UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

February 2, 2006

MEMORANDUM

SUBJECT: **Revised and updated executive summaries for Cacodylic acid (Dimethylarsinic acid) and Methanearsonic Acid and the relevant sodium and calcium salts. DP309103 TXR No. 0054035**

FROM: Anna Lowit
Toxicologist
Toxicology Branch
Health Effects Division (7509C)

THRU: Alberto Protzel
Branch Senior Scientist
Toxicology Branch
Health Effects Division (7509C)

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

The purpose of this memo is to provide the executive summaries for cacodylic acid (dimethylarsinic acid, DMA) and methanearsonic Acid (MMA) to support the human health risk assessment of these pesticides. A Data Evaluation Review previously developed for MRID no. 44762600 by Dr. Bob Fricke is also attached. **The contents and conclusions provided in this memo supersede any previous Toxicology Disciplinary Chapters for any and/or all of these chemicals.** This memo relies, in part, on the data analysis and conclusions provided in the document entitled "Revised Science Issue Paper: Mode of Carcinogenic Action for Cacodylic Acid (Dimethylarsinic Acid, DMA^V) and Recommendations for Dose Response Extrapolation (January 30, 2006)."

Part 1: Executive Summaries for Methanearsonic Acid (MMA)

Two new acute toxicity studies were submitted. A preliminary review of these studies has been performed. The complete data evaluation record is on-going by OPP's Special Review and Reregistration Division.

45405601 Acute Oral LD_{50} in rat

Acute oral toxicity was evaluated in five rats/group/sex (MRID no. 45405601). Doses were 2030, 2740, 3700, and 5000 mg/kg. Mortality and clinical signs were observed up to 14 days post-exposure. For males: LD_{50} = 3184 mg/kg. For females: LD_{50} = 2449 mg/kg. For sexes combined: LD_{50} = 2833 mg/kg.

43840901 Primary eye irritation test in rabbits

Eye irritation to six New Zealand White rabbits was tested with MSMA-SG (MRID no. 43840901). MSMA was instilled into the conjunctival sac of the rabbit eye. Reactions were observed at 1, 24, 48, and 72 hours along with 5 days post exposure. No corneal opacities or iritis was noted in any animal. Irritation was observed in all six rabbits as noted by conjunctival redness or chemosis. Ocular discharge was noted in all six rabbits. Five of six recovered by 96 hours. The remaining rabbit recovered by 120 hour.

870.3100 90-Day Oral Toxicity - Rat

Not available for MMA 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 MMA in the aqueous solution used for dosing was > 99%.

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). Orange discoloration is of unknown toxicological significance. Data provided by the registrant (comments provided 9/30/02) indicate that discoloration of the urine can be an occasional and normal observation in rabbits and that discoloration of the urine does not effect animal health. 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 12 mg/kg/day, based on decreased body weight, food consumption (during the dosing period), and abortions. The maternal toxicity NOAEL was 7 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 13^{th} 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 8^{th} 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 an increased incidence of skeletal variations (increased numbers of 13^{th} thoracic vertebra with ribs and 8^{th} 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)].

870.3800 Reproduction and Fertility Effects - Rat

EXECUTIVE SUMMARY: In a two-generation reproduction study (MRID 43178301), methanearsonic acid (MMA, 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 5.8, 17.8, and 63.5 mg/kg/day and 7.5, 22.5, and 77.6 mg/kg/day, respectively, for F_0 and F_1 males. The dietary concentration corresponded to 6.5, 21.1, and 75.8 mg/kg/day and 7.9, 25.4, and 88.6 mg/kg/day, respectively, for F_0 and F_1 females. 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 MMA 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).

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 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) albeit at the low end.

The reproductive LOAEL was not achieved. The reproductive NOAEL is 300 (17.2 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. Whole litter loss was noted in the 300 ppm (F_2 generation only) and 1000 ppm dose groups (F_1 and F_2; approximately 22.5 mg/kg/day and 61.4/77.6 mg/kg/day, respectively). 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) due to the whole litter loss noted above. Because of pup death, the litter survival index was reduced in these noted groups.

In conclusion, the parental LOAEL was 300 ppm (17.8 mg/kg/day) based on increased food consumption with decreased body weight gain in males (F_0 and F_1) and whole litter loss (in the F_2). The parental NOAEL is 100 ppm (5.8 mg/kg/day).

The offspring LOAEL is 300 ppm (21.1 mg/kg/day) based on increased pup death (day 0-21), reduced litter survival index, and decreased lactation index attributable to whole litter loss in the F_2 (see above). The offspring NOAEL is 100 (6.5 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.

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). 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. Dosing was considered adequate for carcinogenicity testing. MMA is considered ‘not likely’ a human carcinogen.

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, diarrhea, body weight gains, food consumption, histopathology of gastrointestinal tract and thyroid.

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, 10, 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. During the first week of dosing and observed 2-5 hours after administration, these effects were noted at the 40 mg/kg/day dose level.

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 for the first week of dosing was 40 mg/kg/day based on diarrhea and vomiting. The NOAEL for the first week of dosing was 10 mg/kg/day.

The LOAEL was 8 mg/kg/day based on body weight gain and kidney effects (organ weight and histopathology) in females 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)].

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 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)].

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.

870.7600 Dermal Absorption - Rat

No dermal absorption study is available for MMA or its sodium or calcium salts at the time.

REFERENCES

00159390 Rubin, Y. (1986) Methanearsonic Acid: Teratology Study in the Rabbit: PAL/006/MSM. Unpublished study prepared by Life Research Israel Ltd. 170 p.

40546101 Waner, T.; Nyska, A. (1988) Methanearsonic Acid: Fifty-two Week Chronic Oral Toxicity Study in Beagle Dogs: Document Number PAL/MAA/022. Unpublished study prepared by Life Science Research Israel, Ltd. 449 p.

40632601 Fermenta Plant Protection Co. (1988) Justification for Dose Selection in New Methanearsonic Acid (MAA) Mouse Oncogenicity Study. Unpublished compilation. 184 p.

41651902 Chun, J.; Killeen, J. (1989) Salmonella/MaMAAlian-Microsome Plate Incorporation Mutagenicity Assay (Ames Test) with and without Metabolic Activation with Methanearsonic Acid (MAA): Lab Project Number: 89_0087: T8471.501014: 88_0223. Unpublished study prepared by Microbiological Associates Inc. and Ricerca, Inc. 169 p.

41651903 Chun, J.; Killeen, J. (1989) In Vitro Chromosomal Aberration Assay in Chinese Hamster Ovary (CHO) Cells with Methaearsonic Acid (MAA): Lab Project Number: 89_0087: T8471.337001: 88_0220. Unpublished study prepared by Microbiological Assoceates Inc. and Ricerca, Inc. 127 p.

41651904 Chun, J.; Killeen, J. (1989) Mutagenesis Assay with Methanearsonic Acid: L5178Y TK+/_Mouse Lymphoma: Lab Project Number: 89_0087:T8471.701020: 88_0222. Unpublished study prepared by Microbiological Associates, Inc. and Ricerca, Inc. 159 p.

41651905 Chun, J.; Killeen, J. (1989) Unscheduled DNA Synthesis Assay in Rat Primary Hepatocytes with Methanearsonic Acid (MAA): Lab Project Number: 89_0087: T8471.380009: 88_0221. Unpublished study prepared by Microbiological Associates, Inc. and Ricerca, Inc. 130 p.

41669001 Crown, S.; Nyska, A.; Waner, T. (1990) Methanearsonic Acid: Combined Chronic Feeding amd Oncogenicity Study in the Rat: Final Report: Lab Project Number: PAL/004/MAA. Unpublished study prepared by Life Science Research Israel Ltd. 1878 p.

41872701 Margitich, D.; Ackerman, L. (1991) Methanearsonic Acid: 21 Day Dermal Toxicity Study in Rabbits: Lab Project No: PH Unpublished study prepared by Pharmakon Research International Inc. 549 p.

41926401 Mizens, M.; Killeen, J. (1990) A Teratology Study in Rats with Methanearsonic Acid: Lab Project Number: 89_3456: 89_0130. Unpublished study prepared by Bio/dynamics Inc., in cooperation with Ricerca, Inc. 490 p.\

42010501 Wells_Gibson, N.; Marsh, D.; Krautter, G. (1991) Absorption, Distribution and Elimination of [Carbon 14]_Methyl MSMA in the Rat: Lab Project Number: 1344: 462E. Unpublished study prepared by East, Inc. 355 p.

MMA, Executive summaries

42173201 Gur, E.; Pirak, M.; Waner, T. (1991) Methanearsonic Acid: Oncogenicity Study in the Mouse: Lab Project Number: PAL/023/MAA. Unpublished study prepared by Life Science Research Israel Ltd. 1680 p.

43178301 Schroeder, R. (1994) A Two_Generation Reproduction Study in Rats with Methanearsonic Acid (MAA): Final Report: Lab Project Number: 91/3668. Unpublished study prepared by Pharmaco LSR, Inc. 1954 p.

43840901 Brown, J.C. and Hasting, M. (1995). MSMA-SG: Primary eye irritation test in rabbits. IRI Project No. 558353. Unpublished study. 28 p.

45405601 Gur, E. and Nyska, A. (1990). Acute oral toxicity in rat with Target MSMA 6.6. LSRI Project No. PAL/024/MSMA. Unpublished. 55p.

Part 2: Executive Summaries for Dimethanearsinic Acid (DMA)

870.3100 90-Day Oral Toxicity - Rat

In a subchronic feeding study (MRID 42767701; HED Doc. No. 010550) cacodylic acid (99.5%) was administered in diet to 10 specific pathogen free Fischer F344 rats/sex at dose levels of 0, 5, 50, 500, 2000 or 5000 ppm (0, 0.4, 4.0, or 43.2 mg/kg/day in males and 0, 0.4, 4.5, or 45.7 mg/kg/day in females, respectively; actual) for 13 weeks. Body weight, food consumption, food efficiency, water consumption, hematology, clinical chemistries, urinalysis and organ weights were determined. Histopathology was done on all animals in the control and 500 ppm group. Tissues from 2,000 and 5,000 ppm animals were not examined.

All rats in the 2,000 or 5,000 ppm group died or were sacrificed during the first 5 weeks of treatment. Two males and 2 females died at 500 ppm during week 4 and 13. The predominant clinical sings in moribund animals included hunched back, thinness, emaciation, decreased motor activity, urogenital wetting, diarrhea, snout staining and failure to groom.

Treatment with cacodylic acid did not effect food consumption and food efficiency. At 500 ppm body weight gain was decreased 13% in males and 17% in females, respectively ($P < 0.05$). At this dose, in males and females, %HCT, hemoglobin, red cell count, MCV and MCHC decreased < 10% ($P < 0.05$). At 50 ppm, in females, hemoglobin and red cell values decreased < 4%, respectively ($P < 0.05$). A dose-related decrease in absolute and relative adrenal weights in males and absolute adrenal weight in females was observed. At 500 ppm, the absolute/relative adrenal weights in males and absolute adrenal weights in females decreased 25%/18% and 18%, respectively ($P < 0.05$). Decreased adrenal weights were not correlated with any histopathological changes. Generally, the absolute/relative thyroid weights increased in the males (-5 to 21%/4 - 21%) and decreased in the females (-11 to -16%); and weight changes were associated with increased incidence of follicles lined with cuboidal to columnar epithelial cells at the 50 and 500 ppm doses in both sexes. Water consumption at 50 and 500 ppm increased 36 and 44% in males and 22 and 34% in females, respectively ($P<0.05$). At these dose levels increased urine volume (62 - 93%) and decreased urine specific gravity (1.04 to 1.05 vs 1.06 to 1.07) was observed in both sexes ($P < 0.05$), which is consistent with increased water consumption and kidney changes. The relative kidney weights increased 10 and 7%, in males and females, respectively, at the 500 ppm dose ($P < 0.05$). Microscopically, papillary necrosis (2M), hyperplasia of the epithelium lining the renal papilla (4M and 1F) and cystic dilatation (1M) was observed at 500 ppm dose level. At 50 ppm cystic dilatation was seen in one male. In addition reduced bone marrow cellularity (5M and 2F), reduced spermatozoa (2M), reduced uterine smooth muscle cytoplasm (7F), subchronic myocarditis (3M), focal mineralization of aorta (3M) was observed at the 500 ppm. **The systemic toxicity NOAEL = 5 ppm (0.4 mg/kg/day) and LOAEL = 50 ppm (4 mg/kg/day in males and 4.5 mg/kg/day in females), based on decreased hematology parameters in females, increased incidence of cuboidal to columnar epithelial cells lining thyroid follicles in both sexes, increased water consumption and urine output and decreased urine specific gravity in both sexes.**

CLASSIFICATION: The study is **Acceptable/Guideline** and satisfies the guideline requirement for subchronic toxicity study (82-1a) in rats.

870.3100 90-Day Oral Toxicity - Mouse

This mouse subchronic feeding study (MRID 42362501; HED Doc. No. 009775) is unacceptable. However, the requirement was waived since numerous special studies are available in the rat—a more sensitive species.

870.3200 21/28-Day Dermal Toxicity - Rabbit

In a 21-day dermal toxicity study (MRID 41872801; HED Doc. No.010410) cacodylic acid (99.95%, a.i.) was applied dermally under occlusive bandage to 5 New Zealand White rabbits/sex/group at doses of 0, 100, 300 or 1000 mg/kg once daily, five days a week for 3 weeks. Parameters measured were toxic signs, body weight, food consumption, hematology, clinical chemistry, urinalysis, organ weights, and histopathology.

Cacodylic acid did not elicit any effects on the skin. At 1000 mg/kg/day, decreased body weight gains in females (11 - 25%), and decreased testicular weights (19%) associated with hypospermia (3/5 vs 1/5 controls) and tubular hypoplasia (4/5 vs 0/5 controls) in males were observed. **Dermal irritation NOAEL = 1000 mg/kg/day (HDT) and LOAEL was not established**. The **Systemic Toxicity NOAEL = 300 mg/kg/day and the LOAEL = 1000 mg/kg/day, based on body weight changes in females and testicular weights and associated histopathological changes in males.**

CLASSIFICATION: The study is classified as **Acceptable/Guideline** and **satisfies** the guideline requirements for a repeat dermal toxicity study (82-2b) in rabbit.

870.3465 90-Day Inhalation - Rat

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 to 10 rats/sex/dose at aerosol concentrations of 10, 34 and 100 mg/m^3 (analytical concentrations 0.01, 0.034, or 0.1 mg/L). 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 34 and 100 mg/m^3 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.

870.3800a Prenatal Developmental Toxicity Study - Rat

In a developmental toxicity study (MRID 40625701) cacodylic acid (99.8%) was administered in distilled water by gavage to groups of pregnant Charles River Sprague-Dawley rats (22/dose) at dose levels of 0, 4, 12, and 36 mg/kg/day during gestation days 6 through 15.

No adverse effects were seen in mothers or offspring at 4 or 12 mg/kg/day. Maternal toxicity was observed at the highest dose (36 mg/kg/day), as decreased body weights (4- 6%; P < 0.01 to 0.001), body weight gains (16- 30%; P < 0.01 to 0.001), food consumption (11.5 - 18.5%: P < 0.001) and gravid uterine weights (19%; P < 0.001). The data indicate that the decreased body weights and body weight gains were due to lower gravid uterine weights. Developmental toxicity was observed at the 36 mg/kg/day, as decreased fetal body weights (14.7%; P < 0.001), shorter crown-rump length (5%; P <

0.001), and suggestion of diaphragmatic hernia (12% vs 0 in the control, 4 or 12 mg/kg dose; $P < 0.05$). In addition, an increased incidence of delayed/lack of ossification of numerous bones (ant. fontanelle - 5%, supraoccipital - 43%, hyoid - 19%, one or two thoracic vertebral centra - 39%, 3 or more thoracic centra - 12%, bipartite centra - 6%, 13th rudimentary ribs - 9%, 1 or more unossified sternebrae - 16%, irregular ossification of 1 or more sternebrae - 44%, unossified metacarpus V - 89%, unossified pubic bone - 9%; $P < 0.05$ to 0.001) was reported. All the above delayed/lack of ossification of numerous bones were related to a decrease in fetal growth rate, except the increase in 13th rudimentary ribs.

Maternal Toxicity NOAEL = 12 mg/kg/day
Maternal Toxicity LOAEL = 36 mg/kg/day, based on decreased body weights, body weight gains food consumption and gravid uterine weights.

Developmental Toxicity NOAEL = 12 mg/kg/day
Developmental Toxicity LOAEL = 36 mg/kg/day, based on decreased fetal weights, shorter crown rump length, the suggestion of diaphragmatic hernia and delayed/lack of ossification of numerous bones.

The study is classified as **Acceptable/Guideline** and **satisfies** the guideline requirement for a developmental toxicity study (83-3a) in rat.

870.3700b Prenatal Developmental Toxicity Study - Rabbit

In a developmental toxicity study (MRID 40663301) cacodylic acid (99.8%, a.i.) was administered in water by oral gavage to groups of pregnant New Zealand White rabbits (15/dose) at dose levels of 0, 3, 12 or 48 mg/kg/day on gestation days 7 through 19.

No systemic effects were observed at 3 or 12 mg/kg/day. At 48 mg/kg/day, 6 of 15 rabbits died during days 18 to 24 and 9 of 15 rabbits aborted during days 19 to 29; none of the pregnant rabbits survived to the day 29 scheduled sacrifice. At this dose, body weights, weight gains, and food consumption were greatly reduced. There were no cesarian section observations, gross or skeletal fetal findings to indicate a test article effect at 3 or 12 mg/kg/day. None of the high-dose animals survived to the termination to evaluate developmental toxicity.

Maternal Toxicity NOAEL = 12 mg/kg/day
Maternal Toxicity LOAEL = 48 mg/kg/day, based on mortality, abortions, body weight loss and reduced food consumption.

Developmental Toxicity NOAEL = 12 mg/kg/day
Developmental Toxicity LOAEL was not established since no pregnant rabbit survived to the gestation day 29 scheduled sacrifice.

The study is classified as **Acceptable/Guideline** and **satisfies** the guideline requirement for a developmental toxicity study (83-3b) in rabbit.

870.3800 Reproduction and Fertility Effects - Rat

In a two-generation reproductive toxicity study (MRIDs 41059501& 41652201) cacodylic acid (98.7%, a.i.) was administered to 25 Charles River CD rats/sex/dose in the diet at dose levels of 0, 3, 21 or 147 ppm (Mean of 2-gen.: 0, 0.31, 2.16, or 15.5 mg/kg/day for males and 0, 0.38, 2.48, or 17.86 mg/kg/day for females, respectively; calculated) for 10 weeks prior to mating and through both generations and lactation.

DMA, Executive summaries

Treatment with cacodylic acid did not affect clinical signs, body weights, body weight gains, food consumption, water intake, and hematology. At 147 ppm, in the F1 generation females the absolute and relative ovarian weights decreased 12% and 16%, respectively, compared to the controls. Lower ovarian weights suggest mild treatment effects; however, histopathology was unremarkable. At this dose, F1 females exhibited a 3.6 fold increase in the incidence of thyroid follicles lined with cuboidal to columnar epithelium compared to controls ($P < 0.001$). The incidence at 3 and 21 ppm was the same or slightly above the controls. Treatment with cacodylic acid did not effect the reproductive parameters or developmental effects in the offspring.

Parental Toxicity NOAEL = 21 ppm (2.16 mg/kg/day for males and 2.48 mg/kg/day for females)
Parental Toxicity LOAEL = 147 ppm (15.5 mg/kg/day for males and 17.86 mg/kg/day for females), based on lower absolute and relative ovarian weights and increased incidence of thyroid follicles lined with cuboidal to columnar epithelium in females only.

Reproductive Toxicity NOAEL = 147 ppm.
Reproductive Toxicity LOAEL was not established. There was no suggestive evidence of toxicity to the offspring in either generation.

Although, cacodylic acid at the highest dose (147 ppm) tested, did not elicit typical systemic toxicity (i.e., mortality, clinical signs or changes in body weights), there were significant decreases in absolute and relative ovarian weights in F1 females and thyroid lesions in females of both generations. Similar thyroid lesions were also observed in Fischer rats in the subchronic study (MRID 42767701). Additionally, the HDT of 17 mg/kg/day is within the range of LOAELs established in the subchronic (5 mg/kg/day), and the developmental (36 mg/kg/day) toxicity studies. Therefore, it appears that the highest dose used in this study was adequate to assess the reproductive toxicity of cacodylic acid.

The study is classified as **Acceptable/Guideline** and **satisfies** the guideline requirement for a reproduction toxicity study (83-4) in rat.

870.4100a (870.4300) Chronic Toxicity - Rat

In a combined chronic toxicity/carcinogenicity study (MRID 41862101) 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.

Benchmark Dose Estimates for Bladder Effects (as described in DMA MOA Paper, USEPA, 2005b)			
Tumors	104 weeks	BMD_{10} = 7.74 mg/kg/day	$BMDL_{10}$ = 5.96 mg/kg/day
Hyperplasia	10 weeks	BMD_{10} = 2.00 mg/kg/day	$BMDL_{10}$ = 1.54 mg/kg/day

The study is classified as **Acceptable/Guideline** and satisfies the guideline requirements for combined chronic toxicity (83-5a) in rats, even though the study is deficient for lack of interim sacrifice.

870.4100b Chronic Toxicity - Dog

In a chronic feeding study (MRID 41490901; HED Doc. No. 010630) cacodylic acid (99.8%) was administered as a single oral dose by capsule to 5 purebred beagle dogs/sex at dose levels of 0, 6.5, 16 or 40 mg/kg/day 6 days a week for 52 weeks. Food consumption, body weights and weight gains, hematology, clinical chemistries, urinalysis, and organ weights were determined. Ophthalmologic and neurological examinations were conducted.

Treatment with cacodylic acid did not affect, food consumption, ophthalmology, neurology, and organ weights. A dose-related increase in the salivation and diarrhea in both sexes and vomiting in females were observed. The overall incidence of salivation in high dose males and females was 86.5% (range 72.8 to 93.7) and 95.2% (range - 78.9 to 101), respectively, compared to 0 to 0.1% in the controls. In the low and mid-dose males and females, the frequency of salivation was 0.5 and 18.6%, and 13 and 17.9%, respectively, compared to the controls. The mean incidence of diarrhea in high-dose males and females was 44%, respectively, compared to 4 to 5% in controls. In low- and mid-dose males and females the incidence was 6 and 15.9% and 9.4 and 14.4%, respectively. The incidence of vomiting proportionally increased with salivation and diarrhea; in the high dose the mean weekly incidence was 9.2% in males and 19.4% in females, compared to 0.9 and1.5% in controls, respectively. The vomiting incidence in low and mid-dose males and females was 5.3 and 2.2% and 9.4 and 12.3%, respectively. At the highest dose the salivation, vomiting and diarrhea were more pronounced in the incidence and were associated with other effects such as decreased body weight gains, and decreased protein and albumin seen in this study. Body weight gains decreased 29 and 42%, in highest dose males and females, respectively. Body weight of low dose females decreased 30%, however, lacked dose response. In high dose males there was a slight decrease in HCT (10%), HgB (11%) and RBC numbers (11%) ($P < 0.05$ to 0.001) at 25 week sampling time; also total protein/albumin concentration decreased throughout the study and was 13%/21% at termination of the study ($P < 0.001$). The changes in hematology parameters and

protein/albumin levels in high-dose males are consistent with body weight gains and are considered treatment-related, even though it was discounted in the DER. The **Systemic Toxicity NOAEL = 16 mg/kg/day and LOAEL = 40 mg/kg/day, based on salivation, vomiting , diarrhea, and decreased body weight gains (M & F) and decreased HCT%, HgB, RBC counts, and total protein and albumin concentration (M).**

The study is classified as **Acceptable/Guideline** and satisfies the guideline requirements for chronic toxicity study (83-1b) in dogs.

870.4200a Carcinogenicity Study - Rat

See above.

870.4200b Carcinogenicity [feeding] - Mouse

In a carcinogenicity study (MRID 41914601; HED Doc. No. 008891) cacodylic acid (99.5%) was administered in diet to 55 B6C3F1 mice/sex at dose levels of 0, 8, 40, 200, or 500 ppm (0, 1.45, 7, 35.25, or 91.95 mg/kg/day in males and 0, 1.7, 8.65, 43.15 or 97 mg/kg/day in females; mean of maximum and minimum achieved doses) for 104 weeks. Body weights and weight gains, food consumption, water intake, blood smears for differential cell counts, and organ weights were determined.

Treatment with cacodylic acid did not affect survival, food consumption, food efficiency, differential cell counts, or organ weights. At 500 ppm, body weight gains decreased 15.5% in males during the study. The urinary system appears to be the target organ for this chemical in both mice and rats. Microscopically, a dose-related, increased vacoular degeneration of bladder epithelium (focal to diffuse) was seen in males at 200 ppm and above and in females at 40 ppm and above. The incidence at the 0, 8, 40, 200 and 500 ppm was 0, 1.8, 0, 94, 100% in males and 2, 1.9, 40.8, 98 and 100% in females, respectively. Progressive glomerulonephropathy and nephrocalcinosis showed a positive trend ($P < 0.05$ and 0.001, respectively) among males; when combined by sex, the trend persisted ($P < 0.05$ and 0.001, respectively). In males, the glomerulonephropathy incidence was 30.3, 41, 32, 57, and 57% at the 0, 8, 40, 200 or 500 ppm, respectively; females were not effected. Eighty-two percent (82%) of 500 ppm males were observed with nephrocalcinosis of the kidney vs 50% in the control group; the incidence at other dose levels was below the control. There was a statistically significant increase ($P < 0.01$) in fibrosarcomas observed in the abdominal cavity of high-dose female (10.7%) mice. In the males there was a non-significant positive trend for fibrosarcomas. Overall, this study does not demonstrate a tumorigenic response. The **systemic toxicity NOAEL = 40 ppm (7 mg/kg/day) for males and 8 ppm (1.7 mg/kg/day) for females and the LOAEL = 200 ppm (35.25 mg/kg/day) for males and 40 ppm (8.65 mg/kg/day) for females**, based on vacoular degeneration of bladder epithelium.

The dosing was considered adequate.

The study is classified as **Unacceptable/Guideline** because of inadequacy of dosing in females. Previously, the study was classified as core-Supplementary, the Cancer Peer Review Committee concluded that the mouse carcinogenicity study in conjunction with the rat carcinogenicity study provides sufficient information for the carcinogenicity risk assessment, and recommended that there is no need to repeat the mouse cancer study.

Gene Mutation, Chromosomal Aberrations, Etc.

There are numerous studies with DMA and the trivalent metabolite. Refer to Table B4 in the DMA MOA paper (USEPA, 2005).

870.7600 Dermal Absorption - Rat

In a dermal absorption study(43497401), 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 g/cm2, respectively; at 24 hours 10.99, 6.55 or 7.07%, respectively. Generally, the % 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/Guideline** and satisfies the guideline requirement for a dermal penetration study (85-3) in rat.

Dermal Absorption Factor: 3.5%

Special Studies for Mode of Action

There are various special studies available which elucidate the rat bladder tumor mode of action. These are described in detail in the DMA MOA paper (USEPA, 2005).

REFERENCES

40625701 Gal, N., Y. Rubin (1988) Cacodylic Acid, Teratogenicity Study in the Rat. Life Sciences Research Israel Ltd., Israel. Study No. PAL/017/CAC. April 18, 1988. MRID 40625701. Unpublished.

40663301 Rubin, Y., A. Nyska (1988) Cacodylic Acid, Teratogenicity Study in the Rabbit. Life Sciences Research Israel Ltd., Israel. Study No. PAL/019/CAC. May 5, 1988. MRID 40663301. Unpublished.

41059501 Rubin, Y., N. Gal, A. Nyska, et al. (1989) Cacodylic Acid - Two Generation Reproduction Study in the Rat. Life Sciences Research Israel Ltd., Israel. Study No. PAL/015/CAC. February 5, 1989. MRID 41059501. Unpublished.

41490901 Zomber, G., A. Nyska, T. Warner, et al. (1989) Cacodylic acid 52-Week Oral toxicity Study in Beagle dogs. Life Science Research Israel, Ltd., Israel. Study No. PAL/012/CAC. November 21, 1989. MRID 41490901. Unpublished.

41862101 Gur, E., A. Nyske, T. Warner, et al. (1989) Cacodylic Acid Combined Chronic Feeding and Oncogenicity Study in The Rat. Life Science Research Israel, Ltd., Israel. Study No. PAL/010/CAC. October 30, 1989. MRID 41862101. Unpublished.

41872801 Margitich. D., L. Ackerman (1991) Cacodylic Acid - 21-Day Dermal Toxicity Study in rabbits. Pharmakon Research International, Inc., Waverly, PA. Study No. PH 430-LI-002-90. March 13, 1991. MRID 41872801. Unpublished.

41914601 Gur, E., A. Nyska, M. Pirak , et al. (1990) Cacodylic acid Oncogenicity Study in the Mouse. Life Sciences Research Israel Ltd., Israel. Study No. Project ID PAL/014/CAC. December 24, 1990. MRID 41914601. Unpublished.

42341301 Gibson. N., J. Marsh, G. Krautter (1992) Absorption, Distribution and Elimination of [^{14}C]Cacodylic Acid in the Rat. PTRL East, Inc., Richmond, KY. Study No. PTRL Project No. 461. May 29, 1992. MRID 42341301 & 43005801. Unpublished.

42362501 Crown, S; A. Nyska (1992) Cacodylic acid Toxicity in Dietary Administration to Mice for 13 Weeks: A Preliminary Study. Life Science Research Israel, Ltd., Israel. Study No. PAL/013/CAC. April, 1992. MRID 42362501. Unpublished.

42767701 Crown, C., G. Kenan, G, A. Nyska, et al. (1987) Cacodylic acid Toxicity in Dietary Administration to Rats for 13 weeks: A Preliminary Study. Life Science Research Israel, Ltd., Israel. Study No. PAL/009/CAC. May 1987. MRID 42767701. Unpublished.

43497401 Hauswald, C. (1994) A Dermal Radiotracer Absorption Study with ^{14}C-Cacodylic Acid in Rats. Wil Research Lab. Lab. Project No. WIL-198003. March 4, 1994. MRID 43497401. Unpublished.

44762600 Cohen, S. M. and Arnold, L.L. (1999) Evaluation of dose response and mode of action of cacodylic acid on the urinary bladder following administration to rats. Department of Pathology and Microbiology, University of Nebraska Medical Center, Omaha, NE. Project No. 210. February 2, 1999. Unpublished.

44700301 Whitman, F.T. 1994. Subchronic (90-day) inhalation toxicity study in rats with cacodylate 3.25 (MRD-92-416). Exxon Biomedical Sciences, Inc., Toxicology Laboratory, Mettlers Road, CN 2350, East Millstone, N.J. 08875-2350. Laboratory Project ID No. 141618, October 27, 1994. MRID 44700301. Unpublished.

46436501 Cohen, S.; Yamamato, S.; Cano, M.; et. al. (2001) Urothelial Cytotoxicity and Regeneration Induced by Dimethylarsinic Acid in Rats. Toxicological Sciences 59: 68-74; Unpublished material prepared by University of Nebraska. 102 p.

46436502 Cohen, S.; Arnold, L.; Uzvolgyi, E.; et. al. (2002) Possible Role of Dimethylarsinous Acid in Dimethylarsinic Acid-Induced Urothelial Toxicity and Regeneration in the Rat. Chem. Res. Toxicol. 15: 1150-1157; Unpublished material prepared by University of Nebraska and University of Alberta. 73 p.

46436503 Wei, M.; Cohen, S.; Cano, M.; et. al.; (2004) Lack of Inhibition by Melatonin of the Toxic and Proliferative Effects of Dietary Dimethylarsinic Acid on Rat Urothelium. Toxicologist 78; Unpublished study. 136 p.

46436504 Wei, M.; Arnold, L.; Cano, M.; et. al.; (2004) Effects of Co-administration of Antioxidants and Arsenicals on the Rat Urinary Bladder Epithelium. Unpublished study prepared by University of Nebraska and Osaka Municipal University. 91 p.

46436505 Arnold, L.; Cano, M.; Cohen, S.; et. al.; (2002) Effects of the Dose of Dimethylarsinic Acid (DMA) on the Urinary Concentration of Dimethylarsinous Acid (DMAIII). Unpublished study prepared by University of Nebraska and University of Alberta. 26 p.

46671701 Arnold, L.; Cano, M.; St. John, M.; et. al. (1998) Effects of Dietary Dimethylarsinic Acid on the Urine and Urothelium of Rats. Project Number: 210. Unpublished study prepared by University of Nebraska. 415 p.