has been followed by a number of other studies on arsenate.

The first report that trivalent arsenic may adversely affect the conceptus was the study of Hood (1972), using the mouse. More recently, Birge and Roberts (1976) found arsenite to be teratogenic in chick embryos, and Baxley et al. (1981) and Hood and Harrison (1982) compared the effects of orally and intraperitoneally administered arsenite in the mouse and hamster, respectively. Nevertheless, although pentavalent arsenic has received considerable attention from developmental toxicologists, less is known about the effects of prenatal exposure to arsenite. Arsenite is also the most common form used in rodenticides and thus has been involved in most of the cases of human arsenic intoxication. For example Lugo et al. (1969) reported a case of attempted suicide by arsenite ingestion at 30 wk of gestation that resulted in death of the infant following premature delivery.

Although it has been reported that arsenite reaches the offspring following administration to the pregnant rat (Morris et al., 1938) and mouse (Lindgren et al., 1984), and arsenate enters the fetuses of hamsters (Hanlon and Ferm, 1977) and mice (Hood et al., 1987), there appear to be no detailed reports regarding the time course of uptake and loss of arsenic by the fetus following arsenite administration to the mother. In addition, reports such as those of Odonaka et al. (1980) and Braman and Foreback (1973) have described methylation of arsenic by mammals, including humans. The primary arsenic metabolite is usually dimethylarsinic acid (DMA), while significant amounts of methylarsonic acid (MAA) are usually also in evidence. Nevertheless, data on the percentage of total arsenic in the fetus or in maternal tissues that is present as mono- or dimethylarsenic following maternal exposure to arsenite are also lacking.

We undertook the present study to evaluate maternal and fetal arsenic uptake and metabolism in order to further investigate the factors involved in the developmental toxicity of arsenic, and especially arsenite, and to gain further insight regarding the basis for the similarities and differences in biological response to the major inorganic arsenic valence states. Fetuses were sampled late in gestation in order to obtain adequate amounts of tissue for arsenic speciation. Hanlon and Ferm (1986a,b) have recently determined the content of inorganic arsenic and DMA in the blood of pregnant hamsters dosed with arsenate, but they did not analyze their offspring. Thus, the current data should

also add to our knowledge of arsenic metabolism during pregnancy and the relative fetal uptakes of the methylated metabolites versus inorganic arsenite.

MATERIALS AND METHODS

CD-1 albino mice (Charles River Breeding Labs, Wilmington, Mass.) were housed in solid bottom polypropylene cages with hardwood chip bedding and maintained on a diet of Wayne Lab Blox (Allied Mills, Chicago, Ill.) and water. The mice were kept on a 12/12 h light/dark cycle at 22 ± 2°C and 40–60% relative humidity. After acclimatization, mice were mated, and the day on which a copulation plug was seen was designated gestation d 1.

Pregnant mice were injected intraperitoneally on gestation d 18 with a dose of 8 mg/kg sodium arsenite dissolved in distilled H_2O or were given a 25 mg/kg arsenite dose by gavage. Dose volume was 0.01 ml/g body weight. The doses used had been found in pilot tests to be maximum tolerated doses in terms of abortion or maternal death in 18-d pregnant mice over 24 h.

Treated females were then killed at 0.5, 1, 2, 4, 6, 12, 18, or 24 h following injection. Additional females (from the ip treatment group only) were killed at 10 or 20 min after injection. Individual fetuses, pooled placentas, and maternal blood, liver, and kidneys were obtained for total arsenic analysis from three or more mice per time interval for each treatment mode. Samples from two to four fetuses per litter from each of the pregnant females were additionally analyzed to determine the relative proportions of inorganic arsenic and arsenic metabolites in fetal tissue.

Sample Preparation and Arsenic Analysis

Solid tissues were homogenized following addition of 5 ml deionized distilled H_2O. All samples were digested with heating in 5 ml reagent-grade hydrochloric acid prior to analysis.

All arsenic analyses were performed with a Varian model AA-275 atomic absorption spectrophotometer equipped with an electrodeless discharge arsenic lamp and deuterium lamp background correction. A quartz absorption cell was placed in the light path and heated by an air/acetylene flame. Total arsenic was determined by production of arsines in a Varian model 65 vapor generation apparatus (Varian, Palo Alto, Calif.). Each sample (0.01–2.0 ml, dependent on arsenic concentration) was mixed in the arsine generator with 20 ml 5% HCl. An excess of sodium borohydride ($NaBH_4$) in pellet form was added to reduce the arsenicals present to arsines. The volatile arsines were carried in a helium stream to the absorption cell, with arsenic concentration measured by use of a chart recorder. Multiple runs were conducted

for each sample, and total arsenic was quantitated by comparing integrated peak areas with those obtained from standards prepared in a like manner to the samples. Analyses of a National Bureau of Standards liver standard with a known arsenic content yielded values within ±2.5% of the certified value, and testing for recovery of known amounts of arsenicals added to our tissue homogenates gave recoveries of from 87% to 104%. Arsenic concentrations were expressed as μg/g weight or μg/ml.

According to Hinners (1980), this method underestimates the amount of total arsenic if significant proportions of methylated arsenicals are present in the samples. Thus, samples obtained at the later time intervals may contain 5–10% more total arsenic than is indicated. Hinner's contention was confirmed by us when we tested mixtures of equimolar amounts of inorganic arsenic and DMA.

Methylated arsenic concentrations were obtained by a modification of the method of Feldman (1979). Arsines were generated in a custom-made vapor generator (M. J. Zaworotko and R. D. Hood, unpublished) by use of a 2% $NaBH_4$ solution and carried by helium to a U-tube cold trap containing 0.2-mm diameter glass beads. The trap was immersed in a Dewar flask of liquid N_2, causing the arsines to freeze and precipitate in the trap at −196°C. When the liquid N_2 was removed, arsine and mono- and dimethylarsine, derived from inorganic arsenic, MAA, and DMA, respectively, volatilized sequentially as the trap warmed to room temperature. They were carried to the absorption cell for quantitation. The mean of three analyses was determined for each sample.

RESULTS

Total Arsenic

When d-18 pregnant mice were given oral sodium arsenite, significant amounts of arsenic were detected in the earliest samples of all tissues examined (Tables 1 and 2). Arsenic distribution in maternal samples was complete by 0.5 h after either po or ip dosing, followed by apparently uniform washout from the liver, kidney, and blood over the remaining time of the study. This was followed by essentially linear elimination for both administration routes; however, there was a tendency toward tailing after 12 h following oral administration. Arsenic elimination in liver, kidney, and blood from the po-dosed mice was fitted to a first-order one-compartment model with an elimination rate constant (k) of 0.215 h^{-1}. A similar pattern was observed in the mice dosed intraperitoneally, with an estimated k value of 0.234 h^{-1}. The rate constants for po and ip administration were not significantly dif-

TABLE 1. Arsenic Content of Maternal Samples following Intraperitoneal (8 mg/kg) or Oral (25 mg/kg) Sodium Arsenite Administration to Mice on Gestation Day 18

	Samples assayed[b] and route of exposure					
	Liver[c]		Kidneys[c]		Blood[d]	
Sampling time	ip	po	ip	po	ip	po
10 min	26.15 ± 3.80	NA[a]	7.80 ± 2.81	NA[a]	2.36 ± 1.01	NA[a]
20 min	20.55 ± 4.21	NA	17.16 ± 9.72	NA	1.46 ± 0.12	NA
0.5 h	17.50 ± 4.54	17.64 ± 4.14	11.45 ± 4.26	7.07 ± 1.97	1.02 ± 0.48	0.92 ± 0.24
1 h	14.90 ± 4.33	12.70 ± 2.54	8.91 ± 3.34	6.66 ± 2.10	1.24 ± 1.12	0.77 ± 0.22
2 h	9.70 ± 1.35	9.68 ± 3.56	6.42 ± 1.49	5.5 ± 1.70	0.82 ± 0.15	0.50 ± 0.15
4 h	8.80 ± 2.08	7.84 ± 3.09	4.06 ± 1.85	8.94 ± 2.22	0.90 ± 0.39	1.25 ± 1.16
6 h	3.08 ± 0.67	8.44 ± 5.99	4.05 ± 0.42	4.40 ± 2.18	0.57 ± 0.33	0.49 ± 0.33
12 h	2.04 ± 0.46	2.05 ± 0.60	1.52 ± 0.57	1.85 ± 0.46	0.33 ± 0.19	0.48 ± 0.16
18 h	0.39 ± 0.24	2.45 ± 1.26	0.57 ± 0.67	2.19 ± 0.29	0.13 ± 0.02	0.59 ± 0.26
24 h	0.23 ± 0.09	2.19 ± 0.38	0.22 ± 0.16	2.04 ± 0.36	0.11 ± 0.09	0.76 ± 0.54

[a]Samples were not collected at 10 or 20 min from the po treatment group.
[b]Each value represents the mean ± SD of samples from three or more individuals.
[c]μg As/g wet weight.
[d]μg As/ml.

ferent, suggesting that arsenic was reasonably homogeneous in its tissue distribution.

Arsenic entered the circulation significantly more rapidly following ip administration. Peak levels in maternal liver, kidney, and blood were seen in the 10- or 20-min samples and declined to low levels by 24 h. Placental arsenic was also high at 10 min, but declined until 1 h, where levels again increased. Fetal arsenic, however, was comparatively low soon after injection, gradually increased, and was highest at 24 h.

Following po dosing, the amount of arsenic seen in the liver was highest in the initial samples (0.5 h) and declined thereafter. In the maternal blood and kidneys, however, there were high initial levels that then appeared to decline somewhat, rose again at 4 h, and resumed their decline. Placental arsenic levels peaked at 4 h and declined afterward, while fetal concentrations were highest at 24 h.

Methylated Arsenic

Inorganic arsenic as well as mono- and dimethylated arsenic concentrations in mouse fetuses following maternal treatment with ip or po arsenite are shown in Figs. 1 and 2. DMA was the predominate metabolite at times past 1 h, although at the earliest sampling times MAA was equally prevalent. The relative proportion of fetal inorganic arsenic declined during the first 12 h following treatment by either exposure route and tended to plateau thereafter. By 4–6 h after treat-

TABLE 2. Arsenic Content of Maternal Samples following Intraperitoneal (8 mg/kg) or Oral (25 mg/kg) Sodium Arsenite Administration to Mice on Gestation Day 18

	Samples assayed[c] and route of exposure			
	Placentas[a]		Fetuses	
Sampling time	ip	po	ip	po
10 min	3.50 ± 2.76	NA[b]	0.02 ± 0.03	NA[b]
20 min	2.05 ± 0.41	NA	0.12 ± 0.08	NA
0.5 h	2.31 ± 0.97	1.90 ± 0.72	0.24 ± 0.05	0.15 ± 0.05
1 h	3.82 ± 0.93	1.88 ± 0.09	1.07 ± 1.34	0.25 ± 0.11
2 h	3.41 ± 0.74	1.50 ± 0.47	1.21 ± 1.01	0.24 ± 0.05
4 h	2.82 ± 0.81	2.47 ± 0.43	1.29 ± 1.20	0.50 ± 0.30
6 h	2.79 ± 1.27	1.15 ± 0.44	1.13 ± 0.65	0.26 ± 0.05
12 h	2.90 ± 0.91	0.78 ± 0.31	1.38 ± 0.12	0.34 ± 0.05
18 h	0.64 ± 0.53	1.14 ± 0.62	0.98 ± 0.19	0.54 ± 0.09
24 h	0.43 ± 0.48	1.08 ± 0.19	2.10 ± 0.27	0.77 ± 0.14

[a]Placentas were pooled by litters; values given are for total placental arsenic/litter.
[b]Samples were not collected at 10 or 20 min from the po treatment group.
[c]Each value represents the mean ± SD (μg/g wet weight) of fetuses from three or more litters.

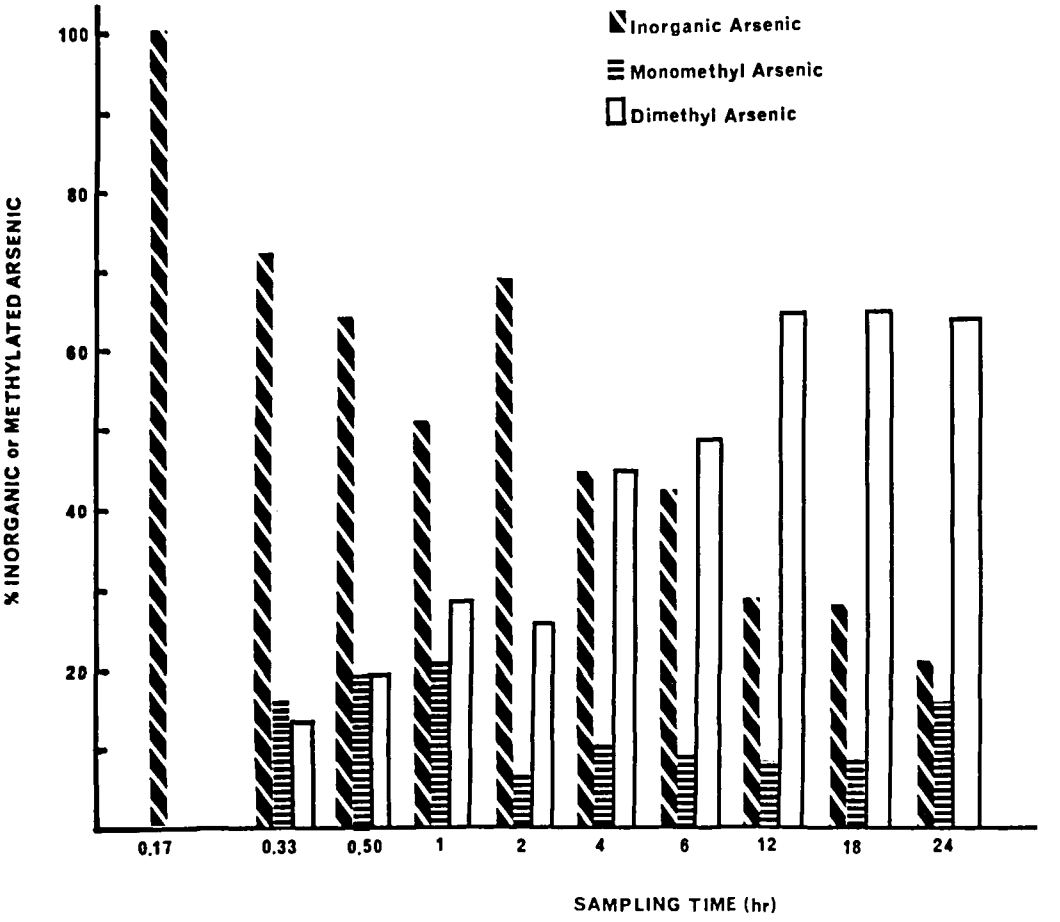

FIGURE 1. Relative amounts of organic and inorganic arsenic in d-18 mouse fetuses following maternal ip injection with 8 mg/kg sodium arsenite.

ment, the preponderance of arsenic in the fetuses consisted of methylated metabolites.

DISCUSSION

As expected, inorganic arsenite readily entered the maternal blood following either intraperitoneal or oral administration, with uptake more rapid in the injected mice. Absorbed arsenic crossed the placenta and was transferred to the fetus. Arsenic levels in the blood and other tissues, including fetuses and placentas, were higher following ip than po administration. This was true even though the dose employed was only one-third as great. The discrepancy between the two treatment groups in fetal arsenic uptake is similar to the difference in

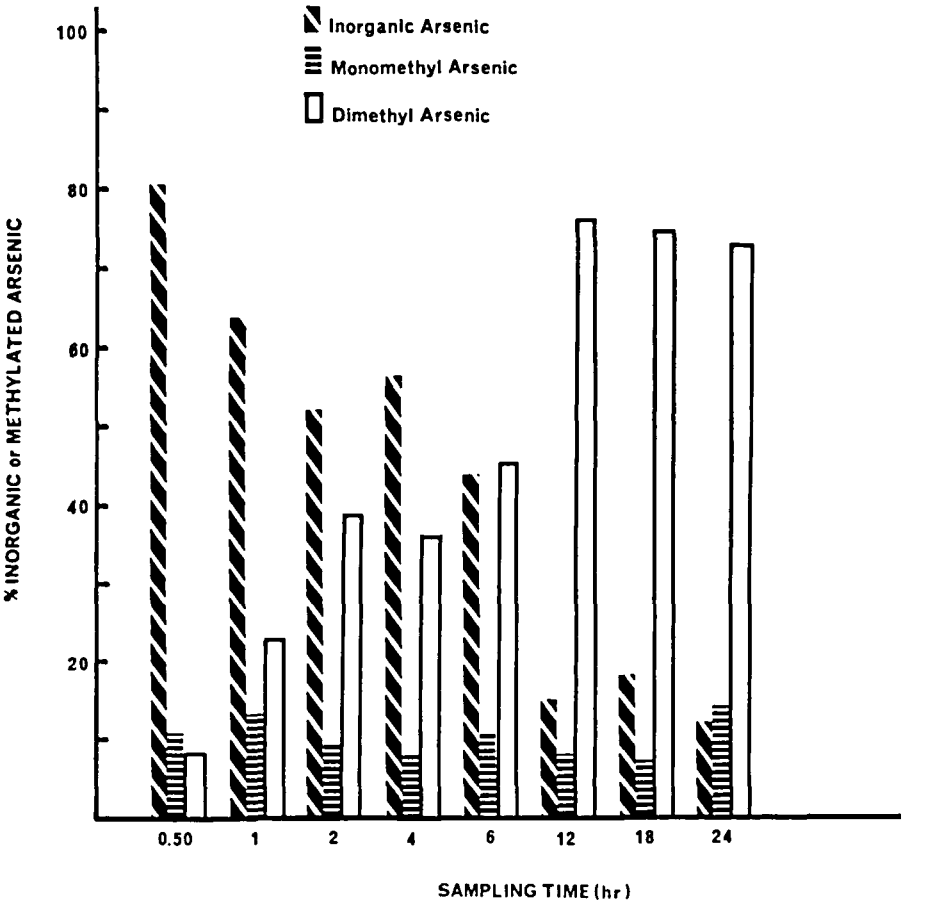

FIGURE 2. Relative amounts of organic and inorganic arsenic *in* d-18 mouse fetuses following maternal gavage with 25 mg/kg sodium arsenite.

dose levels required to cause fetotoxicity in the mouse (10–12 mg/kg, ip, vs. 40–45 mg/kg po) according to the data of Hood (1972) and Baxley et al. (1981). This relationship has also been seen in the hamster (5 mg/kg, ip, vs. 25 mg/kg, po) by Hood and Harrison (1982). Such results lend support to the assumption that embryotoxic and teratogenic effects of arsenic may to be correlated with the dose reaching the offspring.

Early attempts to show fetal arsenic uptake (Hanlon and Ferm, 1977; Hood, 1978) employed the pentavalent form, while more recently Lindgren et al. (1984) used both arsenate and arsenite, but in no case was an attempt made to distinguish inorganic from methylated species. This is an important distinction, as methylated arsenic metabolites are presumed to be much less toxic to the conceptus than are

the parent inorganic forms. For example, although MAA and DMA are both teratogenic and embryotoxic in mice (Harrison et al., 1980), the effective doses were found to be as much as 100-fold higher than those reported for inorganic arsenite (Hood, 1972) or arsenate (Hood and Bishop, 1972).

Relatively high oral doses of dimethylarsinic acid (400 mg/kg·d from d 7–16) were required before adverse effects on the developing offspring of treated mice were seen in the study of Rogers et al. (1981), while maternal intravenous injection of 20–100 mg/kg of either sodium methylarsonate or sodium dimethylarsinate had relatively little effect on the hamster conceptus (Wilhite, 1981). Hamster fetuses were also found to require high doses of either methylated arsenical before teratogenic or fetotoxic effects were seen by Hood et al. (1982). Such results support the premise that the offspring of some species are relatively resistant to adverse effects of methylated arsenicals, although the rat appears to be much more sensitive to at least DMA. The maternal toxic dose in this species has been reported to be some 50 times less than that in the mouse, while there was an even greater discrepancy between the embryotoxic doses in the two species (Rogers et al., 1981). The greater effects of such arsenicals in the rat may be due to that species' unique ability to retain methylated arsenicals in the erythrocytes (Yamauchi et al., 1980; Odonaka et al., 1980).

Data from the foregoing studies indicate that methylated arsenic metabolites are significantly less harmful to the fetus than are the inorganic forms. Therefore, conclusions regarding the amount of inorganic arsenic actually reaching the conceptus that is required to have an adverse effect may be overestimated if arsenic metabolism is ignored. It appears likely that impaired maternal ability to metabolize arsenic could increase the potential for risk to the conceptus. It is also conceivable that the conceptus may be capable of arsenic methylation, but it is not known to what extent, if any, this may occur.

Recently, Hood et al. (1987) examined the content of arsenic and its methylated metabolites in fetal mice following maternal po or ip administration of pentavalent arsenic on gestation d 18. Those results differed somewhat from the current findings with trivalent arsenic. For example, following ip dosing with As(V), both total fetal and placental arsenic peaked around 2–4 h and rapidly declined thereafter. When dams were given ip As(III), fetal arsenic concentrations also rose rapidly but then plateaued for several hours. Placental arsenic then declined while the fetal content exhibited a further increase.

In the case of maternal po treatment, the results with the two valence forms were more similar. Arsenic in both placentas and fetuses from the arsenate-treated group remained almost constant from 12 to 24 h following maternal dosing (Hood et al., 1987), and placental arse-

nic in the arsenite-treated group also plateaued, although the fetal concentration rose steadily and was highest at 24 h.

The time course of conversion of inorganic arsenic to MAA and DMA varied in a similar way following both As(V) and As(III) administration. This was true although the proportion of DMA was slightly lower and that of MAA considerably higher following dosing with As(III) by either treatment route.

In both the current study and that of Hood et al. (1987), first-order elimination was observed for maternal arsenic, the rate of elimination was not influenced by administration route, and a one-compartment model appeared to be appropriate for the data. The elimination rate constants (k) were higher in the case of arsenite, however.

When Hanlon and Ferm (1986b) dosed hamsters ip with arsenate at midgestation, they observed peak maternal blood levels at 0.5 h, followed by a very rapid decline through the end of the test period (6 h). Their results were somewhat like those of the current study, where peak blood levels following ip dosing occurred at 20 min, but elimination from the blood of the mice was much slower. Hanlon and Ferm (1986b) also found that about 50% of the arsenic present in maternal blood at 6 h after dosing was in the form of DMA. This proportion of DMA is remarkably similar to that found in mouse fetuses in the current data, but no mention was made by Hanlon and Ferm (1986b) of the presence of MAA. That metabolite has been found in small amounts in hamsters by Odonaka et al. (1980) following treatment with As(V).

Our findings on arsenite methylation by mice, predominately to dimethylarsinate, are in agreement with those of Vahter (1981). Odonaka et al. (1980) obtained similar results with mice, rats, hamsters, rabbits, and cats following administration of arsenate. Vahter (1981) reported a greater preponderance of DMA in the urine of arsenite-exposed mice than was seen in the fetuses analyzed in the current study; however, this lack of agreement may be due to the difference in the type of sample analyzed (i.e., urine vs. fetal tissue).

That humans also generate methylated arsenic metabolites was first shown by Braman and Foreback (1973), who found dimethylated arsenic to be the predominate human metabolite. Similar results have subsequently been reported by others, including Crecelius (1977) and Buchet et al. (1980).

We conclude that inorganic arsenite administered to the pregnant mother is readily transferred via the placenta and enters the near-term rodent fetus. Arsenic uptake is significantly greater following maternal intraperitoneal versus oral dosing, and such differences are likely to account for dissimilarities in fetotoxic dose following such treatments earlier in gestation as well. Methylation of the administered arsenic

occurs to a considerable extent regardless of treatment mode and is presumed to decrease the toxic effect.

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