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WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Date: **December 19, 2000**

MEMORANDUM

SUBJECT: ***Methanearsonic Acid and its Sodium and Calcium Salts*** - Revised Toxicology Disciplinary Chapter for the Reregistration Eligibility Decision

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PC Code Nos.: 013806, 013803 and 013802
Chemicals: MSMA, DSMA, and CAMA
DP BARCODE: D271308
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ACTION REQUESTED: Prepare a toxicology chapter for the RED for monosodium methanearsonic acid (MSMA), disodium methanearsonic acid (DSMA), and calcium methanearsonic acid (CAMA).

RESPONSE: The toxicology database for methanearsonic acid (MAA) has been reviewed by the Reregistration Branch II. All available toxicology data for MAA are applicable to MAA, MSMA, DSMA, and CAMA. MAA (methanearsonic acid) and its sodium and calcium salts including MSMA, DSMA and CAMA (monosodium methanearsonic acid, disodium methanearsonic acid, and calcium methanearsonic acid) were reviewed by the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) on July 13 and November 14, 2000 by the HED FQPA Safety Factor Committee on July 24 and December 11, 2000. Although there are data gaps for acute neurotoxicity, subchronic neurotoxicity and 28-day inhalation toxicity studies, the toxicology database for MAA is adequate to support a Reregistration Eligibility Decision (RED).

Methanearsonic Acid and its Sodium and Calcium Salts

CAMA, MSMA, and DSMA

PC Codes: 013806, 013803 and 013802

Toxicology Disciplinary Chapter for the Reregistration Eligibility Decision

December 19, 2000

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1.0 HAZARD CHARACTERIZATION

MSMA/DSMA are selective herbicides used on cotton, bearing citrus trees, non-bearing fruit, vines, and nut trees, grass grown for seed, golf courses and other ornamental turf, forestry (crown killer) and general weed control in non-crop areas such as rights of way, drainage ditches, and storage yards. They also have residential uses on lawns and for general weed control. CAMA is a selective herbicide used for post-emergent weed control of annual grasses and broadleaf weeds on residential lawns, golf courses and other ornamental turf. CAMA has been approved for both commercial and residential use.

Although additional studies are being required, the database for MAA is adequate for risk assessment purposes. Acute and subchronic neurotoxicity studies in mice in addition to a 28-day inhalation study are being required for MAA. The developmental neurotoxicity is not required at this time but this requirement will be reevaluated following review of a pending study with cacodylic acid. The target organ of MAA appears to be the gastrointestinal tract, particularly the large intestine. Effects such as histopathology of the cecum, rectum, and colon in addition to increased food consumption, incidence of diarrhea and mucoid feces were observed in mice, rats, and dogs. Vomiting and diarrhea, clinical signs consistent with arsenic poisoning in humans, were observed in the dog.

As stated above, no neurotoxicity studies are available for MAA at this time. There is no evidence of neurotoxicity observed in rat, rabbit, or dog. In the 104-week oncogenicity study in mice, females of the 46 and 104 mg/kg/day groups exhibited increased incidences of hypersensitivity and tonic convulsions. Additional evidence of potential neurotoxicity observed in mice following oral exposure to MSMA is found in the literature. Lopez and Judd (1979) exposed to mice to 477 ppm of MSMA in tapwater for 14 days and observed nest-building behavior in male and female mice. Females treated with MSMA produced significantly smaller nests than control females whereas treated males collected the same amount of cotton as control mice. Prukop and Savage (1986) performed a one-generation reproduction study in mice gavaged with MSMA at 11.9 or 119 mg/kg every other day for 10 weeks. Decreased male fertility was observed at both doses compared to control. Only 50% of the females at 11.9 mg/kg/dose and none of the females at 119 mg/kg/dose became pregnant. This decrease in male fertility was also observed in the guideline two-generation reproduction study in F_0 and F_1 generation of the 61.4 mg/kg/day group. Also notable in this study is the observation that in two of four females in the 11.9 mg/kg/dose group that produced litters, the mothers "did not build a nest, rarely huddled over the young, or retrieved them when they were separated from the young, all of which are maternal instincts." In these two litters, all of the young mice died with 2 to 3 days of birth. This postnatal litter loss parallels postnatal litter loss observed in rats of the guideline two-generation reproduction study. In the guideline study, an equivocal increase in whole litter loss and increased postnatal pup death was observed at 17.2 mg/kg/day. Based on the evidence in both the Lopez and Judd (1979) and the Prukop and Savage (1986) studies, it is plausible that the whole litter loss observed in the two-generation reproduction study is due to changes in the nurturing behavior of the mothers and not a direct toxic effect on the pups. Therefore, the increased pup death is not an indication of infant susceptibility but rather potential neurotoxicity in the females.

These literature studies in mice combined with the clinical signs of hypersensitivity and tonic convulsions observed in female mice in the oncogenicity study provide the justification for the requirement of the acute and subchronic neurotoxicity studies. These studies should be performed using mice.

There is no quantitative or qualitative evidence of increased susceptibility of rats or rabbit fetuses to *in utero* exposure in available developmental toxicities. In the rabbit developmental toxicity study, developmental effects were observed at doses greater than maternally toxic doses. These developmental effects included an increased incidence of skeletal variations in the numbers of 13th thoracic vertebra with ribs and 8th lumbar vertebra) at 12 mg/kg/day. At 12 mg/kg/day, abortions in two rabbits were attributed to decreased body weight gain (mean -75% compared to control). The maternal NOAEL in this rabbit developmental toxicity study is 3 mg/kg/day based on clinical signs and decreased food consumption. The developmental NOAEL is 7 mg/kg/day. In the rat developmental toxicity study, developmental effects were observed at doses greater than maternally toxic doses. In the rat developmental toxicity study, the developmental NOAEL of 100 mg/kg/day is based on decreased fetal body weight was observed at 500 mg/kg/day. The maternal NOAEL of 10 mg/kg/day is based on decreased body weight gains and food consumption observed at 100 and 500 mg/kg/day.

The HIARC classified MAA as **"not likely"** a human carcinogen. Increased incidences of parathyroid adenomas with a positive dose-related trend were observed in both Fischer rats (males: 1/52, 0/49, 4/53, and 4/45 for the control, 50, 400 ppm and high-dose groups, respectively; females: 0/46, 0/44, 0/40, and 4/45 for control, 50 ppm, 400 ppm, and high-dose groups, respectively), although statistical significance was not attained with respect to either sex. It is notable that only the benign tumors were increased and there was no increase in tumor incidence in the mouse oncogenicity study. The acceptable genetic toxicology studies indicate that MAA is not mutagenic in bacteria (*Salmonella typhimurium*) or cultured mammalian cells (Chinese hamster ovary). Similarly, MAA did not induce unscheduled DNA synthesis (UDS) in primary rat hepatocytes.

In a metabolism study in rat, analysis of fecal and urinary samples by HPLC and TLC revealed that the radioactivity of all preparative fractions was associated with parent compound, MSMA, and two unknown metabolites. Unknown metabolite A was detected in the urine and feces (6.7/6.1, 1.8/2.6, and 3.7/3.7%). Unknown metabolite B was detected in the urine and feces at 0.7% of the administered dose for both males and females. Parent compound was detected in the urine and feces of all groups at 79.7-97.4% of the administered dose.

2.0 REQUIREMENTS

The requirements (CFR 158.340) for food use for MAA and its sodium and calcium Salts are in Table 1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Table 1.

Test		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	yes
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Subchronic (rodent)	yes	no
870.3150	Oral Subchronic (nonrodent)	yes	1
870.3200	21-Day Dermal	yes	yes
870.3250	90-Day Dermal	no	no
870.3465	90-Day Inhalation	no,2	no, 2
870.3700a	Developmental Toxicity (rodent)	yes	yes
870.3700b	Developmental Toxicity (nonrodent)	yes	yes
870.3800	Reproduction	yes	yes
870.4100a	Chronic Toxicity (rodent)	3	3
870.4100b	Chronic Toxicity (nonrodent)	yes	yes
870.4200a	Oncogenicity (rat)	3	3
870.4200b	Oncogenicity (mouse)	yes	yes
870.4300	Chronic/Oncogenicity	yes	yes
870.5100	Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300	Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5375	Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5550	Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a	Acute Delayed Neurotox. (hen)	no	no
870.6100b	90-Day Neurotoxicity (hen)	no	no
870.6200a	Acute Neurotox. Screening Battery (rat)	yes	4
870.6200b	90 Day Neuro. Screening Battery (rat)	yes	4
870.6300	Develop. Neuro	no	no
870.7485	General Metabolism	yes	yes
870.7600	Dermal Penetration	no	no, 5
Special Studies for Ocular Effects			
	Acute Oral (rat)	no	no
	Subchronic Oral (rat)	no	no
	Six-month Oral (dog)	no	no

1. Requirement satisfied by chronic oral toxicity in dog
2. 28-Day inhalation toxicity study required by the HIARC (7/13/2000)
3. Requirement satisfied by combined chronic/oncogenicity study in rat.
4. Acute and subchronic neurotoxicity (oral) are required by the HIARC (7/13/2000).
5. The dermal absorption factor for cacodylic acid was selected by HIARC (7/13/2000) for use in risk assessment.

3.0 DATA GAP(S)

Acute neurotoxicity in mice, OPPTS 870.6200a,
Subchronic neurotoxicity in mice OPPTS 870.6200b,
28-day Subchronic inhalation toxicity, OPPTS 870.3465

4.0 HAZARD ASSESSMENT

4.1 Acute Toxicity

Adequacy of data base for acute toxicity: The acute toxicity data on MSMA formulations containing 37-38% active ingredient, technical DSMA, and CAMA formulations containing 10.3% active ingredient are summarized below in Table 2.

The MSMA formulation has moderate acute oral toxicity (Category II) and low acute dermal and inhalation toxicity (Category III). The MSMA formulation did not cause dermal sensitization but resulted in moderate erythema at 72 hours (Category III).

Technical DSMA has low acute oral, dermal, and inhalation toxicity (Categories III and IV). Technical DSMA does not cause dermal irritation or dermal sensitization.

The CAMA formulation has low acute oral, dermal, and inhalation toxicity (Category IV), did not cause dermal sensitization and resulted in slight skin irritation (Category IV).

Table 2.

ACUTE TOXICITY

Acute Toxicity of MSMA*

Guideline No.	Study Type	MRIDs #	Results	Toxicity Category
81-1	Acute Oral, rat	00145491	LD_{50} = 494 mg/kg (M&F)	II
81-2	Acute Dermal, rabbit	41890001	LD_{50} > 2000 mg/kg	III
81-3	Acute Inhalation, rat	42604601	LC_{50} = 2.20 mg/L	III
81-4	Primary Eye Irritation, rabbit	00105173	Iris and conjunctival irritation	III
81-5	Primary Skin Irritation, rabbit	00105174	Moderate erythema at 72 hours	III
81-6	Dermal Sensitization, guinea pig	41890002	None	
81-8	Acute Neurotoxicity	N/A		

*Data presented in table are for formulations containing MSMA, 37-38% a.i.

Acute Toxicity of DSMA*

Guideline No.	Study Type	MRIDs #	Results	Toxicity Category
81-1	Acute Oral, rat	41892004	LD_{50} = 1935 (1631-2295) mg/kg (M&F)	III
81-2	Acute Dermal, rabbit	41892005	LD_{50} > 2000 mg/kg	III
81-3	Acute Inhalation, rat	41892006	LC_{50} > 6 mg/L	IV
81-4	Primary Eye Irritation, rabbit	41892007	Redness and chemosis of the conjunctivae	III
81-5	Primary Skin Irritation, rabbit	41892008	No erythema or edema	IV
81-6	Dermal Sensitization, guinea pig	41890009	None	
81-8	Acute Neurotoxicity	N/A		

*Data presented is for technical DSMA.

Acute Toxicity of CAMA*

Guideline No.	Study Type	MRIDs #	Results	Toxicity Category
81-1	Acute Oral, rat	42880201	LD_{50} > 5000 mg/kg (M&F)	IV
81-2	Acute Dermal, rat	42900101	LD_{50} > 5000 mg/kg	IV
81-3	Acute Inhalation, rat	42900102	LC_{50} > 5 mg/L	IV
81-4	Primary Eye Irritation, rabbit	42900202	Mild eye irritant	III
81-5	Primary Skin Irritation, rabbit	42900203	Slight skin irritant	IV
81-6	Dermal Sensitization, rabbit	42900103	None	
81-8	Acute Neurotoxicity	N/A		

*Acute oral studies listed in table represent a formulation with 10.3% a.i.

4.2 Subchronic Toxicity

Adequacy of data base for subchronic toxicity:
Although incomplete, the data base for subchronic toxicity is considered adequate for risk assessment purposes. The available subchronic oral toxicity study in mice is unacceptable due to numerous deficiencies. A subchronic neurotoxicity study in mice is required at this time (HIARC, 7/13/2000). The 21-day dermal toxicity study in rabbits showed no systemic or dermal toxicity up to the limit dose of 1000 mg/kg/day. The 90-day inhalation toxicity study shown below was performed using *cacodylic acid* and was selected by the HIARC (7/13/2000) for use in risk assessment for MAA and its sodium and calcium salts. In this inhalation toxicity study, the presence of moderate and marked intracytoplasmic eosinophilic granules in the cells of the nasal turbinates was observed. A 28-day inhalation toxicity study in methanearsonic acid is required at this time (HIARC, 7/13/2000).

870.3100 90-Day Oral Toxicity - Rat

Not available for MAA and its sodium and calcium salts.

870.3100 90-Day Oral Toxicity - Mouse

EXECUTIVE SUMMARY: In a subchronic oral toxicity study (MRID 40632601), methanearsonic acid (>99.8% a.i., Batch #: 10784) was administered in the diet to groups of 12 male and 12 female Charles River B6C3F1 hybrid mice at dose levels of 0, 10, 100, 500, and 1250 ppm (0, 2.1, 22.5, 110.6, and 288.6 mg/kg/day for males and 0, 2.8, 27.5, 137.4, and 342.5 mg/kg/day for

females) for 14 weeks. This study was intended as a preliminary, dose selection study and was not conducted in accordance with Good Laboratory Practice standards. The following observations were made: clinical signs, food consumption, body weight, white differential cell counts, gross necropsy, organ weights, and histopathology.

No deaths occurred during this study, and there were no treatment related effects on clinical signs, absolute body weights, food consumption, differential leukocyte counts, organ weights, or gross and histopathological findings. Ophthalmoscopic examinations were not performed. Blood was not collected for hematology and clinical chemistry.
Based on the data presented in this study, a LOAEL and NOAEL can not be established.

This subchronic oral toxicity study in rats is classified as **Unacceptable (non-upgradable)/Guideline** and does not satisfy the [OPPTS: 870.3100 (§82-1)] Subdivision F guideline requirements for a subchronic study. The numerous deficiencies in the conduct of this study preclude meaningful evaluation of the data.

870.3150 90-Day Oral Toxicity - Dog

Requirement satisfied by the one-year chronic oral toxicity study in dog (870.4100).

870.3200 21/28-Day Dermal Toxicity – Rabbit

EXECUTIVE SUMMARY: In a 21-day dermal toxicity study (MRID 41872701/42659701), methanearsonic acid (99.4% a.i., Batch #0030401) was administered dermally to 5 New Zealand white rabbits/sex/group at doses of 0, 100, 300, or 1000 mg/kg/day for 6 hours/day, 5 days/week for 21 days.

There were no treatment related effects on mortality, clinical signs, mean body weight, mean body weight gain, hematology, urinalysis, gross necropsy findings, or histopathology findings. Opthalmological examinations were not conducted. Food consumption was statistically decreased during one interval at 100 mg/kg/day and during two intervals at 1000 mg/kg/day (none of the intervals were not defined). Mean cholesterol concentration was statistically ($p<0.05$) decreased in males at 300 and 1000 mg/kg/day. In females, mean cholesterol concentration was decreased at 100 and 300 mg/kg/day as compared to controls, and increased at 1000 mg/kg/day, but statistical significance was not attained.

In the results section of the original review, it is mentioned that the kidney to body weight ratio and liver to body weight ratio were significantly ($p<0.05$ or $p<0.01$) increased in females at the 100 mg/kg/day dose level, and the liver to body weight ratio was significantly ($p<0.05$ or $p<0.01$) increased in females at the 1000 mg/kg/day dose level. It is important to note that the absolute liver and kidney weights were similar to control among all dose groups. These organ weight findings are considered incidental. Body weights of female rabbits in the 1000 mg/kg/day group at initiation of the study were slightly lower than control (2249 g and 2180 g for control and 1000 mg/kg/day, respectively). Although body weight gain was similar among

all groups, body weights of the high dose group continued to be slightly lower for the duration of the study (at termination 2697 g vs 2509 g for control and 1000 mg/kg/day, respectively).

The systemic toxicity LOAEL > 1000 mg/kg/day. The systemic toxicity NOAEL was = 1000 mg/kg/day.

There was no edema or erythema noted at the exposure sites of any dose group. There were no histological dermatopathology findings at the 1000 mg/kg/day dose level as compared to the control group. **The dermal irritation LOAEL > 1000 mg/kg/day. The dermal irritation NOAEL = 1000 mg/kg/day.**

This study was previously classified unacceptable but has been upgraded to acceptable based on submitted analytical data indicating that the purity MAA in the aqueous solution used for dosing was > 99%.

870.3465 90-Day Inhalation – Rat

EXECUTIVE SUMMARY: In a 90-day toxicity study (MRID 44700301), ***cacodylic acid*** . (Cacodylate 3.25) (active ingredients: cacodylic acid (4.9%) and sodium cacodylate (28.4%); batch 095/93) was administered by inhalation (nose only) to 10 rats/sex/dose at aerosol concentrations of 10, 34 and 100 mg/m^3 (0.01, 0.034, or 0.1 mg/L/day). The control group received filtered air only and the cacodylate was administered as received from the sponsor. Exposures were 6 hours/day, 5 days/week, for a total of 67 (males) or 68 (females) exposures. The mass median aerodynamic diameter (50% size) and geometric standard deviation for Groups 2, 3, and 4 was 3.3 ± 2.8 µm, 2.5 ± 2.0 µm, and 2.3 ± 2.1 µm, respectively.

Mortality, body weights, organ weights, ocular abnormalities, clinical chemistry, and hematology parameters were not affected by treatment. Histomorphologic changes were restricted to the nasal cavity/turbinates of male and female rats of the 0.034 and 0.100 mg/L/day exposure groups and consisted of an increased amount of intracytoplasmic eosinophilic globules (IEG) in the olfactory sustentacular cells and columnar epithelium in the posterior and ventral regions of the nasal cavity. There was no evidence of any adverse effect in any of the other areas of the respiratory tract or any other tissue or organ examined.

Under the conditions of this study, the LOAEL is 0.034 mg/L/day in both male and female rats based on the presence of moderate and marked intracytoplasmic eosinophilic granules (IEG) in the cells of the nasal turbinates. The NOAEL is 0.010 mg/L/day.

This study is classified as **acceptable (Guideline)**, and meets the requirements of Guideline 82-4.

4.3 Prenatal Developmental Toxicity

Adequacy of data base for Prenatal Developmental Toxicity: The data base for prenatal developmental toxicity is considered complete. No additional studies are required at this time.

There is no quantitative or qualitative evidence of increased susceptibility of rats or rabbit fetuses to *in utero* exposure in available developmental toxicities. In the rabbit developmental toxicity study, developmental effects were observed at doses greater than maternally toxic doses.

870.3700a Prenatal Developmental Toxicity Study - Rat

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 41926401), methanearsonic acid (99.73% a.i.; Batch No. 107/84) was administered in deionized water by gavage to 25 mated female CD® (Sprague-Dawley) rats per group at doses of 0, 10, 100, or 500 mg/kg/day on gestation days (GD) 6-15, inclusive. On GD 20, dams were sacrificed and necropsied. Weights of uteri and ovaries, the number of corpora lutea, and the numbers and locations of live and dead fetuses, early and late resorptions, and implantation sites were recorded. All fetuses were weighed, sexed, and examined externally. Approximately one-half of each litter was evaluated for visceral abnormalities by microdissection, then decapitated and the heads fixed in Bouin's solution for subsequent evaluation. The remaining one-half of each litter was processed for skeletal examination.

One rat in the 500 mg/kg/day group died on GD 11 after exhibiting ano-genital staining on GD 10 and weight loss (63 g) during the GD 6-11 interval. At 500 mg/kg/day, there was a slightly increased total incidence of ano-genital staining (7 vs 0) and soft stools (7 vs 0) during treatment.

Mean body weight gain was significantly decreased at the 100 and 500 mg/kg/day dose levels during GD 12-16 (58 and 77% of controls, respectively; $p<0.05$ or $p<0.01$) and GD 6-16 (60 and 83% of controls, respectively; $p<0.01$). Additionally, rats of the 500 mg/kg/day exhibited a mean weight loss during GD 6-9 (-3 g vs. +10 g for controls; $p<0.01$). A dose-dependant decrease in gravid uterine weight was observed (80 g, 76 g, 75 g, and 74 g for control, 10, 100, and 500 mg/kg/day, respectively). This decrease in gravid uterine weight is correlated with the decreased mean fetal body weight observed at 500 mg/kg/day. Group mean food consumption in the 100 and 500 mg/kg/day groups was decreased compared to control at one or more intervals during treatment. **The maternal toxicity LOAEL is 100 mg/kg/day, based on decreased body weight gain and food consumption, and the maternal toxicity NOAEL is 10 mg/kg/day.**

There were no differences between the control and treated groups for number of corpora lutea per dam, number of implantation sites per dam, preimplantation loss, viable fetuses per litter, total resorptions or number of litters with resorptions. At 500 mg/kg/day, mean fetal weight was decreased (9% less than controls; $p<0.01$). There were no treatment related effects on external or visceral malformations or variations. There were also no treatment related effects on skeletal observations. **The developmental toxicity LOAEL is 500 mg/kg/day, based on decreased mean fetal body weight. The developmental toxicity NOAEL is 100 mg/kg/day.**

This study is classified as **Acceptable/Guideline** and satisfies the requirements for a developmental toxicity study [870.3700 (§83-3a)] in rats.

870.3700b Prenatal Developmental Toxicity Study - Rabbit

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 15939001), methanearsonic acid (purity >99.8%; Batch No. 107/84) was administered in distilled water by gavage to 14 mated New Zealand white rabbits per group at doses of 0, 1, 3, or 7 mg/kg/day on gestation days (GD) 7-19, inclusive. Subsequent groups of 13-14 mated New Zealand white rabbits were dosed with 0 and 12 mg/kg/day test material. On GD 29, surviving does were sacrificed and necropsied. Weights of uteri, and the number and locations of live and dead fetuses, early and late resorptions, implantations and corpora lutea were recorded. Fetal weights, crown-rump lengths, and external examination findings were recorded. All fetuses were subjected to fresh dissection, sexed internally, and processed and subjected to skeletal examination.

There were no treatment related deaths. Three animals (1 from control and 2 from 1 mg/kg/day group) died due to gavage error during the main study. Two females of the 12 mg/kg/day aborted and were killed on GD 25 and 29.

There was an increased incidence of orange discoloration of the urine in the 7 and 12 mg/kg/day groups (4 incidences in each group) compared to control (0 incidence). Increased incidence of soft feces and "few or no feces on undertray" at the 12 mg/kg/day dose level ($p<0.05$ or $p<0.01$) were also observed. A decrease in body weight gain (-76%) compared to control was observed during the dosing period for females in the 12 mg/kg/day group. Although maternal body weight change was decreased at the 7 mg/kg/day dose level for GD 7-8 and 10-13 intervals (29 and 63% less than controls), females in the 7 mg/kg/day actually gained 31% more weight during the dosing period than did controls.

Food consumption was decreased at 7 mg/kg/day for the GD 8-10 and 11-14 intervals (82 and 79% of controls, respectively; $p<0.01$) with a compensatory increase postdosing during the GD 20-23 interval (111% of controls; n.s.). At 12 mg/kg/day, food consumption was decreased for the GD 8-10, 11-14, 15-19, intervals (58-65% of controls; $p<0.001$), with compensatory increases postdosing during the GD 24-26 and 27-29 intervals (131-138% of controls; $p<0.01$). **The maternal toxicity LOAEL was 7 mg/kg/day, based on clinical signs (incidence of orange discoloration of the urine) and decreased food consumption. The maternal toxicity NOAEL was 3 mg/kg/day.**

There were no differences between the control and treated groups for number of corpora lutea, number of implantation sites, litter sizes, fetal sex ratios, fetal body weights, crown-rump lengths, or placental weights. There was a single incidence of total litter resorption at 7 mg/kg/day (all early resorptions), which resulted in increased mean early resorptions (1.0 vs. 0.4 for controls; n.s.); total resorptions were similar between groups. Although not observed at 3 mg/kg/day, increased pre-implantation loss was observed at 1 and 7 mg/kg/day (12.3, 19.0, 11.2, and 20.1% for 0, 1, 3, and 7 mg/kg/day groups, respectively; $p<0.001$) and at 12 mg/kg/day (15.1 vs. 10.5% for controls; $p<0.001$).

There were no treatment related effects on the occurrence of fetal external, visceral, or skeletal malformations. The total incidence of a 13th thoracic vertebra with ribs was increased in 12 mg/kg/day groups (1/97, 8/98, 3/124,1/95, 1/112, 13/80 fetuses from the control, 1, 3, 7, control-2, and 12 mg/kg/day groups); however the incidence at 3 and 7 mg/kg/day were similar to both set of controls. The total incidence of an 8th lumbar vertebra (5/97, 22/98, 7/124, 9/95, 27/112 and 51/80 fetuses from the control, 1, 3, 7, control-2, and 12 mg/kg/day groups, respectively; $p<0.001$).

The developmental toxicity LOAEL is 12 mg/kg/day, based on abortions and an increased incidence of skeletal variations (increased numbers of 13th thoracic vertebra with ribs and 8th lumbar vertebra). The developmental toxicity NOAEL is 7 mg/kg/day.

This study is classified as **Acceptable/Guideline** and satisfies the requirements for a developmental toxicity study in rabbits [OPPTS: 870.3700 (83-3b)].

4.4 Reproductive Toxicity

Adequacy of data base for Reproductive Toxicity: The data base for reproductive toxicity is considered complete. No additional studies are required at this time. In the acceptable two-generation reproductive toxicity study, systemic parental effects of increased food consumption with decreased body weight gain were consistent with gastrointestinal effects observed in chronic toxicity studies. Decreased fertility indexes was observed in male and female rats. In addition, an increased pup death attributed to possible maternal neurotoxicity was observed.

870.3800 Reproduction and Fertility Effects - Rat

EXECUTIVE SUMMARY: In a two-generation reproduction study (MRID 43178301), methanearsonic acid (MAA, 99.44% a.i., Batch No. 0030401) was administered to 30 F_0 and F_1 male and 30 F_0 and F_1 female CD® Sprague-Dawley derived rats per group at dietary concentrations of 0, 100, 300, or 1000 ppm. The dietary concentration corresponded to 5.6, 17.2, and 61.4 mg/kg/day, respectively, for F_0 and F_1 males averaged over the entire study and 7.5, 22.5, and 77.6 mg/kg/day, respectively, for F_0 and F_1 females averaged over the premating period. F_0 and F_1 males and females received treated or control food for a 14-week premating period; males remained on treatment until delivery of the last litter and females until weaning of the last litter. F_1 weanlings selected to produce the F_2 generation were weaned onto the same food as their parents.

Administration of MAA at doses of 100, 300, or 1000 caused no treatment-related effects on mortality or clinical signs in either F_0 or F_1 parental animals. Food consumption was increased in F_0 and F_1 males of the 300 and 1000 ppm groups, F_0 females of the 1000 ppm group, and F_1 females of the 300 and 1000 ppm groups. Although food consumption was increased, body weight and body weight gain were reduced by approximately 10% relative to control in males of

the F_0 generation at 300 and 1000 ppm level and in males of the F_1 generation at 1000 ppm. These results of increased food consumption and decreased body weight gain are consistent with results from chronic feeding studies in mice (MRID no. 42173201) and rats (MRID no. 41669001) and are therefore considered treatment related. No effects on absolute body weights or body weight gain were observed in F_0 or F_1 females during the premating, gestation, or lactation periods. Food consumption was increased ($p > 0.05$) for female parental rats at 1000 ppm during the premating and gestation periods for both generations.

Absolute mean weights of the right and left testes (weighed separately) of 1000-ppm group F_0 males were 8% ($p<0.01$) less than that of controls. It is notable that the relative testes weights were only 3% less than control. In 1000-ppm F_1 group males, the absolute and relative prostate gland weighed 19% ($p<0.05$) and 13% less. Females in both generation administered the test material had organ weights similar to those of the controls (pituitary gland was the only organ measured in females).

In conclusion, the parental LOAEL was 300 ppm (17.2 mg/kg/day) for male rats and 1000 ppm (77.6 mg/kg/day) for female rats based on increased food consumption with decreased body weight gain. The parental NOAEL is 100 ppm (5.6 mg/kg/day) for males and 300 ppm (22.5 mg/kg/day) for females.

The evaluation of reproductive performance showed no treatment related effects on sperm/spermatid count, morphology, or motility. The mating index was decreased in F_0 males of the 300 and 1000 ppm groups due to fewer animals who actually mated successfully (24 vs 28 in control). The mating index was actually higher in males of the F_1 generation. The fertility index of F_1 females of the 300 ppm group in addition to F_0 and F_1 males and females of the 1000 ppm group was reduced relative to control due to a reduced number of pregnant females. It is noteworthy that although the fertility indexes for the groups noted above are within the range of historical controls included with the study (76.2-100.0 for males; 71.4-100% for females), the actual values are on the low-end of this historical range (74.1-79.2%). These equivocal effects on reproductive performance are corroborated by Prukop and Savage (1986) who performed a one-generation reproduction study in mice gavaged with MSMA at 11.9 or 119 mg/kg every other day for 10 weeks. Decreased male fertility was observed at both doses compared to control. Only 50% of the females at 11.9 mg/kg/dose and none of the females at 119 mg/kg/dose became pregnant.

The reproductive LOAEL is 300 ppm (17.2 mg/kg/day) based on decreased fertility indexes in both sexes. The reproductive NOAEL is 100 (5.6 mg/kg/day).

Decreased lactation index compared to concurrent and historical controls was observed for 300 ppm F_2 pups and 1000-ppm group F_1 and F_2 pups. The decrease in the lactation index is due primarily to a whole litter loss at both dose levels. There were no treatment related effects on any other pup data. Body weights and body weight gain of F_1 and F_2 pups were comparable to control values throughout lactation. The number of pups that died between day 0-21 was increased in 300 ppm F_2 pups (35) and 1000-ppm group F_1 and F_2 pups (35 and 32, respectively)

compared to control (8 and 15, respectively). Because of pup death, the litter survival index was reduced in these noted groups.

This equivocal data on pup death is corroborated by the Prukop and Savage (1986) study. In two of four females in the 11.9 mg/kg/dose group that produced litters, the mothers "did not build a nest, rarely huddled over the young, or retrieved them when they were separated from the young, all of which are maternal instincts." In these two litters, all of the young mice died with 2 to 3 days of birth. This postnatal litter loss parallels postnatal litter loss observed in rats of the guideline two-generation reproduction study. Additional behavioral affects were observed in the Lopez and Judd (1979) where females treated with MSMA produced significantly smaller nests than did controls. Based on this literature evidence, it is plausible that the whole litter loss observed in the two-generation reproduction study is due to changes in the nurturing behavior of the mothers and not a direct toxic effect on the pups. Therefore, the increased pup death is not an indication of infant susceptibility but rather potential neurotoxicity in the females.

The offspring LOAEL is 300 ppm (17.2 mg/kg/day) based on increased pup death (day 0-21), reduced litter survival index, and decreased lactation index. The offspring NOAEL is 100 (5.6 mg/kg/day).

The reproductive study in rats is classified **Acceptable/guideline** and satisfies the guideline requirement for a two-generation reproductive study [OPPTS 870.3800 (§83-4)] in rats.

4.5 Chronic Toxicity

Adequacy of data base for chronic toxicity: The data base for chronic toxicity is considered complete. Chronic toxicity studies in rat and dog are available. No additional studies are required at this time. In the chronic toxicity study in rats decreased body weights, body weight gains, food consumption, and histopathology of gastrointestinal tract and thyroid were observed. In the chronic toxicity study in dogs, clinical signs (severe diarrhea, vomiting, and excessive salivation) consistent with arsenic poisoning were observed.

870.4300 Combined Chronic Toxicity/Carcinogenicity – Rat

EXECUTIVE SUMMARY:
In a combined chronic toxicity/carcinogenicity feeding study (MRID 41669001), methanearsonic acid (purity 98.42-98.80%; Batch No. 107/84) was administered in the diet to 60 Fischer F344 rats/sex/dose at dose levels of 0, 50, 400 and 800-1300 ppm (0, 3.2, 27.2, and 93.1 mg/kg/day for males and 0, 3.8, 32.9, and 101.4 mg/kg/day for females) for 104 weeks. The high-dose group of 60 animals/sex received 1300 ppm until week 53. Because of excessive mortality (32% of males), the highest dose was reduced to 1000 ppm until week 60 and to 800 ppm for the remainder of the study. At termination, the cumulative mortality was 42, 50, 45, and 67% of males and 20, 33, 22, and 35% of females for the 0, 50, 400, and 800 ppm groups, respectively.

The following were measured during the study: clinical signs, body weight, food consumption, water consumption, opthalmoscopy, hematology, clinical chemistry, urinalysis, organ weights, gross pathology, neoplastic and non-neoplastic histopathology.

Beginning at week 4-5, diarrhea was observed in all rats at the highest dose level and 27/60 males and 45/60 females of the 400 ppm group. Body weights were statistically decreased from week 7 through termination for males of the 400 ppm groups and from week 4 through termination for high-dose males. Body weights were statistically decreased from week 54 through termination for females of the 400 ppm groups and from week 4 through termination for high-dose females. Overall, week 0-104 weight gains were decreased for the 400 ppm (-11% M and -22% F) and high- dose groups (-22% M and -34% F).

Total protein, albumin, cholesterol, and calcium, concentrations were statistically decreased in male and female rats in the highest dose group, results consistent with inanition. Other sporadic statistically significant changes in clinical chemistry parameters were found, but were not of biological or toxicological significance. No remarkable hematological effects were found.

Starting at approximately week 7, food consumption by the high-dose male and female groups was increased compared to control (+37% M and +15% F). Beginning at week 1 for the high-dose females and week 7 for the 400 ppm and high-dose males and 400 ppm females. Throughout the study, water consumption was increased 29% and 31% for males and females of the 400 ppm group and 149% and 108% in males and females of the high-dose group. Urine volume was statistically decreased with a parallel increase in specific gravity in high-dose males and females throughout the study. In females of the 400 ppm group, a decrease in urine volume and increased specific gravity were observed at 12 and 18 months. Urine pH was decreased in males throughout the study in the high-dose.

Absolute kidney weights were statistically increased in females of the 400 ppm group; relative kidney and liver weights were statistically increased in 400 ppm and high-dose females. Gross pathology findings from animals that died or were sacrificed moribund included emaciation and dehydration, reduced abdominal fat pads, along with thickened walls, and edematous, congested, hemorrhagic, necrotic, ulcerated, or perforated stomach, small intestine and/or large intestine, with secondary lesions in adjacent organs including the prostate, testes, kidneys, urinary bladder, epididymides, seminal vesicles, and ureters.

Histopathology findings, including acute inflammation, mucosal congestion, inflammation and ulceration or perforation of the cecum, colon, and rectum, with evidence of acute or chronic peritonitis, were observed mainly in the high-dose groups and sporadically in the 400 ppm groups and indicated that the large intestine was the primary target for the irritant effect of the test material. Ureteral damage occurring as a sequella to intestinal perforation resulted in severe kidney pathology, including hydronephrosis, cortical tubular cystic dilatation, pyelonephritis, papillary necrosis, and glomerulonephropathy.

At 6 months, a dose dependant decrease in T3 with a parallel decrease in T4 was observed in high-dose males. Females exhibited an increase in T4 (no change in T3) at 12 months in the 400

ppm group and at 12 and 18 months in the high-dose group. Increase in height of the thyroid follicular epithelium was observed at the 400 ppm and high-dose levels of both sexes.

Increased incidences of parathyroid adenomas with a positive dose-related trend were observed in both sexes (males: 1/52, 0/49, 4/53, and 4/45 for the control, 50, 400 ppm and high-dose groups, respectively; females: 0/46, 0/44, 0/40, and 4/45 for control, 50 ppm, 400 ppm, and high-dose groups, respectively). Statistical significance was not attained with respect to either sex. The incidence in the present study was outside the incidence range of historical controls given in the study report. Dosing was considered adequate for carcinogenicity testing.

The chronic LOAEL was 400 ppm (27.2 mg/kg/day for males and 32.9 mg/kg/day for females) based on decreased body weights, body weight gains, food consumption, histopathology of gastrointestinal tract, thyroid, and increased incidence of parathyroid adenomas.

The chronic NOAEL was 50 ppm (3.2 mg/kg/day for males and 3.8 mg/kg/day for females).

This study is classified **Acceptable/Guideline** and satisfies the guideline requirements for a combined chronic toxicity/oncogenicity study in rats [OPPTS 870.4300 (§83-5)].

870.4100b Chronic Toxicity - Dog

EXECUTIVE SUMMARY: In a chronic oral toxicity study (MRIDs 40546101 and 41266401), methanearsonic Acid (>99.8% a.i., Batch No. 107/84) was administered to 5 purebred beagle dogs (CPB-DCBE-67)/sex/group by capsule at dose levels of 0, 2.5, 8, or 40 mg/kg/day for one week and at dose levels of 0, 2, 8, and 35 mg/kg/day for 51 weeks. The following were examined in this chronic study: clinical signs, body weight, food consumption, ophthalmoscopy, neurology (including reflexes, postural reactions, clinical signs, behavior), clinical chemistry, hematology, urinalysis, gross pathology, organ weights, and histopathology.

There were no treatment related effects on mortality, ophthalmological, or neurological examinations. Beginning at week 1, treatment related clinical signs included vomiting, diarrhea, excessive salivation and sporadic anorexia were observed. Diarrhea and increased vomiting were observed in increased incidence in all dose groups in both males and females throughout the duration of the study. Compared to control dogs, excessive salivation was increased in dogs of the 8 and 35 mg/kg/day groups compared to controls.

In males of the 35 mg/kg/day group, body weight gain (-34-50%; $p<0.05$ or $p<0.01$) was decreased compared to controls starting at week 26. In females, body weights were decreased in the 8 and 35 mg/kg/day groups starting at week 26 (17-18% and 8-11% respectively) compared to control. Body weight gain in females was significantly decreased beginning at week 26 in the

8 mg/kg/day group (40-58% of controls; $p<0.05$) and throughout the study at 35 mg/kg/day (15-41% of controls; $p<0.05$). There was a marginal treatment related effect on food consumption (<5% less than controls; n.s.) in females at 8 and 35 mg/kg/day.

Changes in hematology and clinical chemistry parameters noted were sporadic, were not consistent over time and/or did not exhibit a dose-response pattern.

No toxicologically relevant differences in absolute organ weights occurred between treatment groups. In male dogs, the relative adrenal weight and relative liver weight were increased in the 35 mg/kg/day group (+29% and +9% for adrenal and liver, respectively, $p < 0.05$). The relative heart weight was increased in male and female dogs of the 35 mg/kg/day group (+17% and +27%, respectively, $p < 0.05$). Relative kidney weights were significantly increased in females of the 8 mg/kg/day group (+17%) in both sexes of the 35 mg/kg/day group (+15% M, +18% F). Moderate tubular nephrosis characterized by small vacuolation in the epithelial cells was noted in females of the 8 and 35 mg/kg/day groups (0/5, 1/5, and 2/5 for control, mid-, and high- dose groups, respectively). The only treatment related gross necropsy finding was a reduction in "abdominal fat pads" of a single high-dose male.

The incidence of estrous in females dogs was noted. The cumulative estrous incidence was 36, 50, 48, and 17 for control, 2, 8, and 35 mg/kg/day dose groups (+38%, +33%, and -47%, respectively). Based on the general poor health of females dogs in the 35 mg/kg/day dose group, this decreased incidence of estrous is considered a secondary toxic effect. Histopathology findings of the female reproductive system included an absence of corpora lutea in the 35 mg/kg/day group (3/5 vs. 0/5 control females).

The LOAEL was 8 mg/kg/day based on body weight gain and kidney effects (organ weight and histopathology) in females and clinical signs (severe diarrhea, vomiting, and excessive salivation) in both sexes. The NOAEL was 2 mg/kg/day.

This study is classified **Acceptable/Guideline** and satisfies the requirements for a chronic oral toxicity study in dogs [OPPTS 870.4100 (§83-1b)].

4.6 Carcinogenicity

Adequacy of data base for Carcinogenicity: The data base for carcinogenicity is considered complete. Carcinogenicity studies in rat and mice are available. No additional studies are required at this time. Dosing was considered adequate for carcinogenicity testing.
in both studies. In the rat study, increased incidences of parathyroid adenomas with a positive dose-related trend were observed in both sexes (although statistical significance was not attained with respect to either sex). In the mouse study, a treatment related increase in tumor incidence was not observed. MAA was classified "not likely" human carcinogens (HIARC, 11/14/2000).

870.4300 Combined Chronic Toxicity/Carcinogenicity – Rat

See executive summary above.

870.4200b Carcinogenicity (feeding) - Mouse

EXECUTIVE SUMMARY: In an oncogenicity study (MRID 42173201), methanearsonic acid (purity 98.7-99.8%; Batch No. 107/84) was administered in the diet to 52 Charles River $C_3B_6F_1$ mice/sex/dose at dose levels of 0, 10, 50, 200, and 400 ppm (0, 1.8, 9.3, 38, and 83 mg/kg/day for males and 0, 2.2, 12, 46, and 104 mg/kg/day for females) for 104 weeks.

There was no treatment related effect on mortality. Treatment related clinical signs of loose and mucoid feces in both sexes at 400 ppm were observed beginning at week 40 and continued until study termination. Females of the 200 and 400 ppm groups exhibited increased incidences of hypersensitivity (2/52, 8/52 and 11/51 for control, 200, and 400 ppm, respectively) and tonic convulsions (1/52, 9/52 and 12/51 for control, 200, and 400 ppm, respectively).

Mean absolute body weights were decreased in both sexes at 400 ppm from week 51 through termination (males: 83-86% of controls; $p<0.001$, females: 78-83% of controls; $p<0.001$), and overall weight gains for weeks 0-104 were decreased at the 400 ppm dose level for males (35% less than controls) and at the 200 and 400 ppm dose levels for females (18 and 46% less than controls, respectively). Food consumption by the females of the 400 ppm group was increased from week 47 until termination (15.8% greater than controls). Mean water consumption was increased in males of the 200 ppm group at weeks 51 and 75 (107-126% of controls; $p<0.05$ or $p<0.001$) and in males of the 400 ppm group from week 45 through termination (143-169% of controls; $p<0.001$). Mean water consumption was increased in females of the 200 ppm group from week 45 through termination (116-135% of controls; $p<0.001$) and in females of the 400 ppm group from weeks 25 through termination (110-179% of controls; $p<0.01$ or $p<0.001$).

No remarkable hematological findings were observed. Clinical chemistry was not observed in this study. Spleen weights adjusted for body weight in females of the 200 and 400 ppm groups were statistically decreased as compared with controls; however, no corresponding gross or microscopic changes were noted.

Increased incidences of mucoid, foamy, fluid or soft cecal contents were noted in males at the 400 ppm dose level (4/51 vs. 0/52 for controls) and in females at the 200 and 400 ppm dose levels (2/52, 4/52, and 12/52 for 0, 200, and 400 ppm females, respectively). The histopathology finding of diffuse, slight cuboidal to squamous metaplasia of the surface epithelial columnar absorptive cells of the cecum, colon, and rectum was observed at increased incidences ($p<0.001$) in males and females at 400 ppm (range of incidence 14/52 to 39/49; none observed in control). The finding of slight, subchronic progressive glomerulonephropathy exhibited a positive significant trend ($p<0.001$) in males (25/52, 27/52, 38/52, 39/52, and 46/52 for control 10, 50, 200, and 400 ppm, respectively). The finding of slight, focal nephrocalcinosis exhibited a positive significant trend in males ($p<0.001$; 25/52, 30/52, 30/52, 45/52, and 45/52 for control 10, 50, 200, and 400 ppm, respectively) and females ($p<0.01$; 0/52, 1/52, 1/52, 2/52, and 5/52 for control 10, 50, 200, and 400 ppm, respectively).

Based on decrease in body weight gain, increased water consumption, and histopathology of the large intestine and kidney, the LOAEL was 200 ppm (38 and 46 mg/kg/day) for males and females. The NOAEL was 50 ppm (9.3 and 12 mg/kg/day) for males and females.

At the doses tested, there was not a treatment related increase in tumor incidence when compared to controls. Dosing was considered adequate.

This study is classified **Acceptable/Guideline** and satisfies the guideline requirements for a combined oncogenicity study in mice [OPPTS 870.4200 (§83-2b)].

4.7 Mutagenicity

Adequacy of data base for Mutagenicity: The acceptable genetic toxicology studies (pre-1991 guidelines) indicate that MAA is not mutagenic in bacteria (*Salmonella typhimurium*) or cultured mammalian cells (Chinese hamster ovary). Similarly, MAA did not induce unscheduled DNA synthesis (UDS) in primary rat hepatocytes. Based on the results of the acceptable studies, there is no concern for mutagenicity at this time.

Gene Mutation

Guideline 870.5100 Gene mutation: *Salmonella typhimurium* reverse gene mutation MRID 41651902 (1989) Acceptable/Guideline	In deionized distilled water at concentrations of 667, 1000, 3333, 6667 and 10,000 µg/plate methanearsonic acid was tested in the presence and absence of mammalian metabolic activation (S9-mix). There was no evidence of induced mutant colonies over background.
Guideline 870.5300 Gene mutation Mouse lymphoma assay MRID 41651904 (1989) Acceptable/Guideline	In deionized water at concentrations of 300, 400, 534, 712, 949, 1266, 1688, 2250, 3000 and 4000 µg/mL methanearsonic acid was tested in the absence of mammalian metabolic activation (S9-mix) and at concentrations of 71, 95, 127, 169, 225, 300, 400, 534, 712, 949, 1266 and 1688 µg/mL in the presence of S9-mix. Methanearsonic acid was tested up to cytotoxic concentrations. There was no evidence of induced mutant colonies over background.

Cytogenetics

Guideline 870.5375 Chromosomal aberration Mouse micronucleus assay MRID 41651903 (1989) Acceptable/Guideline	Methanearsonic acid was tested in distilled water in two independent assays. Concentrations tested in the initial assay were 625, 1250, 2500, 5000 µg/mL, with and without metabolic activation (S9-mix). Methanearsonic acid was tested up to a slightly cytotoxic concentration, limited by solubility in the solvent, distilled water. There was no evidence of chromosomal aberrations induced over background.

Other Genotoxicity

Guideline 870.5550 Unscheduled DNA Synthesis MRID 41651905 (1989) Acceptable/Guideline	In deionized distilled water methanearsonic acid was tested at concentrations of 10, 50, 100, 500, 750 and 1000 µg/mL for 18 to 20 hours in an initial and a confirmatory assay. There was no evidence that unscheduled DNA synthesis, as determined by radioactive tracer procedures [nuclear silver grain counts] was induced.

4.8 Neurotoxicity

Adequacy of data base for Neurotoxicity: As stated above, at present time no neurotoxicity studies are available for MAA. There is no evidence of neurotoxicity observed in rat, rabbit, or dog. In the 104-week oncogenicity study in mice, treated females exhibited increased incidences of hypersensitivity and tonic convulsions. Additional evidence of potential neurotoxicity observed in mice following oral exposure to MSMA is found in the literature. In Lopez and Judd (1979) , females treated with MSMA produced significantly smaller nests than control females whereas treated males collected the same amount of cotton as control mice. Prukop and Savage (1986) performed a one-generation reproduction study where two of four females in the 11.9 mg/kg/dose group "did not build a nest, rarely huddled over the young, or retrieved them when they were separated from the young, all of which are maternal instincts." In these two litters, all of the young mice died with 2 to 3 days of birth. This postnatal litter loss parallels postnatal litter loss observed in rats of the guideline two-generation reproduction study. In the guideline study, an equivocal increase in whole litter loss and increased postnatal pup death was observed at 17.2 mg/kg/day. Based on the evidence in both the Lopez and Judd (1979) and the Prukop and Savage (1986) studies, it is plausible that the whole litter loss observed in the two-generation reproduction study is due to changes in the nurturing behavior of the mothers and not a direct toxic effect on the pups. Therefore, the increased pup death is not an indication of infant susceptibility but rather potential neurotoxicity in the females. These literature studies in mice combined with the clinical signs of hypersensitivity and tonic convulsions observed in female mice in the oncogenicity study provide the justification for the requirement of the acute and subchronic neurotoxicity studies. These studies should be performed using mice.

870.6100 Delayed Neurotoxicity Study - Hen

Not available and not required for MAA or its sodium or calcium salts at this time.

870.6200 Acute Neurotoxicity Screening Battery

An acute neurotoxicity screening battery is not available at this time but is required (HIARC, 7/13/2000). This study should be performed in mice.

870.6200 Subchronic Neurotoxicity Screening Battery

A subchronic neurotoxicity study is not available at this time but is required (HIARC, 7/13/2000). This study should be performed in mice.

870.6300 Developmental Neurotoxicity Study

Not available and not required for MAA or its sodium or calcium salts at this time.

4.9 Metabolism

Adequacy of data base for metabolism: The data base for metabolism is considered complete. No additional studies are required at this time. In a metabolism study in rat, analysis of fecal and urinary samples revealed that the radioactivity of all preparative fractions was associated with parent compound, MSMA (79.7-97.4% of the administered dose) and two unknown metabolites.

870.7485 Metabolism - Rat

EXECUTIVE SUMMARY: This study was designed to identify parent compound and metabolites in the urine and feces over a 7-day period, in expired CO_2 over a 1-day period, and in tissue 7 days after treatment (MRID 42010501).

In this metabolism study, groups Sprague-Dawley CD® (Crl:CDBR) rats were given a [^{14}C-methyl]-monosodium methanearsonate (≥99.4% a.i.; Lot/Batch No. ICN CFO 2289, GPS/2/79/1) in water at concentrations of 0, 5.0, or 200.0 mg/kg according to the following five different dose groups: 1) In the vehicle control group, 3 rats/sex were dosed with water by gavage; 2) Single low dose group: 5 rat/sex were given a single radiolabeled gavage dose of 5.0 mg/kg; 3) Single high dose group: 5 rats/sex were given a single radiolabeled gavage dose of 200 mg/kg; 4) Consecutive dosing group: 5 rats/sex were dosed by gavage for 14 consecutive days with unlabelled MSMA at 5.0 mg/kg/day followed by a single radiolabeled dose of MSMA; 5) I.V. dose group: 5 rats/sex were given a single radiolabeled i.v. dose of 5.0 mg/kg. Expired CO_2 was sampled at 0.5 and 1 day post-dosing, and urine and fecal samples were taken at intervals up to 7 days post-dosing, whereupon the rats were terminated. Tissue samples (blood, bone, brain, fat, heart, kidney, liver, lungs, muscle, ovary, skin, spleen, testis, uterus, and residual carcass) were taken at termination.

There were no treatment related deaths or clinical signs.

At 0.5 day following treatment, 27.5-40% and 12-34% of the administered dose were measured in the urine and feces, respectively, in rats receiving gavage doses, including the low single dose group, high single dose group and consecutive dosing group. Urine accounted for 33-42% of the excretion in the oral 5 and 200 mg/kg treatment groups. Fecal elimination accounted for 38-58% of the radiolabel in the oral 5 and 200 mg/kg groups. By day 1, 69%-88% of the administered dose was excreted in the urine and feces combined. In rats dosed by gavage, at day 3, 83% to 97% of the administered dose was excreted in the urine and feces. Less than 0.5% of the radiolabel was recovered as CO_2 in all groups. Male and females rats excreted radiolabelled MSMA at similar rates.

At 0.5 day following treatment, 82% of the administered dose in both sexes was excreted in the urine of rats dosed by i.v. injection. At day 1 following treatment, 93% and 91% of the administered dose was excreted predominately in the urine; males excreted 4% of the

administered dose in the feces. Less than 0.5% of the radiolabel was recovered as CO_2 in all groups.

Tissue levels of radiolabel ranged from 6-14% in all oral treatment groups and ~3% in the 5 mg/kg iv treatment group 7 days after treatment. The blood (2-4% in gavage dose groups) contained the highest concentrations of radiolabel followed by the liver, kidney, and spleen which contained < 1.0% of the administered dose. Total recovery of administered radioactivity over the 7-day period for all treated groups was ~98.2% of the administered dose.

Analysis of fecal and urinary samples by HPLC and TLC revealed that the radioactivity of all preparative fractions was associated with parent compound and two unknown metabolites. The major product excreted in both urine and feces was unchanged parent, accounting for 80-97% of the administered dose. Unknown metabolite A was detected in the urine and feces of the low-dose groups (6.7/6.1, 1.8/2.6, and 3.7/3.7% of the administered dose for males/females of the single 5.0 mg/kg po, 5.0 mg/kg po following pretreatment, and 5.0 mg/kg iv groups, respectively). Unknown metabolite B was detected in the urine and feces of the group that received 5.0 mg/kg following pretreatment at 0.7% of the administered dose for both males and females.

This study is classified as **Acceptable/ Guideline** and satisfies the requirements for a metabolism study in rats [OPPTS: 870.7485 (§85-1)].

870.7600 Dermal Absorption - Rat

No dermal absorption study is available for MAA or its sodium or calcium salts at the time of this assessment. The dermal absorption factor for cacodylic acid was selected by the HIARC (7/13/2000).

EXECUTIVE SUMMARY: In a dermal absorption study, male rats (28/dose) were administered *[^{14}C]cacodylic acid* (in the equivalent of 3.25W formulation), at dose levels of 0.90, 9.30 or 91.3 µg/cm2. Four rats/dose were sacrificed 0.5, 1, 2, 4, 10 or 24 hours after application. An additional group of 4 rats/group were exposed for 24 hours and sacrificed at 96 hours.

At 10 hours 1.11%, 3.51% or 3.0% of the total dose was absorbed at dose levels of 0.90, 9.30 or 91.3 µg/cm2, respectively; at 24 hours 10.99, 6.55 or 7.07%, respectively. Generally, % dose absorbed decreased with increased concentration of the formulation applied to the skin; however, in the study % absorbed slightly increased with increased dose, indicating damage to the stratum corneum. Approximately 1% of the total applied dose was found in the blood at any dose level tested. Total radioactivity recovery ranged from 99 to 106%. Most of the absorbed dose was excreted in urine and feces. At 10 hours 0.41, 2.23 or 1.89% of the absorbed dose was found in the urine at 0.90, 9.30 or 91.3 µg/cm2, respectively. At the same time point 0.01, 0.00, or 0.00% of the absorbed dose was found in the feces at 0.90, 9.30 or 91.3 µg/cm2, respectively. The radioactivity bound to the skin (application site) ranged from ≈ 10 to 34% of the applied dose.

Based on the results of this study, the dermal absorption factor for 10 hour exposure period was 3.5%.

The study is classified as **Acceptable** and satisfies the guideline requirement for a dermal penetration study (85-3) in rat.

4.10 Special/Other Studies_

1. Lopez, JF and Judd, FW. 1979. Effect of sublethal dietary exposure of monosodium methanearsonic acid herbicide on the nest-building behavior of the white-footed mouse, Peromyscus leucopus. Bull. Environ. Contam. Toxicol. 23: 30-32.

2. Prukop, JA and Savage, NL. 1986. Some effects of multiple, sublethal doses of monosodium methanearsonic acid (MSMA) herbicide on hematology, growth, and reproduction of laboratory mice. Bull. Environ. Contam. Toxicol. 36: 337-341.

Lopez and Judd (1979) exposed to mice to 477 ppm of MSMA in tapwater for 14 days and observed nest-building behavior in male and female mice. Grams of cotton used in nest construction was measured. Females treated with MSMA collected significantly less cotton than control females. Treated males collected the same amount of cotton as control mice.

Prukop and Savage (1986) performed a one-generation reproduction study in mice gavaged with MSMA at 11.9 or 119 mg/kg every other day for 10 weeks. Decreased male fertility was observed at both doses compared to control. Only 50% of the females at 11.9 mg/kg/dose and none of the females at 119 mg/kg/dose became pregnant. This decrease in male fertility was also observed in the guideline two-generation reproduction study in F_0 and F_1 generation of the 61.4 mg/kg/day group. Also notable in this study is the observation that in two of four females in the 11.9 mg/kg/dose group that produced litters, the mothers "did not build a nest, rarely huddled over the young, or retrieved them when they were separated from the young, all of which are maternal instincts." In these two litters, all of the young mice died with 2 to 3 days of birth. This postnatal litter loss parallels postnatal litter loss observed in rats of the guideline two-generation reproduction study. In the guideline study, an equivocal increase in whole litter loss and increased postnatal pup death was observed at 17.2 mg/kg/day. Based on the evidence in both the Lopez and Judd (1979) and the Prukop and Savage (1986) studies, it is plausible that the whole litter loss observed in the two-generation reproduction study is due to changes in the nurturing behavior of the mothers and not a direct toxic effect on the pups. Therefore, the increased pup death is not an indication of infant susceptibility but rather potential neurotoxicity in the females.

5.0 TOXICITY ENDPOINT SELECTION

5.1 See Section 9.2 for Endpoint Selection Table.

5.2 Dermal Absorption

Dermal Absorption Factor: 3.5%

No dermal absorption study is available for MAA or its sodium or calcium salts at the time of this assessment. The dermal absorption factor for cacodylic acid was selected by the HIARC (7/13/2000).

5.3 Classification of Carcinogenic Potential

5.3.1 Conclusions

Although the parathyroid adenomas described above in the combined chronic/carcinogenicity study rats were outside of the historical controls (historical control incidence = 0.1% for both sexes), the tumors are not a concern because of the following rationale:

1) Only the benign tumors were increased in incidence.
2) Pair wise significance was not attained for either sex. A significant trend test was observed only for males.
3) An increase in tumor incidence was not observed in mice.
4) The acceptable genetic toxicology studies indicate that MAA is not mutagenic in bacteria (*Salmonella typhimurium*) or cultured mammalian cells (Chinese hamster ovary). Similarly, MAA did not induce unscheduled DNA synthesis (UDS) in primary rat hepatocytes.

5.3.2 Classification of Carcinogenic Potential

The HIARC classified MAA or its sodium or calcium salts as **"not likely"** a human carcinogens.

5.3.3 Quantification of Carcinogenic Potential

The chronic reference dose for MAA or its sodium or calcium salts is based on a study in cacodylic acid because of potential dietary exposure through food and water to cacodylic acid following CAMA, MSMA, or DSMA application. The Health Effects Division Carcinogenicity Peer Review Committee (CPRC) has concluded that cacodylic acid should be classified as a Group B2 - Probable Human Carcinogen, based on increases in urinary bladder tumors (rare tumor type) in both sexes of the Fischer rat and increases in fibrosarcomas (multiple organs) in female B6C3F1 mice. The CPRC recommended that for the purpose of risk characterization, a low dose extrapolation of human risk [$Q_1^* = 6.23 \times 10^{-2}$ $(mg/kg/day)^{-1}$] , based on the total (papillomas and carcinomas) urinary tumors in the rat, both for females alone and for males and females combined. The HIARC (6/10/99) concurred with the previous classification for cacodylic acid. For the assessment of the lifetime cancer risk through dietary exposure, the Q_1^* of 6.23×10^{-2} $(mg/kg/day)^{-1}$ for cacodylic acid should be applied. This low dose extrapolation will not be performed for residential or occupational dermal or inhalation exposure because actual exposure is expected to be only to CAMA, MSMA, or DSMA.

6.0 FQPA CONSIDERATIONS

6.1 Special Sensitivity to Infants and Children

There is no quantitative or qualitative evidence of increased susceptibility of rats or rabbit fetuses to *in utero* exposure in available developmental toxicity studies. There is also no quantitative or qualitative evidence of increased susceptibility of offspring observed in the two-generation reproduction study in rats. In the developmental toxicity studies and in the two-generation reproduction study, developmental / offspring effects were observed only at doses greater than those demonstrating maternal / parental toxicity.

6.2 Recommendation for a Developmental Neurotoxicity Study

The HIARC determined that the requirement of a developmental neurotoxicity study (DNT) with MAA is "reserved" pending receipt of the acute and subchronic neurotoxicity studies in mice. Additionally, the HED Metabolism Assessment Review Committee (MARC) concluded that the residues of toxicological concern associated with the use of CAMA/MSMA/DSMA are CAMA/MSMA/DSMA *per se* and cacodylic acid expressed as As_2O_3. During its review and evaluation of cacodylic acid, the HIARC required that a DNT be conducted with cacodylic acid. This requirement was based on the observation of endocrine effects in the two-generation reproduction study and in subchronic and chronic studies in rats (Refer to HED Doc. No. 013422 for further details regarding data requirements for cacodylic acid). When available, the results of this study may also indicate whether or not a DNT with MAA is warranted.

7.0 OTHER ISSUES

Endpoints from cacodylic acid studies for chronic dietary and inhalation exposure in addition to the dermal absorption factor were selected by the HIARC for CAMA, MSMA, and DSMA risk assessment. Following application of CAMA, MSMA, or DSMA, methylation to cacodylic acid by plants or bacteria may occur. Dietary exposure through food and water may be to CAMA/MSMA/DSMA, cacodylic acid or a combination.

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9.0APPENDICES
Tables for Use in Risk Assessment

9.1 Toxicity Profile Summary Tables

9.1.1 Acute Toxicity Table - See Section 4.1

9.1.2 Subchronic, Chronic and Other Toxicity Tables

Guideline No./Study Type	MRID No. (year)/Classification/Doses	Results
870.3100 90-Day oral toxicity rodents	MRID no. 40632601 (1985) Unacceptable/Nonguideline 0, 10, 100, 500, and 1250 ppm (0, 2.1, 22.5, 110.6, and 288.6 mg/kg/day for males and 0, 2.8, 27.5, 137.4, and 342.5 mg/kg/day for females)	Based on the data presented in this study, a LOAEL and NOAEL can not be established.The numerous deficiencies in the conduct of this study preclude meaningful evaluation of the data.
870.3200 21/28-Day dermal toxicity (rabbit)	MRID 41872701 (1991) Acceptable/Guideline 0, 100, 300, or 1000 mg/kg/day	Systemic toxicity NOAEL =1000 Systemic toxicity LOAEL >1000 Dermal irritation NOAEL =1000 Dermal irritation LOAEL >1000
870.3465 90-Day inhalation toxicity	Not available for MAA	
870.3700a Prenatal developmental in rodents	MRID 41926401 (1990) Acceptable/Guideline 0, 10, 100, or 500 mg/kg/day	Maternal toxicity NOAEL = 10 mg/kg/day. Maternal toxicity LOAEL = 100 mg/kg/day, based on decreased body weight gain and food consumption. Developmental toxicity NOAEL= 100 mg/kg/day. Developmental toxicity LOAEL = 500 mg/kg/day, based on decreased mean fetal body weight.
870.3700b Prenatal developmental in nonrodents	MRID 15939001 (1986) Acceptable/Guideline 0, 1, 3, 7 mg/kg/day	Maternal toxicity NOAEL = 3 mg/kg/day. Maternal toxicity LOAEL = 7 mg/kg/day, based on clinical signs (incidence of orange discoloration of the urine) and decreased food consumption. Developmental toxicity NOAEL = 7 mg/kg/day. Developmental toxicity LOAEL = 12 mg/kg/day, based abortions and on an increased incidence of skeletal variations (increased numbers of 13th thoracic vertebra with ribs and 8th lumbar vertebra).

Guideline No./Study Type	MRID No. (year)/Classification/Doses	Results
870.3800 Reproduction and fertility effects	MRID 43178301 (1994) Acceptable/Guideline 0, 100, 300, or 1000 ppm. (5.6, 17.2, and 61.4 mg/kg/day, respectively, for males and 7.5, 22.5, and 77.6 mg/kg/day for females.	Parental NOAEL = 100 ppm (5.6 mg/kg/day) for males and 300 ppm (22.5 mg/kg/day) for females. Parental LOAEL =300 ppm (17.2 mg/kg/day) for male rats and 1000 ppm (77.6 mg/kg/day) for female rats based on increased food consumption with decreased body weight gain. Reproductive NOAEL = 100 (5.6 mg/kg/day). Reproductive LOAEL = 300 ppm (17.2 mg/kg/day) based on decreased mating and fertility indexes. Offspring NOAEL = 100 (5.6 mg/kg/day). Offspring LOAEL = 300 ppm (17.2 mg/kg/day) based on increased pup death (day 0-21), reduced litter survival index, and decreased lactation index.
870.4200b Chronic toxicity dogs	MRID 40546101 and 41266401 (1988) Acceptable/Guideline 0, 2, 8, and 35 mg/kg/day	NOAEL = 2 mg/kg/day. LOAEL = 8 mg/kg/day based on body weight gain in females and clinical signs (severe diarrhea, vomiting, and excessive salivation) in both sexes.
870.4300 Combined Chronic/ Carcinogenicity rats	MRID 41669001 (1990) Acceptable 0, 50, 400 and 800 ppm (0, 3.2, 27.2, and 93.1 mg/kg/day for males and 0, 3.8, 32.9, and 101.4 mg/kg/day for females) for 104 weeks.	NOAEL = 50 ppm (3.2 mg/kg/day for males and 3.8 mg/kg/day for females) LOAEL = 400 ppm (27.2 mg/kg/day for males and 32.9 mg/kg/day for females) based on decreased body weights, body weight gains, food consumption, histopathology of gastrointestinal tract, thryoid, and **increased incidence of parathyroid adenomas.** Dosing was considered adequate.
870.4300 Carcinogenicity mice	MRID 42173201 (1991) Acceptable 0, 10, 50, 200, and 400 ppm (0, 1.8, 9.3, 38, and 83 mg/kg/day for males and 0, 2.2, 12, 46, and 104 mg/kg/day for females)	NOAEL = 50 ppm (9.3 and 12 mg/kg/day) for males and females. LOAEL = 200 ppm (38 and 46 mg/kg/day) for males and females based on decrease in body weight gain, increased water consumption, and histopathology of the large intestine and kidney. At the doses tested, there was not a treatment related increase in tumor incidence when compared to controls. Dosing was considered adequate.

Guideline No./Study Type	MRID No. (year)/Classification/Doses	Results
870.5100 Gene mutation *Salmonella typhimurium* reverse gene mutation	MRID 41651902 (1989) Acceptable/Guideline In deionized distilled water at concentrations of 667, 1000, 3333, 6667 and 10,000 µg/plate in the presence and absence of mammalian metabolic activation (S9-mix).	There was no evidence of induced mutant colonies over background.
870.5300 Gene mutation Mouse lymphoma assay	MRID 41651904 (1989) Acceptable/Guideline In deionized water at concentrations of 300, 400, 534, 712, 949, 1266, 1688, 2250, 3000 and 4000 µg/mL in the absence of mammalian metabolic activation (S9-mix) and at concentrations of 71, 95, 127, 169, 225, 300, 400, 534, 712, 949, 1266 and 1688 µg/mL in the presence of S9-mix.	Methanearsonic acid was tested up to cytotoxic concentrations. There was no evidence of induced mutant colonies over background.
870.5375 Chromosomal aberration Mouse micronucleus assay	MRID 41651903 (1989) Acceptable/Guideline In distilled water in two independent assays. Concentrations tested in the initial assay were 625, 1250, 2500, 5000 µg/mL, with and without metabolic activation (S9-mix).	Methanearsonic acid was tested up to a slightly cytotoxic concentration, limited by solubility in the solvent, distilled water. There was no evidence of chromosomal aberrations induced over background.
870.5550 Unscheduled DNA Synthesis	MRID 41651905 (1989) Acceptable/Guideline In deionized distilled water at concentrations of 10, 50, 100, 500, 750 and 1000 µg/mL for 18 to 20 hours in an initial and a confirmatory assay.	There was no evidence that unscheduled DNA synthesis, as determined by radioactive tracer procedures [nuclear silver grain counts] was induced.
870.7485 Metabolism and pharmacokinetics	MRID 42010501 (1991) Acceptable/Guideline In water at concentrations of 0, 5.0, or 200.0 mg/kg according to the following five different dose groups: 1) In the vehicle control group, dosed with water by gavage; 2) a single radiolabeled gavage dose of 5.0 mg/kg; 3) a single radiolabeled gavage dose of 200 mg/kg; 4) dosed by gavage for 14 consecutive days with unlabelled MSMA at 5.0 mg/kg/day followed by a single radiolabelled dose of MSMA at MSMA; 5) a single radiolabeled i.v. dose of 5.0 mg/kg.	Analysis of fecal and urinary samples by HPLC and TLC revealed that the radioactivity of all preparative fractions was associated with parent compound and two unknown metabolites. The major product excreted in both urine and feces was unchanged parent, accounting for 80-97% of the administered dose.

Guideline No./Study Type	MRID No. (year)/Classification/Doses	Results
870.7600 Dermal penetration	Not available for MAA	

9.2 Summary of Toxicological Dose and Endpoints for MAA for Use in Human Risk Assessment[1]

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF and Endpoint for Risk Assessment	Study and Toxicological Effects
Acute Dietary general population including infants and children	NOAEL= 2 mg/kg/day UF = 100 **Acute RfD** = 0.02 mg/kg/day	FQPA SF = 3x aPAD = 0.02 mg/kg/day / 3x = 0.007 mg/kg/day	Chronic Toxicity in Dog, MAA study LOAEL = 8 mg/kg/day based on clinical signs of severe diarrhea, vomiting, and excessive salivation were observed in the first of week of dosing.
Chronic Dietary all populations	NOAEL= 0.14 mg/kg/day UF = 100 **Chronic RfD** = 0.0014 mg/kg/day	FQPA SF = 3x cPAD = 0.0014 mg/kg/day / 3x = 0.0005 mg/kg/day	Combined Chronic/Carcinogenicity in Rat, Cacodylic acid study LOAEL = 0.79 mg/kg/day in males and 3.2 mg/kg/day in females based on Increased thyroid follicular epithelial cell height in males and decreased urine specific gravity, and increased follicular epithelial cell height, and urinary bladder lesions (increased vacoular degeneration of transitional epithelium, lymphocytic infiltration, transitional hyperplasia) in females.
Short-Term Oral (1-7 days) (Residential)	oral study NOAEL= 2 mg/kg/day	LOC for MOE = 300 (Residential, includes the FQPA SF)	Chronic Toxicity in Dog, MAA study LOAEL = 8 mg/kg/day based on clinical signs of severe diarrhea, vomiting, and excessive salivation were observed in the first of week of dosing.
Intermediate-Term Oral (1 week - several months) (Residential)	oral study NOAEL= 2 mg/kg/day	LOC for MOE = 300 (residential, includes the FQPA SF)	Chronic Toxicity in Dog, MAA study LOAEL = 8 mg/kg/day based on clinical signs of severe diarrhea, vomiting, and excessive salivation were observed in the first of week of dosing.

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF and Endpoint for Risk Assessment	Study and Toxicological Effects
Short-Term Dermal (1-7 days) (Occupational/ Residential)	dermal study NOAEL= 1000 mg/kg/day	LOC for MOE = 100 (Occupational) LOC for MOE = 300 (Residential includes the FQPA SF)	21-Day Dermal Toxicity in Rabbit, MAA study LOAEL > 1000 mg/kg/day.
Intermediate-Term Dermal (1 week - several months) (Occupational/ Residential)	dermal study NOAEL= 1000 mg/kg/day	LOC for MOE = 100 (Occupational) LOC for MOE = 300 (Residential includes the FQPA SF)	21-Day Dermal Toxicity in Rabbit, MAA study LOAEL > 1000 mg/kg/day.
Long-Term Dermal (several months - lifetime) (Occupational/ Residential)	oral study NOAEL= 0.14 mg/kg/day (dermal absorption factor = 3.5%)	LOC for MOE = 100 (Occupational) LOC for MOE = 300 (Residential includes the FQPA SF)	Combined Chronic/Carcinogenicity in Rat, Cacodylic acid study LOAEL = 0.79 mg/kg/day in males and 3.2 mg/kg/day in females based on increased thyroid follicular epithelial cell height in males and decreased urine specific gravity, and increased follicular epithelial cell height, and urinary bladder lesions (increased vacoular degeneration of transitional epithelium, lymphocytic infiltration, transitional hyperplasia) in females.
Short-Term Inhalation (1-7 days) (Occupational/ Residential)	inhalation study NOAEL= 0.010 mg/L/day	LOC for MOE = 100 (Occupational) LOC for MOE = 300 (Residential includes the FQPA SF)	90-Day Inhalation Toxicity in Cacodylic acid LOAEL = 0.034 mg/L/day based on based on the presence of moderate and marked intracytoplasmic eosinophilic granules (IEG) in the cells of the nasal turbinates.

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF and Endpoint for Risk Assessment	Study and Toxicological Effects
Intermediate-Term Inhalation (1 week - several months) (Occupational/ Residential)	inhalation study NOAEL= 0.010 mg/L/day	LOC for MOE = 100 (Occupational) LOC for MOE = 300 (Residential - includes the FQPA SF)	90-Day Inhalation Toxicity in Cacodylic acid LOAEL = 0.034 mg/L/day based on based on the presence of moderate and marked intracytoplasmic eosinophilic granules (IEG) in the cells of the nasal turbinates.
Long-Term Inhalation (several months - lifetime) (Occupational/ Residential)	inhalation study NOAEL= 0.010 mg/L/day	LOC for MOE = 100 (Occupational) LOC for MOE = 300 (Residential - includes the FQPA SF)	90-Day Inhalation Toxicity in Cacodylic acid LOAEL = 0.034 mg/L/day based on based on the presence of moderate and marked intracytoplasmic eosinophilic granules (IEG) in the cells of the nasal turbinates.
Cancer (oral, dermal, inhalation)	MAA was classified as "not likely human carcinogens"		

[1] UF = uncertainty factor, FQPA SF = FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, LOC = level of concern, MOE = margin of exposure

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