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DATE: July 26, 2000

MEMORANDUM

SUBJECT: ***MSMA and DSMA*** - Report of the Hazard Identification Assessment Review Committee.

FROM: Anna Lowit, Toxicologist
Reregistration Branch 2
Health Effects Division (7509C)

THROUGH: Jess Rowland, Co-Chair 7/26/00
and
Elizabeth Doyle, Co-Chair for RD
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Diana Locke, Risk Assessor
Reregistration Branch 2
Health Effects Division (7509C)

PC Code: 013803/013802

On July 13, 2000 the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for MSMA and DSMA (monosodium methanearsonic acid and disodium methanearsonic acid) with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for occupational/residential exposure risk assessments. The potential for increased susceptibility of infants and children from exposure to MSMA and DSMA was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996. The conclusions drawn at this meeting are applicable to both MSMA and DSMA (disodium methanarsonic acid) and are presented in this report.

Committee Members in Attendance

Members present were: Y. Yang, D. Nixon, T. Levine, J. Chen, E. Mendez, W; Burnam, and J. Rowland.

Member(s) in absentia: E. Doyle, A; Assaad, P. Hurley, and Brenda Tarplee (Exec. Sec.).

Data evaluation prepared by: Anna Lowit, Reregistration Branch 2

Also in attendance were: Pauline Wagner, Diana Locke, Ken Dockter, and Renee Sandvig of RRB2; Alex Clem of EFED, Steve Malish of AD, Guruva Reddy of RAB1, and Becky Daiess of RAB3.

Data Evaluation / Report Presentation

Anna Lowit
Toxicologist

1. INTRODUCTION

On July 13, 2000, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for MSMA and DSMA with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for occupational/residential exposure risk assessments. The potential for increased susceptibility of infants and children from exposure to MSMA and DSMA was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996. EPA has previously accepted toxicity studies performed with methanearsonic acid for MSMA and DSMA registration. All endpoints selected by the HIARC for methanearsonic are applicable to MSMA and DSMA. It is important to note that although this document contains toxicological endpoints selected for exposure to MSMA and DSMA, for several exposure scenarios, endpoints have been selected based on toxicity studies in cacodylic acid. Where applicable, the rationale for these selections have been given.

2. HAZARD IDENTIFICATION

2.1 Acute Reference Dose (RfD)

Selected Study: Chronic Oral Toxicity in Dog, MSMA Guideline #: 870.4100, 83-1b

MRID No.: 40546101/41266401

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.

Selected Dose and Endpoint for Establishing Acute RfD: NOAEL = 2 mg/kg/day based on clinical signs (severe diarrhea, vomiting, and excessive salivation) in both sexes observed at 8 mg/kg/day.

Uncertainty Factor(s): 100x (10x for intraspecies extrapolation; 10x for interspecies extrapolation).

Comments about Study/Endpoint/Uncertainty Factor(s): Clinical signs of diarrhea and vomiting in addition to excessive salivation were observed. The HIARC noted that these signs were observed only during the first week of dosing and not after a single dose. However, this endpoint was selected because the clinical signs are relevant and consistent with signs seen in humans with arsenic poisoning. The HIARC further concluded that this endpoint will be re-evaluated after receipt of the acute neurotoxicity study in mice that was identified as a data gap.

Acute RfD = $\frac{2 \text{ mg/kg/day (NOAEL)}}{100 \text{ (UF)}}$ =	**0.02 mg/kg**

2.2 Chronic Reference Dose (RfD)

Study Selected: Combined Chronic/Carcinogenicity in Rat, Cacodylic Acid

Guideline #: 870.4300, 83-1

MRID No.: 41862101

Executive Summary: In a combined chronic toxicity/carcinogenicity study (MRID 41862101; HED Doc. Nos. 009391 & 010550) cacodylic acid (99.5%, a.i.) was administered in the diet to 60 Fischer F344 rats/sex at dose levels of 0, 2, 10, 40 or 100 ppm (0, 0.14, 0.73, 2.8, or 7.3 mg/kg/day in males and 0, 0.16, 0.79, 3.2, or 8.0 mg/kg/day in females, respectively) for 104 weeks. Body weight, food consumption, food efficiency, hematology, clinical chemistry, water intake, and organ weights were measured. Eye and urine examinations were done. No satellite group was included for interim sacrifice.

Treatment with cacodylic acid did not effect mortality, food consumption, food efficiency, body weight or body weight gains. Treatment with cacodylic acid had a mild effect on hematology and the clinical chemistries of high-dose males and females and mid-dose males, at 6 months. At 100 ppm, %HCT, HGB, and RBC counts in males and %HCT and HGB in females decreased ≈ 4 - 6%, compared to the controls. There was no consistency between sexes with respect to K, Na, triglycerides, total protein and globulin levels at terminal sacrifice; therefore, toxicological significance can not be determined. Urine volume significantly ($P < 0.05$) increased in high-dose males at 3, 6 and 12 months and in females at 3 and 12 months. At 12 months, urine volume increased 55% in males and 30% in females, compared to controls. Urine specific gravity paralleled the urine volume; at 12 months the specific gravity of 40 and 100 ppm male and female urine was 1.05 vs 1.06 of controls ($P < 0.05$). Urine volume and specific gravity at other doses were comparable to controls. At 100 ppm, kidney weights in males and females increased 4.6% and 4.0%, respectively, compared to the controls ($P < 0.05$). Thickened urinary wall (3/60 vs 1/60), congested mucosa (2/60 vs 0/60), nodules (5/60 vs 0/60) masses (6/60 vs 0/60) were observed in high-dose females. Vacoular degeneration of bladder transitional epithelium was seen in both sexes at 40 (M - 1/58 and F - 21/59 vs 0 in control) and 100 ppm (M - 23/59 and F - 26/50 vs 0 in control). Submucosal lymphocytic infiltration was observed in 25% of males and 20% of the females at 100 ppm and 8.5% in females at 40 ppm, compared to controls. Transitional cell hyperplasia of the bladder in males/females at 40 and 100 ppm was 10.3%/49% and 67.8%/80%, respectively, compared to controls. Kidney lesions were dose-related and were confined to 40 and 100 ppm groups and included pyelonephritis (M- 4/60 at 100 ppm), medullary

nephrocalcinosis (M - 14/59 at 40 ppm and 18/60 at 100 ppm; F - 12/60 at 100 ppm), and medullary tubular cystic dilatation (M - 3/59 at 40 ppm, and 13/60 at 100 ppm; F - 5/60 at 100 ppm). In addition, at 100 ppm, in males the pelvic transitional hyperplasia increased 10% compared to 0% in controls. At 100 ppm, the incidence of hyperplasia of epithelium lining renal papilla increased 25% in males and 8% in females compared to controls. A dose-related increase in the height of thyroid follicular epithelium was noted in males at the 10, 40 and 100 ppm and in the females at the 40 and 100 ppm levels. In males, at the 0, 2, 10, 40 and 100 ppm the incidence was 0, 1.7, 6.7, 8.3 and 62%, respectively; and in females 0, 0, 0, 5 and 85%, respectively.

The systemic toxicity NOAEL = 2 ppm (0.14 mg/kg/day) for males and 10 ppm (0.79 mg/kg/day) for females. The LOAEL = 10 ppm (0.79 mg/kg/day) for males and 40 ppm (3.2 mg/kg/day) for 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.

Selected Dose and Endpoint for Establishing Chronic RfD: NOAEL = 0.14 mg/kg/day based on increased thyroid follicular epithelial cell height in males and decreased urine specific gravity, and increased follicular epithelial cell height observed at 0.79 mg/kg/day.

Uncertainty Factor(s): 100x (10x for intraspecies extrapolation; 10x for interspecies extrapolation)

Comments about Study/Endpoint/Uncertainty Factor(s): This study was previously selected by the HIARC (June 19, 2000) for the establishment of the chronic RfD for cacodylic acid. As described below, following application of MSMA or DSMA, because of methylation of MSMA or DSMA to cacodylic acid, dietary exposure will be to MSMA, cacodylic acid or a combination. The NOAELs of chronic dietary studies with MSMA are 2.0, 3.2, and 9.3 mg/kg/day in dogs, rats, and mice, respectively. The use the cacodylic acid chronic dietary endpoint is more conservative and is therefore more health protective.

Dietary Exposure to MSMA through FOOD:
1) MARC Committee concluded that the residues of concern (i.e., that which is of toxicological concern and requires regulation) associated with the use of MSMA and DSMA are MSMA *per se* and cacodylic acid expressed as As_2O_3. This decision was predicated on the low rate or lack of demethylation, and the inability to distinguish between background arsenic and arsenic resulting from pesticide use.

2) In acceptable plant metabolism studies, a total of 67% of the total radioactive residue (TRR) in cottonseed was identified, with 61% as MSMA and 6 %TRR as CA. In lemons (peel, pulp and juice), with 36-41 % of the TRR was identified as MSMA while 52-61 % TRR was identified as CA. In a field trial study with oranges, all treated citrus fruits bore nondetectable

residues of MSMA; 3 samples of treated fruits bore residues of cacodylic acid.

Dietary Exposure to MSMA through WATER:
MSMA, initially 100% at application time, will be partially transformed into cacodylic acid. Cacodylic acid, initially at zero concentration, will increase to a maximum over a period of months and then decline until the next seasonal application of MSMA. Studies indicate that the maximum amount of cacodylic acid produced by the metabolism of MSMA is chemically equivalent to 30 to 40% of the initial MSMA application. Therefore, depending on probabilistic and episodic rainfall/runoff events, a time-dependent, variable mixture of MSMA and cacodylic acid will be available for runoff.

Chronic RfD = $\frac{0.14 \text{ mg/kg/day (NOAEL)}}{100 \text{ (UF)}}$ = **0.0014 mg/kg/day**

2.3 Occupational/Residential Exposure

2.3.1 Short-Term (1 - 7 days) and Intermediate-term (Week to Several Months) Incidental Oral Exposure,

Selected Study: Chronic Oral Toxicity in Dog, MSMA Guideline #: 870.4100, 83-1b

MRID No.: 40546101/41266401

EXECUTIVE SUMMARY: See above for acute RfD

Selected Dose and Endpoint : 2 mg/kg/day based on body weight gain in females and clinical signs (severe diarrhea, vomiting, and excessive salivation) in both sexes.

Comments about Study/Endpoint: This study is appropriate for both short- and intermediate-term incidental oral endpoints applicable to the population of concern (toddlers) for the following reasons:
1) Clinical signs of diarrhea and vomiting in addition to excessive salivation were observed in the *first of week of dosing* making this study appropriate for the short-term duration.
2) These clinical signs continued throughout the treatment period making this study appropriate for the intermediate-term duration.
3) Diarrhea and vomiting are consistent with clinical signs observed in human acute arsenic poisoning and considered relevant endpoints for incidental oral exposure.

2.3.2 Dermal Absorption

Dermal Absorption Factor:

Study Selected: Dermal Penetration Study in Rats, Cacodylic acid §85-3

MRID No.: 43497401

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%.**

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

Dermal Absorption Factor: 3.5%

Comments about Dermal Absorption: No dermal absorption study is available for MSMA at this time; this study was selected for cacodylic acid dermal absorption. Personal communication with PV Shah, this dermal absorption study can be used for the MSMA dermal absorption.

2.3.3 Short-Term (1-7 days) and Intermediate-Term (One week to several months) Dermal Exposure

Study Selected: 21-Day Dermal Toxicity in Rabbit, MSMA §82-2b

MRID No.: 41872701/42659701

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. 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.**

Dose and Endpoint for Risk Assessment: 1000 mg/kg/day; no systemic toxicity was observed up to the guideline limit dose of 1000 mg/kg/day.

Comments about Study/Endpoint:. This 21-day dermal toxicity study is appropriate for short- and intermediate-term dermal exposure based on the route-specific exposure and also the duration of exposure. In the developmental toxicity studies, developmental toxicity was observed only at doses greater than maternally toxic doses.

2.3.3 Long-Term Dermal (Several Months to Life-Time) Exposure

Study Selected: Combined Chronic/Carcinogenicity in Rat, Cacodylic Acid

Guideline #: 870.4300, 83-1

MRID No.: 41862101

Executive Summary: See chronic RfD

Selected Dose and Endpoint: 0.14 mg/kg/day based on based on increased thyroid follicular epithelial cell height in males and decreased urine specific gravity, and increased follicular epithelial cell height observed at 0.79 mg/kg/day.

Comments about Study/Endpoint/Uncertainty Factor(s): This endpoint was also selected for the chronic RfD. At the time of this document, no long-term dermal exposure scenarios exist. If long-term dermal exposure scenarios are identified in the future, route to route extrapolation will be performed using the 3.5% dermal absorption factor.

2.3.4 Inhalation Exposure (All Durations)

Study Selected: 90-Day Inhalation Toxicity in Cacodylic acid §82-4

MRID No.: 44700301

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.

Dose/Endpoint for Risk Assessment: 0.010 mg/L/day based on the presence of moderate and marked intracytoplasmic eosinophilic granules in the cells of the nasal turbinates.

Comments about Study/Endpoint: At present time, no route-specific data is available for MSMA exposure. A 28-day inhalation toxicity study has been required by the HIARC. This study in cacodylic acid is appropriate for short- and intermediate-term inhalation exposure based on the route-specific exposure and also the duration of exposure.

2.3.5 Margins of Exposure for Occupational/Residential Risk Assessments

A MOE of 100 is required for occupational exposure risk assessment. The MOEs for residential exposure risk assessment will be determined by the FQPA Safety Factor Committee.

2.3.6 Recommendation for Aggregate Exposure Risk Assessments

For acute dietary exposure, exposure from food and water may be aggregated.

For chronic dietary exposure, exposure from food and water may be aggregated.

For short- and intermediate-term residential exposure, incidental oral exposure to MSMA or DSMA may not be aggregated with the chronic (i.e., background) dietary exposure since endpoints for incidental oral exposure and for chronic dietary exposure are based on different chemicals.

For short- and intermediate-term residential and occupational exposure, endpoints for dermal and inhalation exposure to MSMA or DSMA may not be aggregated with endpoints for dietary or non-dietary exposure.

3.0 CLASSIFICATION OF CARCINOGENIC POTENTIAL

3.1 Combined Chronic Toxicity/Carcinogenicity Study in Rats

EXECUTIVE SUMMARY: In a combined chronic toxicity/carcinogenicity feeding study (MRID 41669001), methanearsonic acid (MSMA, 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, ophthalmoscopy, hematology, clinical chemistry, urinalysis, organ weights, gross pathology, neoplastic and non-neoplastic histopathology.

Beginning at week 4-5, diarrhea was observed from 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 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. Urethral 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. Increased 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), although statistical significance was not attained with respect to either sex. 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).

Discussion of Tumor Data: 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), although statistical significance was not attained with respect to either sex.

Adequacy of the Dose Levels Tested: Dosing was considered adequate for carcinogenicity testing because of observed decreases in body weights, body weight gains, increased food consumption, and histopathology of gastrointestinal tract and thyroid.

3.2 Carcinogenicity Study in Mice

EXECUTIVE SUMMARY: In an oncogenicity study (MRID 42173201), methanearsonic acid (MSMA, 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 measured 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.

Discussion of Tumor Data: At the doses tested, there was not a treatment related increase in tumor incidence when compared to controls.

Adequacy of the Dose Levels Tested: Dosing was considered adequate because of observed decreases in body weight gain, increases water consumption, and histopathology of the large intestine and kidney.

3.3 Classification of Carcinogenic Potential

The HIARC classified MSMA as **"not likely"** a human carcinogen. Although the parathyroid adenomas described above in rats were outside of the historical controls (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 MSMA is not mutagenic in bacteria (*Salmonella typhimurium*) or cultured mammalian cells (Chinese hamster ovary). Similarly, MSMA did not induce unscheduled DNA synthesis (UDS) in primary rat hepatocytes.

It is important to note that 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. As described above, the chronic RfD for MSMA is based on a study in cacodylic acid because of potential dietary exposure to cacodylic acid following MSMA application. 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 will 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 MSMA.

4.0 MUTAGENICITY

4.1 Gene Mutation

EXECUTIVE SUMMARY: In a reverse gene mutation assay in bacteria (MRID 41651902), strains TA98, TA100, TA1535, TA1537 and TA1538 of *S. typhimurium* were exposed to Methanearsonic acid (Lot No. 107/84, 99.8% a.i.) 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). Two independent assays were conducted. The S9-fraction was obtained from Aroclor 1254 induced male Sprague-Dawley rat liver.

Methanearsonic acid was tested up to a limit concentration of 10,000 µg/plate. No cytotoxicity (thinning of the background lawn of bacteria and/or a reduction in the number of revertants per plate compared to the respective solvent control) was seen at any test material concentration, with or without S9-mix, in any tester strain in either mutation assay. Slight thinning of the background lawn was, however, seen at 10,000 µg/plate, with and without S9-mix, in strain TA100 in the preliminary cytotoxicity test. The solvent and positive controls produced the appropriate response in the respective tester strains. **There was no evidence that methanearsonic acid increased mutant colonies over background in either the presence or the absence of S9 activation.**

This study is classified as **Acceptable/Guideline.** It satisfies the requirement for FIFRA Test Guideline [OPPTS 870.5100 (§84-2)] for *in vitro* mutagenicity (bacterial reverse gene mutation) data.

4.2 Chromosomal Aberrations

EXECUTIVE SUMMARY: In a mammalian cell cytogenetics assay (chromosomal aberrations) (MRID 41651903), Chinese hamster ovary ($CHO\text{-}K_1$) cell cultures were exposed to Methanearsonic acid (Lot No. 107/84, 99.8% a.i.) 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), and in the confirmatory assay were 1250, 2500, 5000 and 10,000 µg/mL, with and without S9-mix. The S9-fraction was obtained from Aroclor 1254 induced male Sprague-Dawley rat liver.

Methanearsonic acid was tested up to a slightly cytotoxic concentration, limited by solubility in the solvent, distilled water. In the first cytogenetic assay, microscopic examination of the cell monolayer revealed slight cytotoxicity at 2500 and 5000 µg/mL in the absence of S9-mix and at 5000 µg/mL in the presence of S9-mix but the mitotic index was not reduced. In the second cytogenetic assay, cytotoxicity was seen at 5000 and 10,000 µg/mL in the absence of S9-mix and at 10,000 µg/mL in the presence of S9-mix. The mitotic index at 10,000 µg/mL without S9-mix was 50% of the solvent control value. Solvent and positive controls induced the appropriate response. **There was no evidence that Methanearsonic acid induced a clastogenic response at any dose either in the absence or the presence of S9 activation.**

This study is classified as **Acceptable/Guideline.** It satisfies the requirement for FIFRA Test Guideline [OPPTS 870.5375 (§84-2)] for *in vitro* cytogenetic mutagenicity data.

4.3 Gene Mutation

EXECUTIVE SUMMARY: In a mammalian cell gene mutation assay at the TK. locus (MRID 41651904), L5178Y $TK.^{+/-}$ mouse lymphoma cells cultured *in vitro* were exposed to methanearsonic acid (Lot No. 107/84, 99.8% a.i..) 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. A confirmatory assay was conducted at concentrations of 2000, 3000, 4000, 5000 and 6000 µg/mL without S9-mix and at concentrations of 200, 350, 500, 650, 750, 850 and 950 µg/mL in the presence of S9-mix. The S9-fraction was obtained from Aroclor 1254 induced male Sprague-Dawley rat liver.

Methanearsonic acid was tested up to cytotoxic concentrations. The high dose of 4000 µg/mL was based on the solubility limit of the test material in the dosing solution. In the mutation assays without S9-mix, the percent total growth decreased with increasing dose, reaching 48% of the solvent control value at 4000 µg/mL in the initial assay and 20% and 26% of the solvent control value in duplicate cultures at 4000 µg/mL in the confirmatory assay. Concentrations of 5000 and 6000 µg/mL were too toxic to clone in the confirmatory assay. In the mutation assays with S9-mix, the percent total growth decreased with increasing dose, reaching 14% of the solvent control value at 949 µg/mL in the initial assay and 10% of the solvent control value at 750 µg/mL in the confirmatory assay. Higher concentrations in both assays were too toxic to clone. The responses induced by solvent and positive control were appropriate. **There was no evidence that Methanearsonic acid induced a mutagenic response either in the presence or the absence of S9 activation.**

This study is classified as **Acceptable/Guideline.** It satisfies the requirement for FIFRA Test Guideline [OPPTS 870.5300 (§84-2)] for *in vitro* mutagenicity (mammalian forward gene mutation) data.

4.4 Unscheduled DNA Synthesis

EXECUTIVE SUMMARY: In an unscheduled DNA synthesis assay (MRID 41651905), primary rat hepatocyte cultures were exposed to Methanearsonic acid (Lot No. 107/84, 99.8% a.i.) 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. The autoradiographic procedure was used.

Methanearsonic acid was tested up to cytotoxic concentrations (≥ 600 µg/mL). The responses induced by solvent and positive control values (including DMSO, the positive control solvent) were appropriate. **There was no evidence that Methanearsonic acid induced unscheduled DNA synthesis, as determined by radioactive tracer procedures [nuclear silver grain counts].**

This study is classified as **Acceptable/Guideline.** It satisfies the requirement for FIFRA Test Guideline [OPPTS 870.5550 (§84-2)] for other genotoxic mutagenicity data.

4.5 **Conclusion of mutagenicity studies:** The acceptable genetic toxicology studies indicate that MSMA is not mutagenic in bacteria (*Salmonella typhimurium*) or cultured mammalian cells (Chinese hamster ovary). Similarly, MSMA 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.

5.0 FQPA CONSIDERATIONS

5.1 Adequacy of the Data Base: At this time, no neurotoxicity studies are available for MSMA or DSMA. Acute and subchronic neurotoxicity studies in mice have been required by the HIARC. Acceptable developmental toxicity studies in rat and rabbit in addition to an 2-generation reproduction study are available for MSMA at this time.

5.2 Neurotoxicity : As stated above, no neurotoxicity studies are available for MSMA or DSMA at this time. In the 104-week oncogenicity study in mice, females of the 46 and 104 mg/kg/day groups exhibited increased incidences of hypersensitivity (2/52, 8/52 and 11/51 for control, 46, and 104 mg/kg/day, respectively) and tonic convulsions (1/52, 9/52 and 12/51 for control, 46, and 104 mg/kg/day, respectively). Additional evidence of potential neurotoxicity observed in mice following oral exposure to MSMA is found in the literature. This evidence, described in more detail below, suggests that MSMA exposure effects female behavior such as nest building. There is no evidence of neurotoxicity observed in rat, rabbit, or dog. Because evidence of neurotoxicity was only observed in mice, acute and subchronic neurotoxicity studies performed with mice are being required.

5.3 Developmental Toxicity

5.3.1 Rabbit Developmental Toxicity

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID no. 43178301), methanearsonic acid (MSMA, 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 (-75%) 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 abortions and on 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.

5.3.2 Rat Developmental Toxicity

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 41926401), methanearsonic acid (MSMA, 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.**

5.4 Reproductive Toxicity

EXECUTIVE SUMMARY: In a two-generation reproduction study (MRID 43178301), methanearsonic acid (MSMA, 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 in 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 increases in food consumption were 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%).

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.

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).

5.5 Additional Information from Literature Sources *(if available)*

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.

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.

5.6 **Determination of Susceptibility:** 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.

5.7 **Recommendation for a Developmental Neurotoxicity Study**

At this time, the developmental neurotoxicity study for MSMA is **not** required. Following the review of the pending **developmental neurotoxicity study in cacodylic acid**, this requirement will be reevaluated.

Evidence that suggest requiring a Developmental Neurotoxicity study:

As described above, potential neurotoxicity was observed in female mice in the oncogenicity study and female mice behavior in literature studies.

Evidence that do not support a need for a Developmental Neurotoxicity study:.

No neuropathology was observed in any available guideline study.

Only non-specific endocrine disruption effects were observed. In the 2-generation reproduction study, postmortem examination of parental animals showed decreased absolute testes weights of 1000-ppm group of the F_0 generation and decreased prostate weight (absolute and relative) of 1000-ppm group F_1 males. In the chronic toxicity study in dog, 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. In the combined chronic/carcinogenicity study in rat, increased height of the thyroid follicular epithelium was observed at the 400 ppm and high-dose levels of both sexes.

6.0 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.

Although additional studies are being required, the database for MSMA/DSMA 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 MSMA. 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 MSMA 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 MSMA or DSMA 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 MSMA 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 MSMA is not mutagenic in bacteria (*Salmonella typhimurium*) or cultured mammalian cells (Chinese hamster ovary). Similarly, MSMA 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.

7.0 DATA GAPS

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

8.0 ACUTE TOXICITY

Acute Toxicity of MSMA*

Guideline No.	Study Type	MRIDs #	Results	Toxicity Category
81-1	Acute Oral	00145491	LD_{50} = 494 mg/kg (M&F)	II
81-2	Acute Dermal	41890001	LD_{50} = > 2000 mg/kg	III
81-3	Acute Inhalation	42604601	LC_{50} = 2.20 mg/L	III
81-4	Primary Eye Irritation	00105173	Iris and conjunctival irritation	III
81-5	Primary Skin Irritation	00105174	Moderate erythema at 72 hours	III
81-6	Dermal Sensitization	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	41892004	LD_{50} = 1935 (1631-2295) mg/kg (M&F)	III
81-2	Acute Dermal	41892005	LD_{50} = > 2000 mg/kg	III
81-3	Acute Inhalation	41892006	LC_{50} > 6 mg/L	IV
81-4	Primary Eye Irritation	41892007	Redness and chemosis of the conjunctivae	III
81-5	Primary Skin Irritation	41892008	No erythema or edema	IV
81-6	Dermal Sensitization	41890009	None	
81-8	Acute Neurotoxicity	N/A		

*Data presented is for technical DSMA.

9.0 SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

The doses and toxicological endpoints selected for various exposure scenarios are summarized below.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary	NOAEL= 2 mg/kg/day UF = 100	Clinical signs of severe diarrhea, vomiting, and excessive salivation were observed in the first of week of dosing at LOAEL of 8 mg/kg/day.	Chronic Toxicity in Dog, MSMA MRID 40546101/41266401
	Acute RfD = 0.02 mg/kg/day		
Chronic Dietary	NOAEL = 0.14 mg/kg/day UF = 100	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 observed at the LOAEL of 0.79 mg/kg/day for males and 3.2 mg/kg/day for females .	Combined Chronic/ Carcinogenicity in Rat, Cacodylic Acid MRID 41862101
		Chronic RfD = 0.0014 mg/kg/day	
Dermal, Short- and Intermediate-Term	NOAEL=1000 mg/kg/day	No systemic toxicity was observed at the limit dose of 1000 mg/kg/day. No dermal irritation was observed at 1000 mg/kg/day.	21-Day Dermal Toxicity in Rabbit, MSMA MRID 41872701/42659701
Dermal, Long-Term *	Oral NOAEL = 0.14 mg/kg/day	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 observed at the LOAEL of 0.79 mg/kg/day for males and 3.2 mg/kg/day for females .	Combined Chronic/ Carcinogenicity in Rat, Cacodylic Acid MRID 41862101
Inhalation, All durations	NOAEL= 0.010 mg/L/day.	Presence of moderate and marked intracytoplasmic eosinophilic granules (IEG) in the cells of the nasal turbinates observed at the LOAEL of 0.034 mg/L/day.	90-Day Inhalation Toxicity Cacodylic acid MRID 44700301

*An absorption factor of 3.5% is to be used for conversion from oral to dermal route.