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Toxicology 160 (2001) 227–236

TOXICOLOGY

www.elsevier.com/locate/toxicol

A concise review of the toxicity and carcinogenicity of dimethylarsinic acid

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Abstract

Dimethylarsinic acid (DMA) has been used as a herbicide (cacodylic acid) and is the major metabolite formed after exposure to tri- (arsenite) or pentavalent (arsenate) inorganic arsenic (iAs) via ingestion or inhalation in both humans and rodents. Once viewed simply as a detoxification product of iAs, evidence has accumulated in recent years indicating that DMA itself has unique toxic properties. DMA induces an organ-specific lesion — single strand breaks in DNA — in the lungs of both mice and rats and in human lung cells in vitro. Mechanistic studies have suggested that this damage is due mainly to the peroxyl radical of DMA and production of active oxygen species by pulmonary tissues. Multi-organ initiation-promotion studies have demonstrated that DMA acts as a promotor of urinary bladder, kidney, liver and thyroid gland cancers in rats and as a promotor of lung tumors in mice. Lifetime exposure to DMA in diet or drinking water also causes a dose-dependent increase in urinary bladder tumors in rats, indicating that DMA is a complete carcinogen. These data collectively suggest that DMA plays a role in the carcinogenesis of inorganic arsenic. Published by Elsevier Science Ireland Ltd.

Keywords: Arsenic; Cancer; Dimethylarsinic acid

Dimethylarsinic acid[1] (DMA; see Fig. 1) has been used as a herbicide and is also the major metabolite formed after exposure to trivalent (arsenite, AsIII) or pentavalent (arsenate, AsV) inorganic arsenic via ingestion or inhalation in both humans and most rodents (US EPA, 1975; ATSDR, 1993). Methylation of inorganic arsenic to form both DMA and methylarsonic acid (MMA) has traditionally been viewed as a mechanism to facilitate the detoxification and excretion of arsenic. This is principally because DMA, in particular, is over 10-fold less acutely toxic than inorganic arsenic (Kaise et al., 1985, 1989). However, evidence suggesting that DMA itself has unique toxic properties has accumulated in the

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[1] Unless specifically stated otherwise, the abbreviation DMA refers to pentavalent dimethyl form of arsenic. The distinction is important because emerging evidence suggests that both trivalent monomethylated arsenic and trivalent DMA are more tissue-reactive and cytotoxic than their pentavalent counterparts.

0300-483X/01/$ - see front matter Published by Elsevier Science Ireland Ltd.
PII: S0300-483X(00)00458-3

last decade and indicates the need to re-examine this implicit assumption. In this article, we will review the metabolism and toxicology of DMA with particular emphasis on recent findings and their implications for understanding the carcinogenicity of inorganic arsenic.

1. Metabolism and disposition

Following oral administration, DMA is readily absorbed from the gastrointestinal tract. Yamauchi and Yamamura (1984) reported that 49% of a single oral dose of 50 mg/kg DMA was eliminated in the urine of Syrian golden hamsters within 5 days (~ 36% in feces). Marafante et al. (1987) reported similar findings in that 56% of a single oral dose of 40 mg (As)/kg DMA was eliminated in urine of male Syrian golden hamsters within 48 h (41% in feces). Gastrointestinal absorption of DMA may be more extensive in mice. In this same study 68 and 29% of the dose was eliminated in the urine and feces, respectively, of male ICR mice administered the same oral dose of DMA.

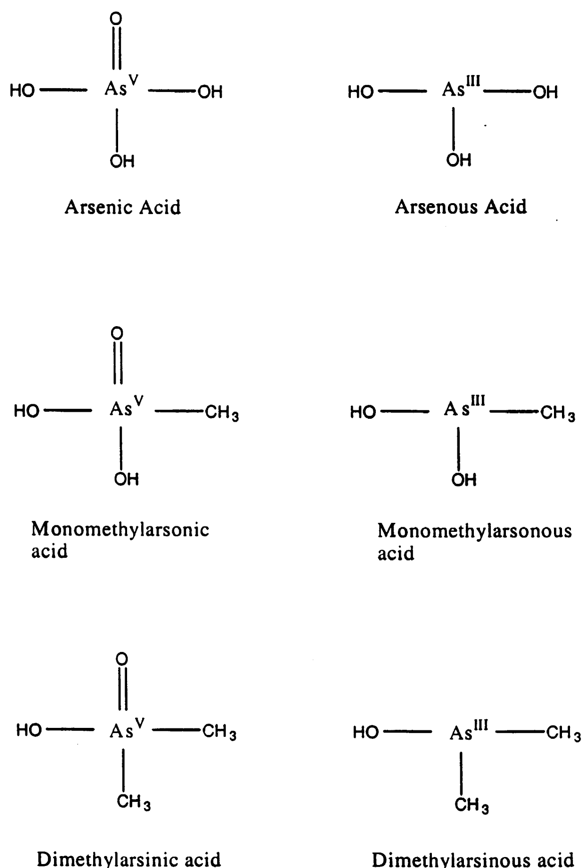

Fig. 1. Structures of some toxicologically relevant arsenic compounds

Vahter et al. (1984) reported a significant interspecies difference in DMA clearance between rats and mice. They compared the whole-body retention of ^{74}As-DMA following a single oral dose of 0.4 mg (As)/kg. In mice, whole-body clearance of DMA was triphasic, with 85% of the dose eliminated with a half-time of 2.5 h, 14% with a half-time of 10 h and the remainder ($<0.5\%$) with a half-time of 20 days. In rats, elimination was biphasic with 45% of the dose having a half-time of 13 h and the remaining 55% having a half-time of 50 days. The longer retention of DMA in the rat is due to its accumulation in erythrocytes (Stevens et al., 1977).

DMA is methylated to trimethylarsenic compounds to a small extent in mice, rats, hamsters and humans (Yamauchi and Yamamura, 1984; Marafante et al., 1987; Yoshida et al., 1997). Marafante et al. (1987) reported that 3 and 6% of a single oral dose of 40 mg (As)/kg DMA was eliminated in urine as trimethylarsine oxide (TMAO) within 48 h in mice and hamsters, respectively; TMAO was not detected in the feces of either species in this study. In this same study, a human volunteer excreted 3.5% of a single oral dose of DMA (0.1 mg As/kg) in urine as TMAO within 3 days. An unidentified DMA complex was also excreted in both urine (7–11% of the dose) and feces (4–5% of the dose) in mice and hamsters in this study with the remainder of the dose excreted as unmetabolized DMA. Hughes and Kenyon (1998) also reported an unidentified and readily oxidizable metabolite in urine of mice administered DMA intravenously. Marafante et al. (1987) speculated that the metabolite observed in their studies might be a thiol complex that could be an intermediate in the further methylation to TMAO.

Because inorganic arsenic and MMA were not detected in the urine of mice, hamsters and rab-

bits administered DMA (Vahter and Marafante, 1983; Marafante et al., 1987) or tissues of mice administered DMA (Hughes et al., 2000), these investigators concluded that demethylation of DMA either does not occur in vivo or is quantitatively insignificant. However, recently Yoshida et al. (1997) have reported increased excretion of arsenite in urine at later time intervals following either oral or i.p. administration of 50 mg/kg of DMA to rats. Given that excretion of arsenite in urine was greater following oral administration and was also delayed in time relative to TMAO urinary excretion, the authors suggest that demethylation of DMA by intestinal microbiota occurs in vivo.

Total (urine + fecal) elimination of DMA is quite rapid in laboratory rodents with 80% or more of the dose eliminated within 48 h following a single oral or parenteral dose. Absorbed DMA is predominantly eliminated in urine. Limited data from studies where multiple dose levels were used (Yamauchi et al., 1988; Hughes and Kenyon, 1998) suggest that urinary elimination is also dose-independent, i.e. the percentage of the dose eliminated in urine does not change with increasing or decreasing dose level. No studies were identified that directly addressed the issue of biliary elimination of DMA. However, given the relatively low amounts of MMA and DMA excreted in the feces (2–9% of the dose) following i.v. administration of these compounds to mice or rabbits (Vahter and Marafante, 1983; Hughes and Kenyon, 1998), it seems unlikely that biliary excretion or other gastric secretory processes contribute significantly to total elimination.

2. Reproductive and developmental toxicity

The developmental toxicity of DMA was examined in several studies in the early 1980s due to the use of cacodylic acid as a herbicide (Rogers et al., 1981; Willhite, 1981; Hood et al., 1982). DMA is fetotoxic in pregnant hamsters with resorption rates ranging from 10 to 100%, depending on the route of administration (i.v., i.p.), the dose (20–100 mg/kg), and the day of gestation (day 8–12) (Willhite, 1981; Hood et al., 1982). DMA (sodium salt, 20–100 mg/kg) induced a low percentage of malformations ($< 6\%$) after intravenous administration on day 8 of gestation in pregnant hamsters; malformations observed included fused ribs, renal agenesis or encephalocoele. No maternal toxicity was observed (Willhite, 1981). DMA (sodium salt, 900–1000 mg/kg) induced (3–100% of fetuses) gross (cleft palate and lip, micromelia, syndactyly, exencephaly, talipes) and skeletal (fused ribs) fetal malformations after i.p. administration on one of days 8–12 of gestation. Up to 50% of the pregnant hamsters in this study died after i.p. administration of DMA (Hood et al., 1982).

Rogers et al. (1981) examined the effect of continuous oral exposure of DMA during days 7–16 of gestation in pregnant mice (200–600 mg/kg/day) and rats (7.5–60 mg/kg/day). They observed significant fetal mortality in mice at 600 mg/kg/day and rats at 50–60 mg/kg/day as well as a significant decrease in fetal weight gain in mice at 400–600 mg/kg and rats at 40–60 mg/kg. Cleft palate in the mice was the major teratogenic response of DMA and was observed at the two highest doses. There was also a significantly decreased incidence of supernumerary ribs. In the rat, the average number of sternal and caudal ossifications were decreased at the two highest doses, and the percentage of irregular palatine rugae increased significantly with dose. A dose-related decrease in maternal weight gain and increase in lethality occurred at the highest dose for the mice (59%) and the two highest doses for the rat (14–67%). Based on these studies, DMA is both fetotoxic and teratogenic in rats and mice. The doses required to produce these effects are clearly maternally toxic in the mouse and close to maternally toxic in the rat. At present, it is unclear how developmental toxicity observed in experimental animals administered inorganic arsenic (Golub et al., 1998) is related to developmental toxicity observed after DMA administration.

3. Cytotoxicity and genotoxicity

DMA is mutagenic in *Escherichia coli* B tester strains, but only at a very high concentration, i.e.

10 mM (Yamanaka et al., 1989c). Experiments indicated that a methylated arsine metabolite was formed, and because the mutagenic effect required the presence of oxygen, it was suggested that a reactive species formed from the reaction of dimethylarsine and oxygen, perhaps a peroxyl radical, may be the ultimate mutagenic metabolite.

DMA is genotoxic in assays using mammalian and human cells (Endo et al., 1992; Oya-Ohta et al., 1996; Eguchi et al., 1997; Moore et al., 1997). Excess tetraploids and mitotic arrest are induced in Chinese hamster V79 lung cells exposed to DMA at concentrations in excess of 0.7 mM, but not in cells exposed to arsenite or arsenate. MMA was less potent than DMA, and TMAO was more potent in inducing both mitotic arrest and tetraploids. In these same studies, DMA was 4000-, 80- and fivefold less cytotoxic compared to arsenite, arsenate and MMA, respectively (Eguchi et al., 1997). It has been suggested that the higher mitotic toxicity reported for organoarsenicals in some studies is a function of their greater disruptive effects on the microtubular organization of the cell (Bernstam and Nriagu, 2000). Moore et al. (1997) reported that DMA induced clastogenic effects in L5 178Y/TK$^{+/-}$ mouse lymphoma cells at concentrations greater than 10 000 μg/ml, whereas MMA, arsenate and arsenite were active at concentrations of 2500–5000, 10–14 and 1–2 μg/ml, respectively.

In human cells, DMA inhibits lymphocyte phytohemagluttin-M stimulated mitogenesis at concentrations of 125–250 μg/ml (Endo et al., 1992). Oya-Ohta et al. (1996) reported that DMA causes chromatid breaks in human umbilical cord fibroblasts at concentrations in excess of 7 mM. In these studies, the clastogenic effects of DMA were suppressed by depletion of glutathione (GSH) with buthione sulfoximine (BSO), and DMA was still highly clastogenic to GSH-depleted cells when the cells were incubated with 5–10 mM added GSH. The opposite effects were observed with arsenate, arsenite and MMA, and the authors suggested that GSH might be involved in the expression of the clastogenic actions of DMA.

DMA (1–5 mM) induced apoptosis (programmed cell death) in human renal carcinoma HL-60 cells, whereas MMA and TMAO were ineffective (Ochi et al., 1996). The apoptotic response induced by DMA was greater than that observed with sodium arsenite, but higher doses of DMA were required, and the concentrations of arsenite that could be tested (0.01–0.05 mM) were limited by cytotoxicity. GSH may play a unique role in the apoptotic response induced by DMA because depletion of cellular GSH by BSO diminished the DMA-induced apoptotic response. In contrast, the apoptotic response to inorganic arsenic in GSH-depleted cells was increased. Interestingly, the mechanism by which arsenic trioxide (As_2O_3) acts as a chemotherapeutic agent in acute promyelocytic leukemia (APL) is by preferential apoptosis of APL cells at high concentrations (2–5 μM) and partial differentiation at low concentrations (0.1–0.5μM) (Chen et al., 1997).

Much work over the past 10 years has focused on the DNA single-strand scissions and DNA-protein cross-links that are observed in human alveolar type II cells (L-132) after incubation with DMA (10 mM) (Tezuka et al., 1993; Yamanaka et al., 1993; Kato et al., 1994; Rin et al., 1995; Yamanaka et al., 1995, 1997). It has been proposed that the genotoxic effects are due to a DMA peroxyl radical, which is formed by the reaction of dimethylarsine, a metabolite of DMA, with oxygen (Yamanaka et al., 1989b, 1990). Tezuka et al. (1993) proposed that DMA actually forms an adduct with DNA before the appearance of the single-strand scissions. This hypothesis is based on the observation of decreased DNA synthesis soon after exposure to DMA, and a shorter nascent DNA chain length of DMA-exposed cells. The proposed adduct renders the DNA susceptible to UV light- (Tezuka et al., 1993) or superoxide radical-induced single-strand scissions (Rin et al., 1995). Alternatively, apurinic/apyriminidic sites may form where the initial damage occurred (Yamanaka et al., 1995), and the damaged DNA may undergo beta-elimination to form DNA single-strand scissions or a Schiff-base reaction to form DNA-protein cross-links.

DNA single-strand scissions and DNA-protein cross-links are also specifically produced in mouse and rat lung after acute oral administration of DMA (1500 mg/kg) (Yamanaka et al., 1989a,b,

1991, 1993). The damage is not observed until 12 h after exposure and is repaired by 24 h. Brown et al. (1997) also observed increased DNA single-strand scissions in rat lung after administration of two doses of DMA (387 mg/kg) at 21 and 4 h before sacrifice. These lesions are not observed in other tissues (Yamanaka et al., 1989a; Brown et al., 1997). One limitation with several of these studies is the high dose (1500 mg/kg) of DMA administered. It is unclear whether concentrations of DMA this high would be achieved in lung after exposure to DMA or inorganic arsenic under realistic conditions. Whether DMA accumulates in lung under conditions of chronic exposure to inorganic arsenic is also unknown. It is worthy of note, however, that following i.v. administration in mice, there is dose-dependent prolonged retention of DMA in lung (Vahter et al., 1984; Hughes et al., 2000).

4. Initiation-promotion assays

Recent initiation-promotion studies have demonstrated that DMA acts as a multi-organ tumor promoter in rodents (Yamamoto et al., 1995; Wanibuchi et al., 1996; Yamanaka et al., 1996, 2000). Yamamoto et al. (1995) sequentially administered five carcinogens (diethylnitrosamine, *N*-methyl-*N*-nitrosourea, 1,2-dimethylhydrazine, *N*-butyl-*N*-(4-hydroxy-butyl)nitrosamine, *N*-bis(2-hydroxypropyl)nitros-amine) to male F344/DuCrj rats over a 4 week period. After a 2 week hiatus, groups of rats received 0, 50, 100, 200 or 400 ppm DMA in their drinking water for 24 weeks prior to termination; survival was not adversely affected in the rats. DMA exposure significantly prpmoted tumor development in urinary bladder, kidney, liver and thyroid gland with the strongest response observed in urinary bladder. Lung tumors were not observed in animals treated with the five carcinogens and promoted with DMA. In initiated rats, DMA exposure also significantly increased the number of hepatic (GSH 5-transferase placental form-positive foci) and renal (atypical tubules) preneoplastic lesions. Ornithine decarboxylase activity, a biological marker of cell proliferation, was significantly elevated in kidney of rats receiving 100 ppm DMA in drinking water compared to controls.

Wanibuchi et al. (1996) further studied the promotion of bladder carcinogenesis by DMA because exposure to inorganic arsenic in drinking water is strongly associated with the development of bladder cancer in humans (NRC, 1999). Male F344 rats were initiated with *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine (0.05% in drinking water for 4 weeks) and then administered 0, 2, 10, 25, 50 or 100 ppm DMA in drinking water for 32 weeks. There was a significant dose-dependent increase in preneoplastic lesions, papillomas and carcinomas in the bladder at 25 ppm and higher. No preneoplastic lesions or tumors were observed in rats treated with DMA alone; survival, body weight and drinking water consumption were not adversely affected in these studies. Urinary pH also did not differ significantly among DMA-exposed rats. This is of interest because it has been reported that increased cell proliferation in urothelium in rat bladder carcinogenesis is correlated with urinary pH (Fukushima et al., 1986).

In this same study, Wanibuchi et al. (1996) reported that after an 8 week exposure to DMA alone, scanning electron microscopic examination of the urinary bladder showed increased alteration of epithelial cell surfaces (ropey or leafy microridges, short uniform microvilli, pleomorphic microvilli) and the 5-bromo-2′-deoxyuridine (BrdU) labeling index was significantly elevated in rats receiving 10 or 25 ppm DMA. The higher DMA exposure group (25 ppm) had a lower labeling index, which was suggested to result from a higher toxicity of DMA. The authors concluded that DMA may promote carcinogenesis in the urinary bladder by enhancing cell proliferation in bladder epithelium (Wanibuchi et al., 1996). The promotion of tumors in male rat bladder by DMA does not appear to be dependent on the presence of $\alpha_{2\mu}$-globulin (Li et al., 1998).

Cohen et al. (1999) reported similar findings to those of Wanibuchi et al. (1996) in female F344 rats fed 2, 10, 40 or 100 ppm DMA in the diet for 10 weeks. Urothelial hyperplasia and BrdU labeling index were significantly increased at 40 and 100 ppm, but not at 2 and 10 ppm. However, necrosis and proliferation were detectable by

scanning electron microscopy at the lower exposure levels. Urine volume and calcium were increased with decreased osmolality and creatinine at the highest exposure levels. Urinary pH was significantly elevated relative to controls, but did not differ markedly between DMA exposure groups. No precipitate, microcrystalluria or calculi formation in urine related to DMA exposure were observed, although increased calcification occurred in the kidneys. The authors suggested that the DMA-induced rat bladder cancer is a consequence of cytotoxicity and regenerative hyperplasia of the urothelium.

DMA also has tumor-promoting activity in mice (Yamanaka et al., 1996, 2000). Yamanaka et al. (1996) initiated male ddY mice with 4-nitroquinoline 1-oxide (4-NQO, 10 mg/kg) and then exposed them to 0, 200 or 400 ppm in drinking water for 25 weeks. The percentage of mice with pulmonary tumor nodules was greater and the number of tumors per mouse was significantly increased in the 4-NQO + DMA group than in groups exposed only to 4-NQO itself or 4-NQO plus the promoter glycerol. Because the 4-NQO-induced tumors were primarily benign, but advanced to adenocarcinomas after exposure to DMA, the authors suggested DMA may be a tumor progressor in mouse lung.

Yamanaka et al. (2000) recently reported that skin tumors induced by UVB (2 kJ/m^2, twice weekly) in hairless mice are promoted by exposure to 1000 ppm DMA in drinking water for 25 weeks (but not to 400 ppm DMA). Malignant tumors with severe atypia were observed, but only in mice treated with UVB and 1000 ppm DMA. No adverse effects on body weight gain or survival were reported in this study.

5. Carcinogenicity and related mechanistic studies

Multiple reports that DMA acts as a multi-organ tumor promotor in rodents have prompted the study of DMA in lifetime rodent bioassays (Van Gemert and Eldan, 1998; Arnold et al., 1999; Wei et al., 1999). Van Gemert and Eldan (1998) reported results of a 2 year DMA feeding bioassay in male and female B6C3F1 mice and F344 rats at the 3rd International Conference on Arsenic Exposure and Health Effects. No evidence of treatment-related tumors was reported in either sex of mice exposed to 8, 40, 200 or 500 ppm DMA in the diet for 104 weeks. However, there was an increased incidence of urinary transitional cell bladder tumors with hyperplasia in both sexes of rats. This effect was statistically significant in females, but not males at the highest exposure level of 100 ppm DMA in the diet. The greater sensitivity of the female rat is consistent with observations of the renal toxicity of DMA in an earlier short-term (4 week) exposure study (Murai et al., 1993).

Wei et al. (1999) have recently reported that DMA is a rat bladder carcinogen after a 2 year drinking water exposure. Male F344/DuCrj rats received 0, 12.5, 50 or 200 ppm DMA in drinking water for 104 weeks starting at age 10 weeks. Survival rates between experimental groups did not differ, and bladder tumors were not observed in the control group. There was a dose-dependent incidence of bladder tumors in the exposed groups (12.5 ppm: 0/33 rats; 50 ppm: 8/31 rats; 200 ppm: 12/31). Histologically, the carcinomas were transitional cell carcinomas. Exposure to DMA did not affect urinary pH, and no bladder calculi were observed in these animals. The authors concluded that DMA is a weak carcinogen and that long periods of exposure are required because the first tumors were not observed until week 97 of exposure.

Arnold et al. (1999) designed a study specifically to investigate the mode of action and dose–response relationship for urothelial injury in rats and to evaluate the reversibility of this effect. This study used primarily female rats because of their greater sensitivity to the effects of DMA. In female rats fed 0, 2, 10, 40 or 100 ppm DMA in Purina 5002 diet for 10 weeks, there was a statistically significant increase in urothelial hyperplasia at 100 ppm and BrdU labeling index at 40 and 100 ppm. The reversibility of these lesions was evaluated by comparing female rats exposed to 0 ppm DMA for 20 weeks (control), 100 ppm DMA for 20 weeks and 100 ppm DMA for 10 weeks followed by 0 ppm for 10 weeks. In rats exposed to DMA for 10 weeks followed by 10 weeks of no

exposure, bladder histology and BrdU labeling index did not differ significantly from control rats, whereas in the 20 week DMA-exposed rats, both urothelial hyperplasia and BrdU labeling index were significantly increased compared to control. These findings indicate that DMA-induced urothelial injury is reversible after a 10 week exposure.

Arnold et al. (1999) also evaluated a number of urine-related parameters in these studies and compared the effects of different diets that are known to modulate urinary pH. The latter studies were motivated by the fact that a variety of chemicals have been shown to produce urinary changes (e.g. urinary pH, protein, calcium) secondary to their administration that further exacerbate the toxicity of said chemicals (Cohen, 1995, 1998). Two different diets (Purina and Altromin) were compared in these studies, and although diet-related changes in urinary pH did occur, there was no difference in the occurrence of DMA-induced urothelial hyperpl asia. Consistent with the results of Wei et al. (1999), the authors reported no evidence for the formation of microcrystals, urinary precipitates or calculi. However, marked increases in urinary calcium as well as increased renal calcification related to DMA administration were observed, and these observations correlated well with the severity of urothelial injury in rats fed the Purina diet, but not the Altromin diet. The authors suggested that bladder tumors in rats are a consequence of regenerative hyperplasia secondary to urothelial cytotoxicity, which may be related to altered calcium metabolism and/or DMA or its metabolites.

6. Conclusions

The key question raised by DMA research published over the last decade is how relevant to human risk assessment is the tumor promoting activity and carcinogenicity reported for DMA in laboratory animals? The weight of evidence indicates that DMA has multi-organ tumor promoting activity in two rodent species and is a complete carcinogen in the rat urinary bladder, although the doses required to produce these effects are relatively high. Mechanistic studies indicate several important conclusions regarding the effects on urinary bladder observed in rats: (1) there is a long latency period required for the induction of bladder tumors, (2) the presumptive precursor lesion to bladder tumors (urothelial hyperplasia) is reversible, and (3) the observed urothelial hyperplasia does not appear to be related to formation of microcrystals or urinary calculi. In aggregate, these studies support the conclusion of various authors that the tumorigenic effect of DMA in rat urinary bladder is unlikely to be mediated through direct interaction with DNA.

The relevancy of DMA-induced bladder toxicity and carcinogenicity in the rat to humans may be questioned on the basis of known differences in disposition of DMA in the rat compared to both humans and other common laboratory animals. The biological half-life of DMA in the rat is markedly longer (approximately fivefold) than that of the mouse and apparently the result of binding of DMA to rat hemoglobin (Stevens et al., 1977; Vahter et al., 1984). The effect of this species difference on long-term tissue distribution and retention of DMA has not been directly evaluated; however, one would expect that under conditions of chronic exposure to inorganic arsenic or DMA, the rat would experience higher continuous concentrations of DMA in both kidney and urinary bladder since the kidney is the primary excretory organ for DMA, and hemoglobin serves as a long-term storage and release depot for DMA in the rat. This may in fact be the basis for the greater sensitivity of the rat compared to the mouse for DMA-induced toxicity that can be inferred from various studies (e.g. Rogers et al., 1981; Van Gemert and Eldan, 1998).

While there are clear reasons to be cautious in the direct application of rat DMA carcinogenicity data to human risk assessment, these findings should not be dismissed as irrelevant as regards to the mechanism of cancer induction by inorganic arsenic. There are several reasons for this. Positive results have been reported in a variety of in-vitro experimental systems, e.g. apoptosis, clastogenesis, tetraploidy, mitotic arrest and DNA single-strand scissions. Tumor-promoting activity has

been demonstrated in species other than the rat, e.g. promotion of mouse skin and lung tumors. Additionally, DMA does have organ-specific effects in both lung and urinary bladder, and these are known target organs for inorganic arsenic carcinogenesis in humans (NRC, 1999). In addition, recent evidence suggests that trivalent methylated arsenicals are both highly cytotoxic (Styblo et al., 2000) and able to interact directly with DNA to produce genotoxic effects (Mass et al., 2001). The fact that some mechanistic studies have suggested that metabolic products of DMA are responsible for observed effects (e.g. DNA single-strand scissions) and that relatively large amounts of intermediary trivalent methylated arsenicals are formed during metabolism of inorganic arsenic, strongly suggests that DMA plays a role in the carcinogenesis of inorganic arsenic.

7. Disclaimer

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