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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: ***CACODYLIC ACID*** - Report of the Hazard Identification Assessment Review Committee.

FROM: Toxicologist. Guruva B. Reddy 10/12/98
Reregistration Branch II
Health Effects Division (7509C)
and
Brenda Tarplee, Executive Secretary
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

THROUGH: Mike Ioannou, Chairman, 12/22/98
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)
and
Pauline Wagner, Co-Chairman 12/22/98
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

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

PC Code: 012501

On November 19, 1998, the Health Effects Division's Hazard Identification Assessment Review Committee evaluated the toxicology data base of **Cacodylic Acid,** established a Reference Dose (RfD) and selected the toxicological endpoints for acute and chronic dietary, occupational and residential (dermal and inhalation) exposure risk assessments. The HIARC also addressed the potential enhanced sensitivity of infants and children from exposure to cacodylic acid as required by the Food Quality Protection Act (FQPA) of 1996. The Committee's conclusions are presented in this report.

Committee Members in Attendance

Members present were: Mike Ioannou, Pauline Wagner, Jess Rowland, Bill Burnam, Tina Levine, Karen Hamernik, Kathleen Raffaele, Virginia Dobozy, P.V. Shah, Nicole Paquette, and David Anderson. Members in absentia were Nancy McCarroll and Susan Makris: Data were presented by Guruva B. Reddy of Reregistration Branch II.

In attendance were also Jonathan Becker, Diana Locke, Richard Griffin, and Bonnie Cropp-Kohlligian from HED and Linda Werrell from SRRD attended the meeting to discuss exposure.

Data Presentation:
and
Report Presentation

Guruva B. Reddy
Toxicologist

Report Concurrence:

Brenda Tarplee
Executive Secretary

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I. INTRODUCTION

Cacodylic acid is an organic arsenical herbicide and defoliant registered for use on cotton, non-bearing citrus, weed control around buildings, sidewalks and for lawn renovation. Therefore, risk assessments for residential and occupational exposures are applicable. There is a potential for mixer/loader/applicator exposure to cacodylic acid sprays. The exposure route for handlers and residential uses is via the dermal and inhalation routes.

The OPP has established a provisional RfD of 0.000750 mg/kg/day using an uncertainty factor (UF) of 1000. This was based on a NOEL of 0.75 mg/kg/day (HT) in a 90-day feeding study in dogs. In addition, the HED RfD/Peer Review Committee on July 27, 1994 has classified **Cacodylic acid as a Group B2 carcinogen** based on urinary bladder tumors in both sexes of Fischer rats (HED Doc. No. 009391 and 010550) and increases in fibrosarcomas in multiple organs in female B6C3F1 mice (HED Do. No. 008891).

II. HAZARD IDENTIFICATION

A. Acute Reference Dose (RfD)

i) **For Females 13+**

Study Selected: Developmental Toxicity - Rat (main) **Guideline #:** 83-3a

MRID No.: 40625701

Executive Summary: In a developmental toxicity study 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.

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

Dose and Endpoint for Establishing RfD: Developmental 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.

Comments about Study/Endpoint: This endpoint is appropriate for acute risk assessment because developmental effects could occur following a single exposure and is applicable to females 13+.

Uncertainty Factor(UF): An uncertainty factor of 100 was applied to account for inter-species extrapolation (10X) and intra-species variability (10X).

ACUTE RfD: 12 mg/kg/day ÷ 100 (UF) = 0.12 mg/kg

This Risk Assessment is required.

ii **For General Population**

Study Selected: Developmental Toxicity - Rabbit **Guideline #:** 83-3b

MRID No.: 40663301

Executive Summary: In a developmental toxicity study 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. The **Maternal Toxicity NOAEL = 12 mg/kg/day and LOAEL = 48 mg/kg/day,**

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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 rabbits 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.

Dose and Endpoint for Establishing RfD: Maternal NOAEL = 12 mg/kg/day and LOAEL = 48mg/kg/day, based on mortality, abortions, body weight loss and reduced food consumption.

Comments about Study/Endpoint: There is no evidence of increased susceptibility to offspring, since no pregnant rabbits survived in the high dose group. This study is suitable for general population because decrease in maternal body weight gain, abortion and reduced food consumption occurred on the first measurement time point (3 days). It is reasonable to assume that the affects could occur after a single dose.

Uncertainty Factor(UF): An uncertainty factor of 100 was applied to account for inter-species extrapolation (10X) and intra-species variability (10X).

ACUTE RfD: 12 mg/kg/day ÷ 100 (UF) = 0.12 mg/kg

This Risk Assessment is Required.

B. Chronic RfD

Cacodylic acid was not reviewed by HED RfD/Peer Review Committee; however, the OPP and EPA established a provisionally acceptable daily intake (PADI) of 0.000750 and 0.010000 mg/kg/day, respectively. In establishing the PADI, the OPP considered a 90-day dog feeding study with a NOAEL of 0.75 mg/kg/day (HDT), and applied an uncertainty factor (UF) of 1,000 for lack of demonstrable toxicity and inter- and intra species variability. The rationale for establishment of PADI was not provided. However, the chronic toxicity/carcinogenicity in rat is more appropriate for chronic dietary risk assessment than a 90-day study.

Type of Study: Combined Chronic/Carcinogenicity Study - Rat **Guideline #:** 85-3

MRID No.: 41862101

Executive Summary: In a combined chronic toxicity/carcinogenicity study cacodylic acid (99.5%, a.i.) was administered in diet to 60 Fischer F344 rats/sex at dose levels of 0, 2,

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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 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 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 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 the 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 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 exceeded the range of historical controls from the study laboratory. Additionally, in the high-dose females the incidence of papillomas + carcinomas was

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statistically significant in pairwise comparison to controls.

The dosing was considered adequate for testing the neoplastic potential of cacodylic acid since the 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 cells lining of the 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.

Dose and Endpoint for Establishing RfD: The Systemic Toxicity NOAEL = 0.14 mg/kg/day and LOAEL = 0.79 mg/kg/day in male rat, based on increased thyroid follicular epithelial cell height.

Uncertainty Factor(s): An uncertainty factor of 100 is proposed to account for inter-species extrapolation (10X) and intra-species variability (10X).

Chronic RfD: 0.14 mg/kg/day ÷ 100 = 0.0014 mg/kg/day

Comments about Study/Endpoint/Uncertainty Factor(s): Rodents are the most sensitive species. Same effects (thyroid toxicity) were seen in the 90-day and 2-generation reproduction studies.

This risk assessment is required.

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C. Occupational/Residential Exposure

1. Dermal Absorption

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

At 10 hours 1.11%, 3.51% or 3.0% of the total dose was absorbed at dose levels of 0.90, 9.30 or 91.3 μg/cm2, respectively; at 24 hours 10.99, 6.55 or 7.07%, respectively. Generally, % dose absorbed decreased with increased concentration of the formulation applied to the skin, however, in the study % absorbed slightly increased with increased dose, indicating damage to the stratum corneum. Approximately 1% of the total applied dose was found in the blood at any dose level tested. Total radioactivity recovery ranged from 99 to 106%. Most of the absorbed dose was excreted in urine and feces. At 10 hours 0.41, 2.23 or 1.89% of the absorbed dose was found in the urine at 0.90, 9.30 or 91.3 μg/cm2, respectively. At the same time point 0.01, 0.00, or 0.00% of the absorbed dose was found in the feces at 0.90, 9.30 or 91.3 μg/cm2, respectively. The radioactivity bound to the skin (application site) ranged from ≈ 10 to 34% of the applied dose. **Based on the results of this study, the dermal absorption factor for 10 hour exposure period was 3.5%.**

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

Dermal Absorption Factor: 3.5%

2. Short-Term Dermal - (1-7 days)

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

MRID No.: 41872801

Executive Summary: In a 21-day dermal toxicity study 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.

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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.

Dose and Endpoint for Risk Assessment: Systemic toxicity NOAEL = 300 mg/kg/day, based on decreased body weight gain in females, and decreased testicular weights, hypospermia, and tubular hypoplasia in males at 1,000 mg/kg/day (LOAEL).

Comments about Study/Endpoint:. The dermal NOAEL of 300 mg/kg/day is appropriate for short-term dermal risk assessment since decreased body weight gains occur following single or short term exposure. In a supportive rat developmental study females had decreased body weight gains.

This risk assessment is required.

Supportive Study:

Study Selected: Developmental Toxicity - Rat **Guideline #:** 83-3a

MRID No.: 40625701

Executive Summary: In a developmental toxicity study 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

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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 satisfies the guideline requirement for a developmental toxicity study (83-3a) in rat.

Dose and Endpoint for Risk Assessment: Maternal Toxicity NOAEL = 12 mg/kg/day; LOAEL = 36 mg/kg/day based on decreased body weights, body weight gains, food consumption and gravid uterine weight.

Comments about Study/Endpoint: The maternal effects (decreased body weights in females) were measured at 3 days which is appropriate for this route and exposure period (1 - 7 days) of concern.

This developmental toxicity study in rats provides support for the use of dermal toxicity study for Short-term dermal exposure. When the developmental NOAEL of 12 mg/kg/day is adjusted for 3.5% dermal absorption (DA), the resulting equivalent dermal dose is 343 mg/kg/day (i.e., 12 mg/kg/day ÷ 3.5% DA = 342.85 mg/kg/day). This NOAEL (343 mg/kg/day) is comparable to the NOAEL (300 mg/kg/day) of the 21-Day dermal toxicity study in rabbits. In both rat and rabbit developmental studies the toxic endpoints are decreased body weights.

3. Intermediate-Term Dermal (7 Days to Several Months)

Study Selected: 90-Day Feeding Study in the Rat §82-1a

MRID No.: 42767701

Executive Summary: In a subchronic feeding study 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

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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 signs 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 weights 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), and focal mineralization of aorta (3M) were 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.

Dose/Endpoint for Risk Assessment: 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, increased water consumption and urine output and decreased urine specific gravity in both sexes.

Comments about Study/Endpoint: Although a 21-day dermal toxicity study is available, it is not adequate to cover the risk assessment for 1-Week to several months duration; therefore, for exposure scenarios longer than 21-days, this 90-day feeding study in the rat is used. This study is appropriate for this route (dermal) and exposure period of concern. When the subchronic toxicity NOAEL of 0.4 mg/kg/day is adjusted for 3.5% absorption (DA), the resulting dermal equivalent dose is 11 mg/kg/day.

This risk assessment is required.

4. Long-Term Dermal (Several Months to Life-Time)

Study Selected: None §

MRID No.: None
Executive Summary: None

Dose and Endpoint for Risk Assessment: None

Comments about Study/Endpoint:. Based on the current use pattern, there is minimal concern for potential Long-Term dermal exposure/risk.

This risk assessment is NOT required.

5. Inhalation Exposure (Short- and Intermediate-Term).

Except for an acute inhalation toxicity study, for which cacodylic acid is placed in Toxicity Category IV (LC_{50} = 4.9 mg/L), no other studies are available via this route. Therefore, the HIARC selected the oral NOAEL of 12 mg/kg/day from the developmental toxicity study in rats for Short-Term and the oral NOAEL of 0.4 mg/kg/day from 90-day feeding study in rats for Intermediate-Term inhalation risk assessments. This dose was used in respective dermal risk assessments. The use

pattern does not indicate a need for Long-Term exposure risk assessment. Since the doses identified for inhalation risk assessment are from oral studies route-to-route extrapolation should be as follows:

Step I: The inhalation exposure component (i.e. μg a.i./day) using a 100% absorption rate (default value) and an application rate should be converted to an **equivalent oral dose** (mg/kg/day)

Step II: The dermal exposure component (i.e. mg/kg/day) using a 3.5% dermal absorption factor and an application rate should be converted to an **equivalent oral dose.** This dose should then be combined with the converted oral dose in Step I.

Step III: To calculate MOE's, the combined dose from Step II should then be compared to the oral NOAEL of 12 mg/kg/day for Short-Term and oral NOAEL of 0.4 mg/kg/day for Intermediate-Term exposures.

This Risk Assessment is Required.

D. Recommendation for Aggregate Exposure risk Assessments

For acute aggregate exposure risk assessment, combine the high end exposure values from food + water and compare it to the acute RfD.

Short- and Intermediate-Term aggregate exposure risk assessment compare separate MOE's for each exposure route since the toxicological endpoints are different.

E. Margins of Exposures for Occupational/Residential Exposure Risk Assessments

A MOE of 100 is adequate for occupational exposure and the MOEs for residential (dermal and inhalation) exposure will be determined during risk characterization by the FQPA Safety Factor Committee.

III. CLASSIFICATION OF CARCINOGENIC POTENTIAL

1. Combined Chronic Toxicity/Carcinogenicity Study in Rats

MRID No. 41862101

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 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 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 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 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. **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 exceeded the range of historical controls from the study laboratory. Additionally, in

the high-dose females the incidence of papillomas + carcinomas was statistically significant in pairwise comparison to controls.

The dosing was considered adequate for testing the neoplastic potential of cacodylic acid since the 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 cells 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.

Discussion of Tumor Data : **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 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 exceeded the range of historical controls from the study laboratory. Additionally, in the high-dose females the incidence of papillomas + carcinomas was statistically significant in pairwise comparison to controls.

Adequacy of the Dose Levels Tested: 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.

2. Carcinogenicity Study in Mice

MRID No. 41914601

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 Fibrosarcomas 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 LOAEL = 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 Fibrosarcomas combined with fibroma as two stages of the same disease in the male. The study does not satisfy the guideline requirement for a carcinogenicity study (83-2b) in mice.

Discussion of Tumor Data

There was a statistically significant increase ($P < 0.01$) in Fibrosarcomas 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.

Adequacy of the Dose Levels Tested

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).

3. Classification of Carcinogenic Potential:

The Health Effects Division Carcinogenicity Peer Review Committee (CPRC) met on December 8, 1993 to discuss and evaluate the weight-of-the-evidence on cacodylic acid with particular reference to its carcinogenic potential. The CPRC concluded that cacodylic acid should be classified as a Group B2 - Probable Human Carcinogen, based on increases in urinary bladder tumors (rare tumor type) in both sexes of the Fischer rat and increases in fibrosarcomas (multiple organs) in female B6C3F1 mice. The CPRC recommended that for the purpose of risk characterization, a low dose extrapolation of human risk (Q_1^*), based on the total (papillomas and carcinomas) urinary tumors in the rat, both for females alone and for males and females combined. The HIARC concurred with the previous classification.

IV. MUTAGENICITY

On December 8, 1993, the CPRC concluded that cacodylic acid has no mutagenic potential based on salmonella, mouse lymphoma and mouse micronucleus assay.

GENE MUTATION

1) *Salmonella typhimurium* reverse gene mutation assay: The test is negative in *S.*

typhimurium strains TA1535, TA1537, TA1538, TA98 and TA100 at doses ranging from 100 to 10,000 μg/plate, in the presence/absence of S9 activation. This study is classified as acceptable-guideline study and satisfies the requirement for FIFRA Test Guideline 84-2 (MRID No. 41892706).

2) Mouse lymphoma assay: Doses of cacodylic acid ranging from 1600 to 1792 μg/mL -S9 and 1600 to 5769 μg/mL +S9 did not induce a mutagenic response in L5178Y $TK^{+/-}$ mouse lymphoma cells. Higher levels (9434 μg/mL-S9 and 7692 μg/mL +S9) were severely toxic. This study is classified as acceptable-guideline study and satisfies the requirement for FIFRA Test Guideline 84-2 (MRID No. 41892707).

CHROMOSOMAL ABERRATIONS

Mouse micronucleus assay: The single intraperitoneal injection of 147, 293, or 586 mg/kg cacodylic acid (actual concentrations based on the analytical determination of dose solutions were 183.3, 317.0 and 416.1 mg/kg, respectively) to male and female ICR mice did not cause a significant increase in the frequency of micronucleated polychromatic erythrocytes (MPEs) in bone marrow cells harvested 24, 48 and 72 hours post treatment. Therefore, it was concluded that cacodylic acid failed to induce clastogenic response in the mouse micronucleus assay. This study is classified as acceptable-guideline study and satisfies the requirement for FIFRA Test Guideline 84-2 (MRID No. 41892708).

V. FQPA CONSIDERATIONS

1. Neurotoxicity: There were no acute or subchronic neurotoxicity studies available.

2. Developmental Toxicity

(1) 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). 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.

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.

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

(2) 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 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.

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.

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

3. Reproductive Toxicity:

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 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 (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 (guideline)** and **satisfies** the guideline requirement for a reproduction toxicity study (83-4) in rat.

4. Additional information from the literature

There are no additional neurotoxicity studies or developmental neurotoxicity studies via inhalation or any other routes from the published literature.

5. Determination of Susceptibility

There appears to be no increased susceptibility of fetuses based on the prenatal developmental toxicity studies and the 2-generation reproduction study. In these studies the toxicity to the offspring was noted only at doses which were less than or equal to the doses at which maternal toxicity was observed. In the developmental toxicity study in rats there is a slight severity noted in the offspring (hernia attributed to decreased body weight) at maternally toxic doses. These offspring effects (diaphragmatic hernia in 5 fetuses of 3 litters, increased fetal and litter incidences of skeletal alterations that may be primarily due to growth reduction) appear to be a direct effect on fetuses. This same effect (diaphragmatic hernia) was also seen in one pup in the 2-generation reproduction study. In the prenatal rabbit study, the high dose level of 48 mg/kg/day, the LOAEL, resulted in both fetal and maternal deaths.

6. Recommendation for a Developmental Neurotoxicity Study

The HIARC recommended the requirement for a developmental neurotoxicity study because of endocrine effects in the reproduction study (decreased ovarian weight and thyroid lesions in females), and in the chronic and subchronic rat studies (similar hyperplastic thyroid lesions in females of both generations). Thyroid toxicity parameters such T3/T4/TSH levels were not examined in these studies. However, the HIARC also noted that there is no evidence that cacodylic acid causes neurotoxicity or neuropathology, and because no neurotoxicity studies were submitted.

7. Determination of the FQPA Safety Factor:

There appears to be no increased susceptibility of fetuses based on the prenatal developmental toxicity studies and the 2-generation reproduction study. However, in the developmental toxicity study in rat, there appears to be a slight increase in the severity of effects in the offspring at maternally toxic doses which may be attributed to decreased

fetal body weights. In addition, there is concern for thyroid toxicity seen in several subchronic studies (2-generation reproduction study and 90-day feeding study) which may adversely affect fetuses and offspring. Due to lack of information on the severity of these effects, it is recommended that an FQPA safety factor be retained.

The final recommendation on the FQPA Safety Factor, however will be made during the risk characterization by the FQPA Safety Committee.

VI. HAZARD CHARACTERIZATION

Cacodylic acid has low acute toxicity (Category III and IV) via dermal, oral, and inhalation routes. It is mildly irritating to eyes and non-irritating to skin. It is not a skin sensitizer. The primary target organ for cacodylic acid in rat studies is the thyroid. Thyroid lesions were seen in the 2-year carcinogenicity study, the 90-day subchronic study and the 2-generation reproduction study. The doses ranged from 0.79 mg/kg/day for the 2-year carcinogenicity study to 15.5 mg/kg/day for 2-generation reproduction study. Thyroid lesions were not seen in the 1-year oral gavage study in the dog, 18-month carcinogenicity study in mouse, developmental toxicity study in rabbit and 21-day dermal toxicity study in rabbits. In the rat developmental study decreased body weights and decreased fetal body weights could be secondary effects of hypo/hyperthyroidism, since thyroid has been identified as the target organ in subchronic and chronic toxicity studies in rats. In a developmental study in rabbit the NOAEL of 12 mg/kg/day was based on effects such as mortality, abortions, body weight loss and reduced food consumption seen at 48 mg/kg/day (HDT). There were no developmental affects seen in rabbits, since none of high dose animals survived. In a 21-day dermal toxicity study no dermal irritation was observed. The NOAEL of 300 mg/kg/day was based on decreased body weight gains in females and decreased testicular weights, hypospermia and tubular hypoplasia in males at 1,000 mg/kg/day (LOAEL ; HDT). Decreased body weight/body weight gains seen in this study were also observed in various oral toxicity studies.

Carcinogenicity studies in rats and mice indicated cacodylic acid was carcinogenic to male and female rats, based on transitional cell papillomas and carcinomas of the bladder and females based on fibrosarcomas in multiple organs. The HED CPRC has classified cacodylic acid a B2-carcinogen.

The database is adequate to evaluate FQPA assessment and consists of developmental studies in the rat and rabbit, and two generation reproduction study in the rat. Based on the findings in the developmental toxicity study in rats, there appears to be an increased severity of effects noted in the offspring at maternally toxic doses.

VII. DATA GAPS

The HIARC considered the requirement for a developmental neurotoxicity study as the data gap because of the lack of information on severity of fetal effects seen in the developmental toxicity

study in rats and thyroid effects seen in the reproduction toxicity study (decreased ovarian weight and thyroid lesions in females), and in the chronic and subchronic rat studies (similar hyperplastic thyroid lesions). The committee also recommended acute- and subchronic neurotoxicity studies because of the concern of neurotoxic and neuropathological effects of arsenical compounds.

VIII. ACUTE TOXICITY

Acute Toxicity of Cacodylic acid 3.25 Formulation (4.9%, a.i.)

Guideline No.	Study Type	MRID #(s)	Results	Category
81-1	Acute Oral	41925601	LD_{50} (M&F) = 2.8 gm/kg	III
81-2	Acute Dermal	41892701	LD_{50} > 2.0 gm/kg	III
81-3	Acute Inhalation	41892702	LC_{50} (4 hr):combined = 4.9 mg/L; M = 5.8 mg/L & F = 4.0 mg/L	IV
81-4	Primary Eye Irritation	41892703	Primary eye irritant - conjunctival redness in 1 hr. In al animals; persisted for 24 hrs. In 1/6 animals.	III
81-5	Primary Skin Irritation	41892704	Negligible irritation in 0.5 hr. Cleared 24 - 48 hrs.	IV
81-6	Dermal Sensitization	41892705	Not a sensitizer	N/A

IX SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

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

EXPOSURE SCENARIO	Dose (mg/kg/day)	ENDPOINT	STUDY
Acute dietary only for females 13+	Developmental NOAEL = 12 mg/kg/day UF = 100	LOAEL = 36 mg/kg/day is based on decreased body weights, body weight gains, food consumption and gravid uterine weights.	Developmental rat
		Acute RfD = 0.12 mg/kg/day	
Acute Dietary General population	Maternal NOAEL = 12 mg/kg/day	Based on abortions and decreased body weights occurring at 3 days	Developmental rabbit
		Acute RfD = 0.12 mg/kg/day	
Chronic Dietary	NOAEL = 0.14 mg/kg/day UF = 100	LOAEL = 0.79 mg/kg/day is based on increased thyroid follicular epithelial cell height in males.	Two year rat feeding study
		Chronic RfD = 0.0014 mg/kg/day	
Short-Term (Dermal)	Dermal NOAEL = 300 mg/kg/day	LOAEL = 1,000 mg/kg/day is based on decrease in body weight gain in females, decreased testicular weights, hypospermia and tubular hypoplasia in males.	21-Day dermal toxicity study in rabbits
*Intermediate-Term (Dermal)	Oral NOAEL = 0.4 mg/kg/day	LOAEL = 4 mg/kg/day (male) is based on increased incidence of incidence of cuboidal to columnar epithelial lining thyroid follicles and water consumption and urine output; decreased sp.gravity.	13-Week feeding study in rats
Long-Term (Dermal)	Not required	Not required	Not required
Short-Term (Inhalation)	Developmental NOAEL = 12 mg/kg/day	LOAEL = 36 mg/kg/day is based on decreased body weights, body weight gains, food consumption and gravid uterine weights.	Developmental rat
Intermediate-Term (Inhalation)	Oral NOAEL = 0.4 mg/kg/day	LOAEL = 4 mg/kg/day (male) is based on increased incidence of incidence of cuboidal to columnar epithelial lining thyroid follicles and water consumption and urine output; decreased sp.gravity.	13-Week feeding study in rats
Long-Term (Inhalation)	Not required	Not required	Not required

* Use Route-to-Route extrapolation; 3.5% dermal absorption rate