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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

014666

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

DATE: August 28, 2001

MEMORANDUM:

SUBJECT: Cacodylic Acid - Review of subchronic inhalation study and updating executing summaries

Barcode No.: D251139
Submission No.: S551828
PC Nos.: 012501
Tox. Chem. No.: 133

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Registration Action Branch I
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8/28/01

Thru: George Jeffery Herndon, Branch Senior Scientist
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I. CONCLUSIONS

The subchronic inhalation toxicity study in rat (MRID 44700301) using cacodylic acid (Cacodylate 3.25 formulation) has been reviewed and it is found **Acceptable/Guideline.** In addition, the executive summaries for 90-day feeding rat (MRID 42767701), 21-day dermal rabbit (MRID 41872801), developmental toxicity studies rat (MRID 40625701), and rabbit (MRID 40663301), reproduction toxicity rat (MRID 41059501), combined chronic toxicity/carcinogenicity rat (MRID 41862101), carcinogenicity study mouse (MRID 41914601), dermal penetration study in rat (MRID 43497401) and general metabolism study in rat (42341301 & 43005801) have been updated. The DER for the 90-day inhalation toxicity study and the updated executive summaries are attached.

II. ACTION REQUESTED

The registrant Luxembourg Industries (Pamol), Tel Aviv, Israel, submitted an 90-day inhalation toxicity study using the formulation containing 4.9% cacodylic acid, in support of reregistration of cacodylic acid technical. The product is registered for use on cotton, non-bearing citrus, weed control around buildings and lawn renovations.

III. STUDIES REVIEWED

The subchronic inhalation toxicity study in rat (MRID 44700301) using cacodylic acid (Cacodylate 3.25 formulation) has been reviewed and it is found **Acceptable/Guideline.** In addition, the the database on cacodylic acid have been reevaluted and theexecutive summaries for 90-day feeding rat (MRID 42767701), 21-day dermal rabbit (MRID 41872801), developmental toxicity studies rat (MRID 40625701), and rabbit (MRID 40663301), reproduction toxicity rat (MRID 41059501), combined chronic toxicity/carcinogenicity rat (MRID 41862101), carcinogenicity study mouse (MRID 41914601), dermal penetration study in rat (MRID 43497401) and general metabolism study in rat (42341301 & 43005801) have been updated. Following are the conclusions:

1. 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 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.

2. EXECUTIVE SUMMARY: In a subchronic feeding study (MRID 42767701) 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** and satisfies the guideline requirement for subchronic toxicity study (82-1a) in rats.

3. EXECUTIVE SUMMARY: In a 21-day dermal toxicity study (MRID 41872801) 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. **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** and **satisfy** the guideline requirement for a repeat dermal toxicity study (82-2b) in rabbit.

4. EXECUTIVE SUMMARY: 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). All the above delayed/lack of ossification of numerous bones were related to a decrease in fetal growth rate, except increase in 13th rudimentary ribs. The **Maternal Toxicity NOAEL = 12 mg/kg/day and LOAEL = 36 mg/kg/day,** based on decreased body weights, body weight

gains, food consumption and gravid uterine weights. The **Developmental Toxicity NOAEL = 12 mg/kg/day and 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.

CLASSIFICATION: The study is classified as **Acceptable** and satisfy the guideline requirement for a developmental toxicity study (83-3a) in rat.

5. EXECUTIVE SUMMARY: 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 and 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. The **Maternal Toxicity NOAEL = 12 mg/kg/day and LOAEL = 48 mg/kg/day**, based on mortality, abortions, body weight loss and reduced food consumption. The **Developmental Toxicity NOAEL = 12 mg/kg/day and LOAEL was not established since no pregnant rabbit survived to the gestation day 29 scheduled sacrifice.**

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

6. EXECUTIVE SUMMARY: In a two-generation reproductive toxicity study (MRID #s 41059501& 41652201) cacodylic acid (98.7%, a.i.) was administered to 25 Charles River CD rats/sex/dose in 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 during both generations and lactation.

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 same or slightly above the controls.

Treatment with cacodylic acid did not effect the reproductive parameters or developmental effects in the offspring. The **Parental Toxicity NOAEL = 21 ppm (2.16 mg/kg/day for males and 2.48 mg/kg/day for females) and 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. The **Reproductive Toxicity NOAEL = 147 ppm, 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), however, 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 (MRID 40625701; 36 mg/kg/day) toxicity studies in this species. Therefore, it appears that the highest dose used in this study was adequate to assess the reproductive toxicity of cacodylic acid.

CLASSIFICATION: The study is classified as **Acceptable** and **satisfy** the guideline requirement for a reproduction toxicity study (83-4) in rat.

7. EXECUTIVE SUMMARY: In a combined chronic toxicity/carcinogenicity study (MRID 41862101) cacodylic acid (99.5%, a.i.) was administered in 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 done. Eye and urine examinations were done. There was no satellite group included for interim sacrifice.

Treatment with cacodylic acid did not effect mortality, food consumption, food efficiency, body weight and body weight gains. Treatment with cacodylic acid had a mild effect on hematology and clinical chemistries of high-dose males and females and mid-dose males, at the 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 sp. gr. of 40 and 100 ppm male and female urine was 1.05 vs 1.06 of controls ($P < 0.05$). Urine volume and sp. gr. 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. Vacuolar 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). Submucosal lymphocytic infiltration was observed in 25% of males and 20% of the females at 100 ppm. Lymphocytic infiltration also increased 8.5% in females at the 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 include 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 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. **Neoplastic lesions were observed in both sexes at the 100 ppm dose.** In males, the transitional cell papilloma was found one each at 10 and 40 ppm and 0 at 100 ppm. In females, 0, 0, and 4 in 10, 40 and 100 ppm, respectively; these papillomas reached significance ($P < 0.05$) in females. At the high-dose the combined incidence of papillomas + carcinomas in high-dose males and females was 3.4% and 16.7%, respectively. The trend was significant in both sexes and the incidence at 100 ppm in both sexes exceed the range of historical controls from the study laboratory. Additionally, the high-dose females was statistically significant incidence in pairwise comparison to controls.

The dosing was considered adequate for testing the neoplastic potential of cacodylic acid since highest dose tested induced bladder neoplasms in both sexes. Further, in the subchronic toxicity study (MRID 42767701) a LOAEL of 50 ppm was based on decreased hematology parameters in females, increased incidence of cuboidal to columnar epithelial cell lining thyroid follicles in both sexes, increased water consumption and urine output and decreased urine specific gravity. The NOAEL was 5 ppm. The 100 ppm dose in the carcinogenicity study is 2X the LOAEL from the subchronic toxicity study.

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, increased follicular epithelial cell height, and urinary bladder lesions (increased vacuolar degeneration of transitional epithelium, lymphocytic infiltration, transitional hyperplasia) in females.

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

8. EXECUTIVE SUMMARY: In a carcinogenicity study (MRID 41914601) 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, and organ weights. At 500 ppm, body weight gains decreased 15.5%in males during the study. As noticed in the rat urinary system is the target for this chemical. Microscopically, a dose-related, increased vacuolar 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, 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 fibrosarcoma in the high-dose females (10.7%) observed in the abdominal cavity; in the males there was a non-significant positive trend. The trend in the data combined by sex was significant ($P < 0.01$). When these two lesions were combined as two forms of the same disease, a significant result($P < 0.01$) was observed in females and in the data combined by sex. The **Systemic Toxicity NOAEL = 40 ppm (7 mg/kg/day) for males and 8 ppm (1.7 mg/kg/day) for females and the LOEL = 200 ppm (35.25 mg/kg/day) for males and 40 ppm (8.65 mg/kg/day) for females**, based on vacuolar degeneration of bladder epithelium.

The dosing was considered adequate based on the neoplastic response in high-dose females, decreased body weight gains > 15% in high-dose males, and urinary bladder lesions in males above 200 ppm and in females above 40 ppm. In addition, the 13 week mouse feeding study (MRID 42362501), demonstrated a NOAEL of 50 ppm and LOAEL of 500 ppm, based on decreased food efficiency (M), increased water consumption (F), and vacuolar degeneration of bladder transitional epithelium (M & F).

CLASSIFICATION: The study is classified as **Unacceptable** and may be upgraded by the submission of (1) the criteria for exclusion of organ weights from the group means, (2) an

explanation of why the clinical pathology data from all animals was not reported, and (3) clarification of the statement regarding the significance of the incidence of fibrosarcoma combined with fibroma as two stages of the same disease in the male. The study does not satisfy the guideline requirement for a oncogenicity study (83-2b) in mice.

9. EXECUTIVE SUMMARY: In a dermal absorption study (MRID 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 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 satisfy the guideline requirement for a dermal penetration study (85-3) in rat.

10. EXECUTIVE SUMMARY: In a general metabolism study (MRID 42341301 & 43005801) [^{14}C]Cacodylic acid was administered to male and female Sprague-Dawley CD rats as a single oral dose at 0, 5.0, and 50.0 mg/kg, a repeated oral doses (14 daily doses) of unlabeled Cacodylic Acid at 5 mg/kg followed by a single dose of labeled Cacodylic Acid at 5.0 mg/kg and single i.v. dose at 5.0 mg/kg.

Highest absorption (100%) was observed in the single i.v. dose followed by the low and high dose animals (≈ 72%), and the repeated dose (≈ 79%) . About 19 to 29% of the orally administered dose was distributed in the blood and whereas ≈ 10% of the i.v. dose was recovered in the blood. The majority of the radioactivity in the blood was associated with erythrocytes as the parent compound, Cacodylic Acid. The radioactivity found in the carcasses accounted for 6 to 20%; lowest levels were detected by i.v. route. Other tissues and organs, except the skin of the oral low dose males contained < 5% of the administered dose. Over a 7-day period, most (≈ 90 - 98%) of the test compound administered was excreted from

the animals. The total radioactivity recovered in the urine, feces, and CO_2 in the exhaled air was 28 - 82, 4 - 33, 0 - 0.1%, respectively. Urinary excretion was highest (81%) in the i.v. dose group, and was lowest (28%) in the low dose oral group. Fecal excretion accounted for 4 - 33%; lowest (4%) amount was excreted in the i.v. dose group.

Three metabolites i.e., unknown metabolite C , D, and Monosodium Methanearsenic Acid (MSMA) and the parent Cacodylic Acid were identified. Major urinary metabolite Cacodylic Acid accounted for 17 - 20% in the oral low and high dose groups. Metabolite C and Metabolite D accounted for 7 - 13% and < 2%, respectively; MSMA (< 1%) was present only in the urine of high dose groups. The repeated dose groups showed a different urinary profile, Metabolite C (28 - 36%) was the major metabolite followed by cacodylic acid (12%) and Metabolite D (6 - 10%). Fecal excretion of Cacodylic Acid in the oral dose groups ranged from 8.6% in the low dose female to 32% in the high dose male; and the Metabolite C ranged from 0.3% in the high dose male to 6.2% in the repeated dose male and the Metabolite D ranged from 0 to 0.3%. Fecal Metabolite C was higher in the repeated dose groups vs the low and high dose groups.

CLASSIFICATION: The study is classified as **Acceptable** and **satisfies** the guideline requirements for a General Metabolism study (85-1) in rat.

014666

DATA EVALUATION REPORT

CACODYLATE 3.25

STUDY TYPE: SUBCHRONIC (90 DAY) INHALATION TOXICITY - RAT

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Chemical Hazard Evaluation Group
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Oak Ridge, TN 37831
Task Order No. 99-9

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Robert H. Ross, M.S., Group Leader	Signature:	Robert H. Ross
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Quality Assurance: Eric B. Lewis, M.S.	Signature:	Eric B. Lewis
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Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

Oak Ridge National Laboratory, managed by Lockheed Martin Energy Research Corp. for the U.S. Department of Energy under contract number DE-AC05-96OR22464.

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EPA Reviewer: G. Reddy, Ph.D. _____, Date 3/1/99
Toxicology Branch 2 (7509C)
EPA Work Assignment Manager: S. Diwan, Ph.D. _____, Date 3/1/99
Toxicology Branch 2 (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Subchronic (90 day) inhalation toxicity - rat (OPPTS 870.3465) (§82-4)

DP BARCODE: D 251139
P.C. CODE: 012501

SUBMISSION CODE: S 551828
TOX. CHEM. NO.: 133

TEST MATERIAL (PURITY): Cacodylate 3.25 (active ingredients: cacodylic acid (4.9%) and sodium cacodylate (28.4%), batch 095/93, EPA Reg. No. 42519-4)

SYNONYMS: hydroxydimethylarsine oxide; dimethylarsinic acid; dimethylarsonic acid; dimethylarsenic acid; (Exxon MRD-92-416)

CAS NO. 75-60-5

CITATION: 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.

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EXECUTIVE SUMMARY: In a 90-day toxicity study, 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.

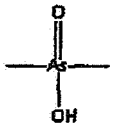
COMPLIANCE: Signed and dated Quality Assurance, Data Confidentiality, GLP Statements were provided. Flagging statements were not provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: Cacodylate 3.25 (MRD -92-416) (active ingredients: cacodylic acid and sodium cacodylate)

   Description: colorless liquid
   Batch #: 095/93
   Purity: Formulation consisting of 4.9% cacodylic acid and 28.4% sodium cacodylate. The formulation contains less than 1% surfactants.
   Stability of compound: stable; compound was stored at room temperature, expiration date of the test material was given as June 1998 (five years from receipt date)
   CAS #: 75-60-5
   Structure: Cacodylic acid



2. Vehicle and/or positive control

   There was no vehicle or positive control. The product was used directly as received from the sponsor and was described as a formulation of water soluble solids in water.

3. Test animals

   Species: rat

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Strain: Crl:CDBR (Sprague-Dawley)
Age and weight at study initiation: age: 6-7 weeks; weight: 209.2-240.7 g (males) 175.4-215.8 g (females)
Source: Charles River Laboratories, Inc., Stone Ridge, NY
Housing: individually in suspended stainless steel cages, except during exposure
Diet: Purina Certified Rodent Chow, *ad libitum*, except when the rats were in the exposure chamber (6 hours/day, 5 days/week)
Water: potable water was supplied *ad libitum*
Environmental conditions:
Temperature: Animal Room: 68-76°F, Chamber: 68-75°F
Relative Humidity: Animal Room: 40-70%, Chamber: 40-60%
Air changes: not specified, Chamber exhaust flow rate 91-95 L/min (1 m^3 chamber equivalent to less than 6 changes per hour)
Photoperiod: 12 hours of light and 12 hours of dark
Acclimation period: 13 days

B. STUDY DESIGN

1. In life dates

Start: July 12, 1993; end: October 14, 1993

2. Animal assignment

Animals were assigned to the test groups in Table 1. A computer-generated body weight sorting program was used to equalize the initial group means by sex. Within an individual test group, weight variation did not exceed ±20% of the population mean body weight by sex. The animals were subjected to nose-only exposure for 6 hours/day, 5 days/week for 67 (males) or 68 (females) total exposure days. The control and test groups were handled equally. Control groups were exposed to filtered air only.

TABLE 1. Study design

Test Group (10 rats/sex/dose)	Nominal Concentration (mg/L/day)	Analytical Concentration (mg/L/day)[1]	MMAD[2] (μm)	GSD[3] (μm)	%≤ 10 μm
#1 Control - air only	0	0	NA	NA	NA
#2	0.140	0.010	3.3	2.8	89.6
#3	0.355	0.034	2.5	2.0	96.6
#4	0.761	0.100	2.3	2.1	97.5

Data taken from pg. 38. MRID 4470031.
[1]Concentration given is for the total test material formulation (Cacodylate 3.25)
[2]MMAD = mass median aerodynamic diameter
[3]Geometric standard deviation; NA = not assessed

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3. Dose selection rationale

The exposure levels for this study were chosen based on the results of a previously conducted 9-day probe study in rats using chamber concentrations of 94, 321 or 1085 mg/m^3 (not specified if these were the actual analytical concentrations or nominal concentrations). Both head-only and whole-body exposures were tested. There was a significant difference in mortality between the head-only and whole-body exposures (not specified as to which exposure method was more toxic). Mortality occurred at 321 mg/m^3 (exposure method not specified). It was decided to use nose-only exposures at target analytical concentrations of 0.010, 0.030, and 0.100 mg/L/day. (Reviewer note: Information in HSDB states that the safe parenteral dose to cacodylic acid is much higher (~5 times) than the safe oral dose because acidic gastric juice rapidly frees inorganic arsenic, which is ultimately reduced to trivalent arsenous oxide. This could account for the differences of whole-body versus head-only exposures, if whole body exposures were more toxic, given oral exposure from grooming.)

4. Generation of the test atmosphere and description of the chamber

Test atmospheres were generated as liquid droplet aerosols. The test material was pumped at a controlled rate with a syringe pump at low level exposures or a laboratory piston pump to atomizers operating with compressed air at higher levels. The test material was mixture of solids in water. The water volatilized rapidly as it mixed with the chamber air. The animals were exposed to essentially a dry dust aerosol.

The chamber was a whole body 1 m^3 stainless steel chamber. Individual flow-past nose only chambers were mounted in place of windows in the chamber. There were no specific details of exhaust air except that the chamber used the existing ventilation system. The time to equilibration was less than 30 minutes based on in-line aerosol monitors. The exhaust flow rate was 91-95 L/min (slightly less than 6 air changes/ hour). Empty ports in the chamber were used for sampling and monitoring. Chamber temperature and relative humidity were monitored continuously with a dry bulb/wet bulb hygrometer and recorded at 30 minute intervals. The chamber pressure was maintained slightly negative to the room. Oxygen concentration was not reported. Test chamber conditions are reported in Table 2.

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TABLE 2. Chamber temperature and relative humidity		
Test Group	**Average Temperature (°F)**	**Relative Humidity (%)**
Control - air only	72	72
10 mg/m^3	72	66
34 mg/m^3	72	62
100 mg/m^3	72	63

Data taken from pg. 38.

5. Test atmosphere concentration and particle size

Test atmosphere concentrations are presented in Table 1. The nominal concentrations were calculated daily by dividing the net weight of material used daily by the total volume of air passing through the chamber during the exposure. The air in the exposure chambers was sampled continuously with a Sibata P-5 on-line digital aerosol monitor. Particle size determinations were conducted weekly for each exposure level using a Sierra Instruments Model 210 Cascade Impactor. The mass median aerodynamic diameter (MMAD) was determined using the stage constants, the bulk estimation technique, and a computer program. The MMAD and geometric standard deviation (GSD) for the three test samples are given in Table 1. Graphical representations of the particle size distributions were given and the aerosols were reasonably normally distributed. The percentage of particles less than 10 μm was 89.6%, 96.6% and 97.6% for Groups 2, 3 and 4, respectively; and the GSD,s were 2.8, 2.0 and 2.1, respectively.

Analytical concentrations were obtained by dividing the dry aerosol concentration by the fraction of the dry weight in the formulation (0.49). The dry fraction was obtained by spiking glass 5 fiber filters with known amounts of test material and drying them to a constant weight. The chamber samples were collected by drawing a known volume of chamber air, metered by a calibrated critical orifice, through a preweighed 25 mm glass fiber filter. The samples were determined to be dry upon collection and did not require additional drying to achieve a constant weight.

6. Statistics

Statistical analysis comparing the group means of the treated and control animals was conducted for hematology, clinical chemistry, body weights, and organ weights. Significance was reported at the 1% and 5% levels. The statistical methods used were determined by an appropriate analysis of variance. Depending on the results, parametric and nonparametric techniques were applied. The reviewer statistically analyzed the respiratory system pathology findings using the Fisher exact test.

C. METHODS

1. Observations

Animals were observed for mortality and obvious toxic signs during the first and sixth hour and after each 6-hour exposure.

2. Body weight

Individual body weights were measured prior to the initiation of exposure, weekly thereafter, again prior to terminal sacrifice, and for all animals which died prior to terminal sacrifice.

3. Food consumption

Food consumption data was not provided and food efficiencies could not be calculated; however, there were no statistical differences in terminal body weights.

4. Ophthalmoscopic examination

All animals were observed by a veterinarian ophthalmologist prior to exposure and during the final week of the study. Mydriasis was induced with 1% atropine.

5. Blood was collected from all animals after 67 or 68 exposures (prior to terminal sacrifice) for hematology and clinical chemistry analysis. All animals were fasted overnight and blood was collected from the abdominal aorta while the animals were anesthetized with sodium pentobarbital. Hematology samples used EDTA as an anticoagulant, but serum chemistry samples were collected in tubes without anticoagulants. The CHECKED (X) parameters were examined.

a. Hematology

X		X	
x	Hematocrit (HCT) (packed cell vol.)	x	Leukocyte differential count
x	Hemoglobin (HGB)	x	Mean corpuscular HGB (MCH)
x	Leukocyte count (WBC)	x	Mean corpusc. HGB conc.(MCHC)
x	Erythrocyte count (RBC)	x	Mean corpusc. volume (MCV)
x	Platelet count		Reticulocyte count
	Blood clotting measurements		
	(Thromboplastin time)		
	(Kaolin-cephalin time)		
	(Prothrombin time)		

b. Clinical chemistry

X	ELECTROLYTES
x	Calcium
x	Chloride
	Magnesium
x	Phosphorus
x	Potassium
x	Sodium
	ENZYMES
x	Alkaline phosphatase (ALK)
	Cholinesterase (ChE)
	Creatine phosphokinase
	Lactic acid dehydrogenase (LDH)
x	Plasma alanine amino-transferase (also Plasma alanine transaminase)
x	Plasma aspartate amino-transferase (also plasma aspartate transaminase)
x	Gamma glutamyl transferase (GGT)
	Glutamate dehydrogenase
x	Sorbital dehydrogenase

X	OTHER
x	Albumin
x	Blood creatinine
x	Blood urea nitrogen
x	Total Cholesterol
x	Globulins
x	Glucose
x	Total bilirubin
x	Total serum protein (TP)
x	Triglycerides
	Serum protein electrophores

6. Urinalysis

Urinalysis was not conducted.

7. Sacrifice and pathology

At the end of the 67 or 68 daily treatments (5 days/week), all rats were sacrificed by exsanguination under sodium pentobarbital anesthesia and necropsied. The CHECKED (X) tissues were examined histologically in control and high dose animals after being fixed, processed, embedded in paraffin wax, sectioned, and stained with hematoxylin and eosin. The skull with nasal turbinates and nasopharynx was decalcified prior to tissue processing. The (XX) organs, in addition, were weighed at necropsy. The lungs, trachea, larynx, and nasal tissues from the low and mid-dose groups were also examined microscopically.

X	DIGESTIVE SYSTEM	X	CARDIOVASC./HEMAT.	X	NEUROLOGIC
	Tongue	x	Aorta	xx	Brain (3 regions)
x	Salivary glands	x	Heart	x	Periph. nerve
x	Esophagus	x	Bone marrow	x	Spinal cord (3 levels)
x	Stomach	x	Lymph nodes	x	Pituitary
x	Duodenum	x	Spleen	x	Eyes (optic n.)
x	Jejunum	x	Thymus		
x	Ileum				GLANDULAR
x	Cecum		UROGENITAL	xx	Adrenal gland
x	Colon	xx	Kidneys	x	Lacrimal gland
x	Rectum	x	Urinary bladder	x	Mammary gland
xx	Liver	xx	Testes	x	Parathyroids
x	Pancreas	xx	Ovaries	x	Thyroids
			Epididymides		
	RESPIRATORY	x	Prostate		OTHER
xx	Trachea	x	Seminal vesicle	x	Bone
xx	Lung (with bronchi)	x	Uterus	x	Skeletal muscle
x	Nose (nasal turbinates)	x	Cervix	x	Skin
	Pharynx			x	All gross lesions and masses
x	Larynx			x	Whole head

II. RESULTS

A. OBSERVATIONS

1. Toxicity

The rats in all groups appeared normal during the nose-only exposures with sporadic ocular discharges, oral discharges, rales, sores, alopecia, abdominal staining, and dental abnormalities reported. Abdominal staining and dental abnormalities also occurred in control animals. One control female was observed with ataxia from study day 8 until study termination.

2. Mortality

Five animals died prior to terminal sacrifice but none were considered to be related to exposure to the test material. Three animals, two males and one female, in the 10-mg/m^3 exposure group were found dead in the exposure tubes. The deaths were attributed to accidental asphyxiation within the tube. Two 34-mg/m^3 males were found dead after the instillation of atropine in their eyes for the final ophthalmoscopic examination (study day 93). The deaths were probably due to handling rather than due atropine administration.

B. BODY WEIGHT AND WEIGHT GAIN

The body weights and body weight gains of all the study groups were similar throughout the experimental period.

C. FOOD CONSUMPTION

1. Food consumption

No data was provided regarding the food consumption by the rats.

2. Food efficiency

Food efficiency was not given and could not be calculated by the reviewer due to the lack of food consumption data.

D. OPHTHALMOSCOPIC EXAMINATION

All animals were examined prior to exposure. Two animals were identified with ocular lesions and were not included in the study. Prior to the termination of the study, all animals were examined again. Four animals (two control females, one 10-mg/m^3 female, and one 34-mg/m^3 male) were observed to have focal retinopathy. This retinopathy was described as common in the posterior segment of the eyes of laboratory rats and was considered to be unrelated to the exposure to the test material.

E. CLINICAL PATHOLOGY

1. Hematology

The differences between the controls and the compound-treated groups were statistically analyzed by the study author. Compared to the controls, statistically significant ($p \leq 0.05$) differences were seen in males in the decreased WBC count (26% reduction) and the increased percentage of eosinophils (67% increase) of the 34 mg/m^3 group. There was no dose response effect. The females showed a significantly decreased mean corpuscular hemoglobin concentration (3% decrease) in the 100 mg/m^3 group. The hematocrit was increased 4% over the controls in the 10 and 34 mg/m^3 females. The absolute number of lymphocytes was significantly reduced 36% in the 100 mg/m^3 groups and the percentage of eosinophils was increased 53% but not significantly so. These changes are all within the normal ranges for CD rats and show no definite dose response effects. The possible exception is the non-significant decrease in WBC in the 100 mg/m^3 females. The value is below the normal range of 5 to 14 given in the 1995 CRC Handbook of Toxicology. The results are summarized in Table 3.

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TABLE 3. Hematology parameters altered in rats given Cacodylate 3.25 by inhalation for 90 days[1,2]							
Parameter	Air only control	0.010 mg/L/day		0.034 mg/L/day		0.100 mg/L/day	
Males							
Mean Corpuscular Hemoglobin Conc. (g/dL)	34.1	34.3	(+0.5)	34.0	(+0.2)	34.3	(+0.5)
Hematocrit (%)	42.5	43.0	(+1)	44.0	(+4)	43.9	(+3)
WBC count (10^3/cmm)	10.7	8.6	(-20)	7.9*	(-26)	9.4	(-12)
Eosinophils (%)	0.9	1.2	(+3.3)	1.5*	(+67)	1.4	(+56)
Lymphocytes (Abs.)	8.42	6.83	(-19)	6.22	(-26)	7.53	(-11)
Females							
Mean Corpuscular Hemoglobin Conc. (g/dL)	35.7	35.2	(-1)	34.9	(-2)	34.7*	(-3)
Hematocrit (%)	40.9	42.5*	(+4)	42.5*	(+4)	41.8	(+2)
WBC count (10^3/cmm)	5.2	4.9	(-6)	5.9	(+13)	3.9	(-25)
Eosinophils (%)	1.5	1.6	(+1)	1.8	(+20)	2.3	(+50)
Lymphocytes (Abs.)	4.36	3.74	(-14)	4.75	(+9)	2.81*	(-36)

Data taken from Tables 8 & 9, pp. 64-65.
[1]Significantly different from air only controls: *p ≤ 0.05.
[2]Numbers in parentheses are the percent increase or reduction compared to air-only controls, calculated by reviewer.

2. Clinical chemistry

There were no significant differences in any of the measured serum chemistry parameters in male rats. In the female rats, the urea nitrogen was significantly elevated above the control levels in the 34 mg/m^3 (40% increase, p≤ 0.01) and 100 mg/m^3 groups (24% increase, p≤ 0.05), chloride ion levels were significantly increased (p≤ 0.05) above the controls in the 10 and 34 mg/m^3 treatment groups (both increased 1.9%), and the globulin levels of the 34 mg/m^3 group were increased over the controls by 11% (p≤ 0.05). All of these changes were within the normal range reported by the authors. The reviewer finds the chloride ion levels of all female rats to be slightly elevated above normal values.

F. URINALYSIS

Urinalysis was not conducted in this study.

G. SACRIFICE AND PATHOLOGY

1. Organ weight

There were no statistically significant differences in mean absolute or relative organ weight between control animals and the exposed animals of either sex. A slight increasing linear trend was seen in the weight of the lungs and trachea of treated female animals.

2. Gross pathology

At terminal sacrifice, the majority of animals in all groups were free of any macroscopic abnormalities. Two males in the 10 mg/m^3 groups and two males in the 34 mg/m^3 were observed with nodules on the epididymis. There were also observations considered to be unrelated to exposure for single or low incidences of kidney nodules, urinary bladder calculi, foci on adrenals, dental abnormalities, sores, stomach mass, discolored ovary, raised area on spine, enlarged or discolored lymph nodes, and discolored thymus. The animals found dead from accidental asphyxiation or atropine administration had firm, discolored, and/or enlarged heart; discolored lungs, thymus, liver, and/or lymph nodes; abnormal contents in the cecum, stomach, small intestines, or urinary bladder; and dilated kidney with embedded foci. There were no treatment related gross findings.

3. Microscopic pathology

The only significant histopathologic findings were restricted to the olfactory and respiratory epithelium of the nasal turbinates of the male and female rats in the 34 and 100 mg/m^3 groups. These changes consisted of an increased incidence and severity of intracytoplasmic eosinophilic globules (IEG) in the olfactory sustentacular cells and in the columnar epithelium in the posterior and ventral regions of the nasal cavity. While the control and 10 mg/m^3 exposure groups showed IEG in nasal turbinate sections 3 and 4 (up to 7 of 10 animals), all occurrences were noted to be minimal or slight severity. The 0.034 mg/m^3 and 0.100 mg/L/day groups showed significant increases in the incidence (up to 10 of 10 animals) and severity of the IEG with all higher exposure levels showing moderate and marked severity. There were no other changes in the respiratory system or evidence of any other systemic toxicity in any of the other organs or tissues examined. The summary of histopathology for the nasal turbinates is given in Table 4.

TABLE 4: Microscopic findings in rats exposed to Cacodylate 3.25 for 90 days (6 hours/day, 5 days/week)				
Organ/tissue: lesion	**Air only control**	**0.010 mg/L/day**	**0.034 mg/L/day**	**0.100 mg/L/day**
Males				
Nasal Turbinate #2 IEG-Total	0/10	0/10	0/10	0/10
Nasal Turbinate #3 IEG-Total IEG- minimal and slight IEG moderate and marked	4/10 4 0	4/10 4 0	7/10 5 2	5/10 1 4*
Nasal Turbinate #4 IEG-Total IEG- minimal and slight IEG moderate and marked	6/10 6 0	4/10 4 0	8/10 4 4*	8/10 2 6**
Females				
Nasal Turbinate #2 IEG-Total IEG- minimal and slight	0/10 0	0/10 0	1/10 1	4/10 4*
Nasal Turbinate #3 IEG-Total IEG- minimal and slight IEG moderate and marked	3/10 3 0	5/10 5 0	10/10** 3 7*	10/10** 2 8**
Nasal Turbinate #4 IEG-Total IEG- minimal and slight IEG moderate and marked	7/10 7 0	7/10 7 0	10/10 1 9**	9/9 1 8**

Data taken from Appendix J, Table 1, page 133. Significantly different from air-only controls (Fisher exact test by reviewer): *$p \leq 0.05$, **$p \leq 0.01$.

III. DISCUSSION

A. DISCUSSION

The MMAD for the exposure groups ranged from 2.3 to 3.3 μm and were reasonably distributed. The average percent of the aerosol less than 10 μm was between 89.6 and 97.5% in all groups. The product became a dry aerosol particulate by the time it reached the test animals. This dry matter consisted of cacodylic acid, cacodylate salt, surfactants, and other inert constituents of the product.

There were no significant toxicological effects in mortality, body weight, organ weights, ocular abnormalities, clinical chemistry and hematology parameters. Histopathologic changes were restricted to the nasal turbinates of the two highest exposure groups. This failure to see any other toxicological effects in the deep respiratory system may be due to a low number of small, inspirable particles (less than 1 μm) and a high degree of impaction of dry particles in the nasal turbinates. The significance of IEG is unclear with toxicologists and pathologists divided over the significance. Eosinophilic globules are normally found in respiratory secretory cells in low numbers in controls rat and increase with age. Increases in quantity and severity are seen after exposure to certain irritant chemicals, perhaps as an adaptive response (Monticello, et. al, Env. Health Persp., Vol. 85 pp. 249-274, 1990, and Boorman et al., Pathology of the Fischer Rat Reference Atlas, Academic Press, San Diego, 1990). Maronpot (Env. Health Persp., Vol. 85 pp. 331-352,

1990) gave the following comments on eosinophilic cytoplasmic inclusions: "Eosinophilic cytoplasmic inclusions are generally not associated with inflammation, but are typically associated with secretory cells. These changes frequently localize in three areas: sustentacular cells of the olfactory epithelium, glands at the olfactory-respiratory junction lining the dorsal meatus, and in the respiratory epithelium particularly along the septum. It has been suggested that these eosinophilic inclusions may be a hormonal response of some sort, or may be associated with ammonia in the microenvironment. The issue as to whether or not to document this change as a lesion is a judgement call generally influenced primarily by severity of the change." The severity of change in IEG seen in this study is considered to be an adverse response.

The exposure levels selected in this study were based on a previous limit test in which mortality was seen at 321 mg/m^3 but the method of exposure (whole body or nose-only) was not specified. The next lowest level used in the limit test was 94 mg/m^3. The upper exposure level used in the limit test was 1085 mg/m^3 (1.085 mg/L, which met the limits suggested in the OPPTS 870.3465). Aside from the increased incidence and severity of IEG in nasal turbinates, there were no other obvious signs of toxic effects at the levels used in this study 10, 34, or 100 mg/m^3 (0.01, 0.034, or 0.1 mg/L). There is uncertainty in this study as to what the intended exposures were. The measured analytical concentrations were an order of magnitude less than the nominal concentrations. It is also not known if the concentrations specified in the limit test were nominal concentrations or analytical concentrations.

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 acceptable (Guideline) and fulfills the requirements of Guideline §82-4.

B. STUDY DEFICIENCIES

The reporting of test compound exposure concentrations was deficient because the analytically measured concentrations were only a fraction of the "nominal" concentrations and the animals could have tolerated higher actual concentrations. There was a lack of information on the previously conducted limit test (exposure method) to assess the adequacy of the selected levels. There were about 6 air changes per hour in the test chamber instead of the recommended 10.

Food consumption and food efficiency were not reported but there were no significant differences in the body weights of the control and test groups; therefore the lack of data does not affect the outcome of the study. No blood clotting measurements were taken. No Flagging statements were provided.

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0146664

[Cacodylic Acid **90-Day Feeding Study - Rat (82-1a)]**

Supplement to Document No. 010550- DER for MRID No. 42767701: Cacodylic Acid - Toxicity in Dietary Administration to Rats for 13 Weeks: A Preliminary Study. This amendment provides an Revised Executive Summary to the original DER.

EPA Reviewer: Guruva B. Reddy, D.V.M., Ph.D., Date 3/1/99
Registration Action Branch 1
Health Effects Division (7509C)

Secondary Reviewer: P. V. Shah, Ph.D., Date 3/1/99
Registration Action Branch 1
Health Effects Division (7509C)

AMENDED DATA EVALUATION RECORD

STUDY TYPE: 82-1 Subchronic Oral Toxicity - Rat

OPP Number: 82-1
DP BARCODE: D251139
PC CODE: 012501

OPPTS Number: 870.3100
SUBMISSION CODE: S551828
TOX CHEM NO: 133

TEST MATERIAL (PURITY): 99.5%

CHEMICAL NAME: Cacodylic Acid

CITATION: 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.

SPONSOR: Luxembourg Industries (Pamol), Ltd.
Tel-Aviv 61000, Israel

EXECUTIVE SUMMARY: In a subchronic feeding study (MRID 42767701) 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.

[Cacodylic Acid **90-Day Feeding Study - Rat (82-1a)]**

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** and satisfies the guideline requirement for subchronic toxicity study (82-1a) in rats.

014666

[Cacodylic Acid 21-Day Dermal Toxicity - Rabbit (82-2b)]

Supplement to Document No. 010410 - DER for MRID No. 41872801: Cacodylic Acid - 21 Day Dermal Toxicity Study in Rabbits. This amendment provides an Revised Executive Summary to the original DER.

Guruva B. Reddy, D.V.M., Ph.D.,
Registration Action Branch 1
Health Effects Division (7509C)

Date 3/1/99

Secondary Reviewer: P. V. Shah, Ph.D.,
Registration Action Branch 1
Health Effects Division (7509C)

Date 3/1/99

AMENDED DATA EVALUATION RECORD

STUDY TYPE: 82-2 Repeated Dose Dermal Toxicity - Rabbit

OPP Number: 82-2
DP BARCODE: D251139
PC CODE: 012501

OPPTS Number: 870.3200
SUBMISSION CODE: S551828
TOX CHEM NO: 133

TEST MATERIAL (PURITY): 99.95% a.i.

CHEMICAL NAME: Cacodylic Acid

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

SPONSOR: Luxembourg Industries (Pamol), Ltd.
Tel Aviv 61000, Israel

EXECUTIVE SUMMARY: In a 21-day dermal toxicity study (MRID 41872801) 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. **Dermal irritation**

[Cacodylic Acid 21-Day Dermal Toxicity - Rabbit (82-2b)]

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** and **satisfy** the guideline requirement for a repeat dermal toxicity study (82-2b) in rabbit.

014666

[Cacodylic Acid Developmental Toxicity - Rat (83-3a)]

Supplement to Document No. 010696 - DER for MRID No. 40625701: Cacodylic Acid, Teratogenicity Study in the Rat. This amendment provides an Revised Executive Summary to the original DER.

EPA Reviewer: Guruva B. Reddy, D.V.M., Ph.D., Date 3/1/99
Registration Action Branch 1
Health Effects Division (7509C)

Secondary Reviewer: P. V. Shah, Ph.D., Date 3/1/99
Registration Action Branch 1
Health Effects Division (7509C)

AMENDED DATA EVALUATION RECORD

STUDY TYPE: Developmental Toxicity Study - Rat

OPP Number: 83-3a
DP BARCODE: D251139
PC CODE: 012501

OPPTS Number: 870.3700
SUBMISSION CODE: S551828
TOX CHEM NO: 133

TEST MATERIAL (PURITY): 99.8%

CHEMICAL NAME: Cacodylic Acid

CITATION: 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.

SPONSOR: Luxembourg Industries (Pamol) Ltd.
Tel-Aviv, Israel

EXECUTIVE SUMMARY: 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%: $P \leq 0.001$) 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). All the above delayed/lack of ossification of numerous bones were related to a decrease in fetal growth rate, except increase in 13th rudimentary ribs. The **Maternal Toxicity NOAEL = 12 mg/kg/day and LOAEL = 36 mg/kg/day,** based on decreased body weights, body weight gains, food consumption and gravid uterine weights. The **Developmental Toxicity NOAEL = 12 mg/kg/day and 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.

CLASSIFICATION: The study is classified as **Acceptable** and satisfy the guideline requirement for a developmental toxicity study (83-3a) in rat.

01461

[Cacodylic Acid Developmental Toxicity - Rabbit (83-3b)]

Supplement to Document No. 010672 - DER for MRID No. 40663301: Cacodylic Acid, Teratogenicity Study in the Rabbit. This amendment provides an Revised Executive Summary to the original DER.

EPA Reviewer: Guruva B. Reddy, D.V.M., Ph.D., Date 3/1/99
Registration Action Branch 1
Health Effects Division (7509C)

Secondary Reviewer: P. V. Shah, Ph.D., Date 3/1/99
Registration Action Branch 1
Health Effects Division (7509C)

AMENDED DATA EVALUATION RECORD

STUDY TYPE: Developmental Toxicity Study - Rabbit

OPP Number: 83-3b
DP BARCODE: D251139
PC CODE: 012501

OPPTS Number: 870.3700
SUBMISSION CODE: S551828
TOX CHEM NO: 133

TEST MATERIAL (PURITY): 99.8%

CHEMICAL NAME: Cacodylic Acid

CITATION: 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.

SPONSOR: Luxembourg Industries (Pamol) Ltd.
Tel-Aviv, Israel

EXECUTIVE SUMMARY: 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 and indicate a test article effect at 3 or 12 mg/kg/day. None of the high-

31

dose animals survived to the termination to evaluate developmental toxicity. The **Maternal Toxicity NOAEL = 12 mg/kg/day and LOAEL = 48 mg/kg/day**, based on mortality, abortions, body weight loss and reduced food consumption. The **Developmental Toxicity NOAEL = 12 mg/kg/day and LOAEL was not established since no pregnant rabbit survived to the gestation day 29 scheduled sacrifice.**

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

014661

[Cacodylic Acid **Reproduction Toxicity - Rat (83-4)]**

Supplement to Document No. 010672 - DER for MRID No. 41059501: Cacodylic Acid, Two Generation Reproduction Study in the Rat. This amendment provides an Revised Executive Summary to the original DER.

EPA Reviewer: Guruva B. Reddy, D.V.M., Ph.D., Date 3/1/99
Registration Action Branch 1
Health Effects Division (7509C)

Secondary Reviewer: P. V. Shah, Ph.D., Date 3/1/99
Registration Action Branch 1
Health Effects Division (7509C)

AMENDED DATA EVALUATION RECORD

STUDY TYPE: Two Generation Reproduction and Fertility - Rat

OPP Number: 83-4
DP BARCODE: D251139
PC CODE: 012501

OPPTS Number: 870.3800
SUBMISSION CODE: S551828
TOX CHEM NO: 133

TEST MATERIAL (PURITY): 98.7%

CHEMICAL NAME: Cacodylic Acid

CITATION: 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.

SPONSOR: Luxembourg Industries (Pamol) Ltd.
Tel-Aviv, Israel

EXECUTIVE SUMMARY: In a two-generation reproductive toxicity study (MRID #s 41059501& 41652201) cacodylic acid (98.7%, a.i.) was administered to 25 Charles River CD rats/sex/dose in 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 during both generations and lactation.

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 same or slightly above the controls. Treatment with cacodylic acid did not effect the reproductive parameters or developmental effects in the offspring. The **Parental Toxicity NOAEL = 21 ppm (2.16 mg/kg/day for males and 2.48 mg/kg/day for females) and 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. The **Reproductive Toxicity NOAEL = 147 ppm, 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), however, 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 (MRID 40625701; 36 mg/kg/day) toxicity studies in this species. Therefore, it appears that the highest dose used in this study was adequate to assess the reproductive toxicity of cacodylic acid.

CLASSIFICATION: The study is classified as **Acceptable** and **satisfy** the guideline requirement for a reproduction toxicity study (83-4) in rat.

01466

[Cacodylic Acid Combined Chronic Toxicity/Carcinogenicity - Rat (83-5)]

Supplement to Document Nos. 009391 & 010550 - DER for MRID Nos. 41862101 & 42767701: Cacodylic Acid - Combined Chronic Feeding and Oncogenicity Study in The Rat. This amendment provides an Revised Executive Summary to the original DER.

EPA Reviewer: Guruva B. Reddy, D.V.M., Ph.D., Date 3/1/99
Registration Action Branch I
Health Effects Division (7509C)

Secondary Reviewer: P. V. Shah, Ph.D., Date 3/1/99
Registration Action Branch I
Health Effects Division (7509C)

AMENDED DATA EVALUATION RECORD

STUDY TYPE: Combined Chronic Feeding/Oncogenicity Study - Rat

OPP Number: 83-5
DP BARCODE: D251139
PC CODE: 012501

OPPTS Number: 870.4300
SUBMISSION CODE: S551828
TOX CHEM NO: 133

TEST MATERIAL (PURITY): 99.5%

CHEMICAL NAME: Cacodylic Acid

CITATION: 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.

SPONSOR: Luxembourg Industries (Pamol) Ltd.
Tel-Aviv 61000, Israel

EXECUTIVE SUMMARY: In a combined chronic toxicity/carcinogenicity study (MRID 41862101) cacodylic acid (99.5%, a.i.) was administered in 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 done. Eye and urine examinations were done. There was no satellite group included for interim sacrifice.

Treatment with cacodylic acid did not effect mortality, food consumption, food efficiency, body

weight and body weight gains. Treatment with cacodylic acid had a mild effect on hematology and clinical chemistries of high-dose males and females and mid-dose males, at the 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 sp. gr. of 40 and 100 ppm male and female urine was 1.05 vs 1.06 of controls ($P < 0.05$). Urine volume and sp. gr. 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. Vacuolar 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). Submucosal lymphocytic infiltration was observed in 25% of males and 20% of the females at 100 ppm. Lymphocytic infiltration also increased 8.5% in females at the 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 include 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 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. **Neoplastic lesions were observed in both sexes at the 100 ppm dose.** In males, the transitional cell papilloma was found one each at 10 and 40 ppm and 0 at 100 ppm. In females, 0, 0, and 4 in 10, 40 and 100 ppm, respectively; these papillomas reached significance ($P < 0.05$) in females. At the high-dose the combined incidence of papillomas + carcinomas in high-dose males and females was 3.4% and 16.7%, respectively. The trend was significant in both sexes and the incidence at 100 ppm in both sexes exceed the range of historical controls from the study laboratory. Additionally, the high-dose females was statistically significant incidence in pairwise comparison to controls.

The dosing was considered adequate for testing the neoplastic potential of cacodylic acid since highest dose tested induced bladder neoplasms in both sexes. Further, in the subchronic toxicity study (MRID 42767701) a LOAEL of 50 ppm was based on decreased hematology parameters in females, increased incidence of cuboidal to columnar epithelial cell lining thyroid follicles in both sexes, increased water consumption and urine output and decreased urine specific gravity. The NOAEL was 5 ppm. The 100 ppm dose in the carcinogenicity study is 2X the LOAEL from

the subchronic toxicity study.

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, increased follicular epithelial cell height, and urinary bladder lesions (increased vacuolar degeneration of transitional epithelium, lymphocytic infiltration, transitional hyperplasia) in females.

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

014666

[Cacodylic Acid **Carcinogenicity - Mouse (83-2)**

Supplement to Document No. 008891 - DER for MRID No. 41914601: Cacodylic Acid Oncogenicity Study in Mouse. This amendment provides an Revised Executive Summary to the original DER.

EPA Reviewer: Guruva B. Reddy, D.V.M., Ph.D., Date 3/1/99
Registration Action Branch 1
Health Effects Division (7509C)

Secondary Reviewer: P. V. Shah, Ph.D., Date 3/3/99
Registration Action Branch 1
Health Effects Division (7509C)

AMENDED DATA EVALUATION RECORD

STUDY TYPE: Carcinogenicity - mouse

OPP Number: 83-2
DP BARCODE: D251139
PC CODE: 012501

OPPTS Number: 870.4200
SUBMISSION CODE: S551828
TOX CHEM NO: 133

TEST MATERIAL (PURITY): 99.5%

CHEMICAL NAME: Cacodylic Acid

CITATION: 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. MRID 41914601. December 24, 1990. Unpublished.

SPONSOR: Luxembourg Industries (Pamol) Ltd.
Tel-Aviv, Israel

EXECUTIVE SUMMARY: In a carcinogenicity study (MRID 41914601) 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, and organ weights. At 500 ppm, body weight gains decreased 15.5%in

males during the study. As noticed in the rat urinary system is the target for this chemical. Microscopically, a dose-related, increased vacuolar 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, 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 fibrosarcoma in the high-dose females (10.7%) observed in the abdominal cavity; in the males there was a non-significant positive trend. The trend in the data combined by sex was significant ($P < 0.01$). When these two lesions were combined as two forms of the same disease, a significant result($P < 0.01$) was observed in females and in the data combined by sex. The **Systemic Toxicity NOAEL = 40 ppm (7 mg/kg/day) for males and 8 ppm (1.7 mg/kg/day) for females and the LOEL = 200 ppm (35.25 mg/kg/day) for males and 40 ppm (8.65 mg/kg/day) for females,** based on vacuolar degeneration of bladder epithelium.

The dosing was considered adequate based on the neoplastic response in high-dose females, decreased body weight gains > 15% in high-dose males, and urinary bladder lesions in males above 200 ppm and in females above 40 ppm. In addition, the 13 week mouse feeding study (MRID 42362501), demonstrated a NOAEL of 50 ppm and LOAEL of 500 ppm, based on decreased food efficiency (M), increased water consumption (F), and vacuolar degeneration of bladder transitional epithelium (M & F).

CLASSIFICATION: The study is classified as **Unacceptable** and may be upgraded by the submission of (1) the criteria for exclusion of organ weights from the group means, (2) an explanation of why the clinical pathology data from all animals was not reported, and (3) clarification of the statement regarding the significance of the incidence of fibrosarcoma combined with fibroma as two stages of the same disease in the male. The study does not satisfy the guideline requirement for a oncogenicity study (83-2b) in mice.

014666

[Cacodylic Acid **Dermal Penetration - Rat (85-3)]**

Supplement to Document No. NONE - DER for MRID No. 43497401: a dermal radiotracer study with ^{14}C-cacodylic acid in rats. This amendment provides an Revised Executive Summary to the original DER.

EPA Reviewer: Guruva B. Reddy, D.V.M., Ph.D., Date 3/1/99
Registration Action Branch 1
Health Effects Division (7509C)

Secondary Reviewer: P. V. Shah, Ph.D., Date 3/1/99
Registration Action Branch 1
Health Effects Division (7509C)

AMENDED DATA EVALUATION RECORD

STUDY TYPE: Dermal Penetration - Rat

OPP Number: 85-3
DP BARCODE: D251139
PC CODE: 012501

OPPTS Number: 870.7600
SUBMISSION CODE: S551828
TOX CHEM NO: 133

TEST MATERIAL (PURITY): 99.8% (cold), > 98% (radiolabeled)

CHEMICAL NAME: Cacodylic Acid

CITATION: 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.

SPONSOR: Luxembourg Industries (Pamol) Ltd.
Tel-Aviv, Israel

EXECUTIVE SUMMARY: In a dermal absorption study (MRID 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 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 satisfy the guideline requirement for a dermal penetration study (85-3) in rat.

014666

[Cacodylic Acid General Metabolism - Rat (85-1)]

Supplement to Document No. 010353 - DER for MRID Nos.: 42341301 & 43005801. Absorption, Distribution and Elimination of [^{14}C] Cacodylic Acid in the Rat. This amendment provides an Revised Executive Summary to the original DER.

EPA Reviewer: Guruva B. Reddy, D.V.M., Ph.D., Date 3/1/99
Registration Action Branch I
Health Effects Division (7509C)

Secondary Reviewer: P. V. Shah, Ph.D., Date 3/1/99
Registration Action Branch I
Health Effects Division (7509C)

AMENDED DATA EVALUATION RECORD

STUDY TYPE: Metabolism Study - Rat

OPP Number: 85-1
DP BARCODE: D251139
PC CODE: 012501

OPPTS Number: 870.7485
SUBMISSION CODE: S551828
TOX CHEM NO: 133

TEST MATERIAL (PURITY): 99.8% (tech), Radiolabeled 50 and 99%

CHEMICAL NAME: Cacodylic Acid

CITATION: 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.

SPONSOR: Luxembourg Industries (Pamol) Ltd.
Tel-Aviv 61000, Israel

EXECUTIVE SUMMARY: In a general metabolism study (MRID 42341301 & 43005801) [^{14}C]Cacodylic acid was administered to male and female Sprague-Dawley CD rats as a single oral dose at 0, 5.0, and 50.0 mg/kg, a repeated oral doses (14 daily doses) of unlabeled Cacodylic Acid at 5 mg/kg followed by a single dose of labeled Cacodylic Acid at 5.0 mg/kg and single i.v. dose at 5.0 mg/kg.

Highest absorption (100%) was observed in the single i.v. dose followed by the low and high dose animals (≈ 72%), and the repeated dose (≈ 79%) . About 19 to 29% of the orally

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administered dose was distributed in the blood and whereas ≈ 10% of the i.v. dose was recovered in the blood. The majority of the radioactivity in the blood was associated with erythrocytes as the parent compound, Cacodylic Acid. The radioactivity found in the carcasses accounted for 6 to 20%; lowest levels were detected by i.v. route. Other tissues and organs, except the skin of the oral low dose males contained < 5% of the administered dose. Over a 7-day period, most (≈ 90 - 98%) of the test compound administered was excreted from the animals. The total radioactivity recovered in the urine, feces, and CO_2 in the exhaled air was 28 - 82, 4 - 33, 0 - 0.1%, respectively. Urinary excretion was highest (81%) in the i.v. dose group, and was lowest (28%) in the low dose oral group. Fecal excretion accounted for 4 - 33%; lowest (4%) amount was excreted in the i.v. dose group.

Three metabolites i.e., unknown metabolite C , D, and Monosodium Methanearsenic Acid (MSMA) and the parent Cacodylic Acid were identified. Major urinary metabolite Cacodylic Acid accounted for 17 - 20% in the oral low and high dose groups. Metabolite C and Metabolite D accounted for 7 - 13% and < 2%, respectively; MSMA (< 1%) was present only in the urine of high dose groups. The repeated dose groups showed a different urinary profile, Metabolite C (28 - 36%) was the major metabolite followed by cacodylic acid (12%) and Metabolite D (6 - 10%). Fecal excretion of Cacodylic Acid in the oral dose groups ranged from 8.6% in the low dose female to 32% in the high dose male; and the Metabolite C ranged from 0.3% in the high dose male to 6.2% in the repeated dose male and the Metabolite D ranged from 0 to 0.3%. Fecal Metabolite C was higher in the repeated dose groups vs the low and high dose groups.

CLASSIFICATION: The study is classified as **Acceptable** and **satisfies** the guideline requirements for a General Metabolism study (85-1) in rat.