Revised Toxicology Chapter for RED for Cacodylic acid. Supercedes January 27, 2000 TXR 013973 to correct for clinical signs associated with the toxicity in the chronic dog study. The sentence "Although the incidences of salivation, vomiting and diarrhea in low- and mid-dose animals were dose-related and chemical/compound related, but were not associated with any other signs of systemic toxicity, therefore, were not considered to be of biological or toxicological significance and were not considered at the two lower doses in the establishment of the NOAEL" has been deleted.

DATE: February 28, 2001

MEMORANDUM

SUBJECT: CACODYLIC ACID: **TOXICOLOGY CHAPTER FOR RED**

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

THRU: George Herndon, Branch Senior Scientist
Registration Action Branch I
Health Effects Division (7509C)

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

PC Code No.: 012501
DP Barcode No.: D251009
Submission No.: S551612

ACTION REQUESTED: Prepare a toxicology chapter for the Cacodylic acid RED.

RESPONSE: The toxicology database for cacodylic acid has been reviewed by the Reregistration Branch 1I. The database has undergone QA/QC by the Toxicology Science Advisory Council (TOX SAC) on October 28, 1998 and peer reviewed by the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) on November 19, 1998 and April 29, 1999 and by the HED FQPA Safety Factor Committee on December 20, 1999. Although there are data gaps for acute- , subacute neurotoxicity and developmental neurotoxicity studies, the toxicology database for cacodylic acid is adequate to support a Reregistration Eligibility Decision (RED). The toxicology chapter for the cacodylic acid RED is included in the following pages:

CACODYLIC ACID: TOXICOLOGY CHAPTER FOR RED

DP Barcode No. D251009
Submission No. S551612
Tox. Chem. No. 133

Reregistration Case No. 2080
P.C. Code No. 012501

Prepared by: Guruva B. Reddy, D.V.M., Ph.D.
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CACODYLIC ACID: TOXICOLOGY CHAPTER FOR RED

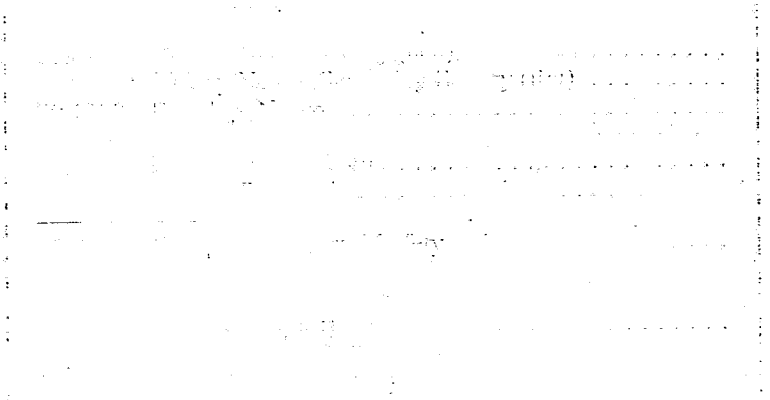
TABLE OF CONTENTS

1.0 HAZARD CHARACTERIZATION

HAZARD PROFILE

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 and urinary tract. In a carcinogenicity study in the rat, carcinomas of the bladder were observed in both sexes. 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 the thyroid has been identified as the target organ in subchronic and chronic toxicity studies in rats. In a developmental study in the 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 indicated cacodylic acid was carcinogenic to male and female rats, based on transitional cell papillomas and carcinomas of the bladder. In a mouse carcinogenicity study, fibrosarcomas of abdominal cavity was observed in female mice. The HED CPRC has classified cacodylic acid a B2-carcinogen.



2.0 REQUIREMENTS

The requirements (CFR 158.135) for terrestrial food use for Cacodylic Acid are in Table 1.

Table 1.

Test	Technical	
	Required	**Satisfied**
870.1100 Acute Oral Toxicity	Y	Y
870.1200 Acute Dermal Toxicity	Y	Y
870.1300 Acute Inhalation Toxicity	Y	Y
870.2400 Primary Eye Irritation	Y	Y
870.2500 Primary Dermal Irritation	Y	Y
870.2600 Dermal Sensitization	Y	Y
870.6100 Acute Delayed Neurotox. (Hen)	N	-
870.6200a Acute Neurotox. Screening Battery (Rat)	N	-
870.3100 Oral Subchronic (Rodent)	Y	Y
870.3150 Oral Subchronic (Non-Rodent)	Y	W
870.3200 21-Day Dermal	Y	Y
870.3250 90-Day Dermal	-	-
870.3465 90-Day Inhalation	Y	Y
870.3700a Developmental Toxicity (rodent)	Y	Y
870.3700b Developmental Toxicity(non-rodent)	Y	Y
870.3800 Reproduction	Y	Y
870.4100a Chronic Toxicity (Rodent)	Y	Y
870.4100b Chronic Toxicity (Non-rodent)	Y	Y
870.4200a Oncogenicity (Rat)	Y	Y
870.4200b Oncogenicity (Mouse)	Y	N1
870.4300 Chronic/Oncogenicity	Y	Y
870.5100 Mutagenicity—Gene Mutation - bacterial	Y	Y
870.5300 Mutagenicity—Gene Mutation - mammalian	Y	Y
870.5385 Mutagenicity—Structural Chromosomal Aberrations	Y	Y
870.5XXX Mutagenicity—Other Genotoxic Effects	N	-
870.6100 90-Day Neurotoxicity (hen)	N	N
870.6200b 90 Day Neuro. Screening Battery (Rat)	Y	Y
870.6300 Develop. Neuro	Y	Y
870.7485 General Metabolism	Y	Y
870.7600 Dermal Penetration	Y	Y
870.7200 Companion Animal Safety	N	-
Special Studies for Ocular Effects	N	-
Acute Oral (Rat)	N	-
Subchronic Oral (Rat)	N	-
Six-month Oral (Dog)	N	-

Y - Yes; **N** - no

W - waived. An acceptable one year study is available

1 - There is an unacceptable study in data base. CPRC concluded that mouse data in conjunction with rat data are adequate to perform risk characterization. There is no need to repeat mouse Oncogenicity study.

3.0 DATA GAP(S)

The HIARC considered the requirement for a developmental neurotoxicity study as a 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). Thyroid effects were also seen in the chronic and subchronic rat studies. The committee also recommended acute and subchronic neurotoxicity studies because of the concern of neurotoxic and neuropathological effects of arsenical compounds.

4.0 HAZARD ASSESSMENT

4.1 Acute Toxicity

Adequacy of data base for acute toxicity: The data base for acute toxicity is considered complete. No additional studies are required at this time.

Table 1 summarizes the acute toxicity data for cacodylic acid. Although, the acute toxicity profile of the chemical was established using 4.9% (a.i.) formulation, the HIARC considered that these studies are appropriate since this formulation is the end use product. Cacodylic acid is not acutely toxic *via* the oral [rats], dermal [rabbits], or inhalation [rats] routes of exposure in the studies required for labeling. In guinea pigs, cacodylic acid is not a skin sensitizer or skin irritant. Cacodylic acid is mildly irritating to the rabbit eye.

Table 2. **Acute Toxicity of Cacodylic acid 3.25 Formulation (4.9%, a.i.)**

Guideline No.	Study Type	MRID #(s)	Results	Category
81-1	Acute Oral - Rat	41925601	LD_{50} (M&F) = 2.8 gm/kg	III
81-2	Acute Dermal- Rabbit	41892701	LD_{50} > 2.0 gm/kg	III
81-3	Acute Inhalation - Rat	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 - Rabbit	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 - Rabbit	41892704	Negligible irritation in 0.5 hr. Cleared 24 - 48 hrs.	IV
81-6	Dermal Sensitization - Guinea pig	41892705	Not a sensitizer	N/A

The above studies satisfy the acute toxicity data requirements (OPPTS 870.1100-870.1300, 870.2400-870.2600; formerly §81-1 through §81-6) for cacodylic acid.

4.2 Subchronic Toxicity

Adequacy of data base for subchronic toxicity: The data base for subchronic toxicity is considered complete. No additional studies are required at this time.

870.3100 90-Day Oral Toxicity - Rat

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

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

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

females), based on decreased hematology parameters in females, increased incidence of cuboidal to columnar epithelial cells lining thyroid follicles in both sexes, increased water consumption and urine output and decreased urine specific gravity in both sexes.

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

870.3100 90-Day Oral Toxicity - Mouse

This mouse subchronic feeding study (MRID 42362501; HED Doc. No. 009775) is unacceptable. However, the requirement was waived since an acceptable chronic study in the rat is available to adequately determine the carcinogenic potential of cacodylic acid.

870.3150 90-Day Oral Toxicity - Dog

There is no 90-day feeding study in the dog available. This requirement was waived since a 1-year acceptable oral (gelatin capsule) study in dogs is available.

870.3200 21/28-Day Dermal Toxicity - Rabbit

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

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

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

870.3465 90-Day Inhalation - Rat

In a 90-day toxicity study (MRID 44700301), cacodylic acid [(Cacodylate 3.25) (active ingredients: cacodylic acid (4.9%) and sodium cacodylate (28.4%); batch 095/93)] was administered by inhalation to 10 rats/sex/dose at aerosol concentrations of 10, 34 and 100 mg/m^3 (analytical concentrations 0.01, 0.034, or 0.1 mg/L). The control group received filtered air only and the cacodylate was administered as received from the sponsor. Exposures were 6 hours/day, 5

days/week, for a total of 67 (males) or 68 (females) exposures. The mass median aerodynamic diameter (50% size) and geometric standard deviation for Groups 2, 3, and 4 was 3.3 ± 2.8 µm, 2.5 ± 2.0 µm, and 2.3 ± 2.1 µm, respectively.

Mortality, body weights, organ weights, ocular abnormalities, clinical chemistry, and hematology parameters were not affected by treatment. Histomorphologic changes were restricted to the nasal cavity/turbinates of male and female rats of the 34 and 100 mg/m^3 exposure groups and consisted of an increased amount of intracytoplasmic eosinophilic globules (IEG) in the olfactory sustentacular cells and columnar epithelium in the posterior and ventral regions of the nasal cavity. There was no evidence of any adverse effect in any of the other areas of the respiratory tract or any other tissue or organ examined.

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

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

4.3 Developmental Toxicity

Adequacy of data base for Developmental Toxicity: The data base for developmental toxicity is considered complete. No additional studies are required at this time. Cacodylic acid is not a development toxicant in two species.

870.3800a Prenatal Developmental Toxicity Study - Rat

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

No adverse effects were seen in mothers or offspring at 4 or 12 mg/kg/day. Maternal toxicity was observed at the highest dose (36 mg/kg/day), as decreased body weights (≈ 4 - 6%; $P < 0.01$ to 0.001), body weight gains (≈ 16 - 30%; $P < 0.01$ to 0.001), food consumption (11.5 - 18.5%: $P < 0.001$) and gravid uterine weights (19%; $P < 0.001$). The data indicate that the decreased body weights and body weight gains were due to lower gravid uterine weights. Developmental toxicity was observed at the 36 mg/kg/day, as decreased fetal body weights (14.7%; $P < 0.001$), shorter crown-rump length (5%; $P < 0.001$), and suggestion of diaphragmatic hernia (12% vs 0 in the control, 4 or 12 mg/kg dose; $P < 0.05$). In addition, an increased incidence of delayed/lack of ossification of numerous bones (ant. fontanelle - 5%, supraoccipital - 43%, hyoid - 19%, one or two thoracic vertebral centra - 39%, 3 or more thoracic centra - 12%, bipartite centra - 6%, 13th rudimentary ribs - 9%, 1 or more unossified sternebrae - 16%, irregular ossification of 1 or more sternebrae - 44%, unossified metacarpus V - 89%, unossified pubic bone - 9%; $P < 0.05$ to 0.001) was reported. All the above delayed/lack of ossification of numerous bones were related to a

decrease in fetal growth rate, except the increase in 13th rudimentary ribs.

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

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

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

870.3700b Prenatal Developmental Toxicity Study - Rabbit

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

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

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

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

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

4.4 Reproductive Toxicity

Adequacy of data base for Reproductive Toxicity: The data base for reproductive toxicity is complete. No additional studies are required at this time. Cacodylic acid did not affect reproductive parameters.

870.3800 Reproduction and Fertility Effects - Rat

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 the diet at dose levels of 0, 3, 21 or 147 ppm (Mean of 2-gen.: 0, 0.31, 2.16, or 15.5 mg/kg/day for males and 0, 0.38, 2.48, or 17.86 mg/kg/day for females, respectively; calculated) for 10 weeks prior to mating and through both generations and lactation.

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

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

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

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

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

4.5 Chronic Toxicity

Adequacy of data base for chronic toxicity: The data base for chronic toxicity is considered complete. No additional studies are required at this time.

870.4100a (870.4300) Chronic Toxicity - Rat

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

Treatment with cacodylic acid did not effect mortality, food consumption, food efficiency, body weight or body weight gains. Treatment with cacodylic acid had a mild effect on hematology and the clinical chemistries of high-dose males and females and mid-dose males, at 6 months. At 100 ppm, %HCT, HGB, and RBC counts in males and %HCT and HGB in females decreased ≈ 4 - 6%, compared to the controls. There was no consistency between sexes with respect to K, Na, triglycerides, total protein and globulin levels at terminal sacrifice; therefore, toxicological significance can not be determined. Urine volume significantly ($P < 0.05$) increased in high-dose males at 3, 6 and 12 months and in females at 3 and 12 months. At 12 months, urine volume increased 55% in males and 30% in females, compared to controls. Urine specific gravity paralleled the urine volume; at 12 months the specific gravity of 40 and 100 ppm male and female urine was 1.05 vs 1.06 of controls ($P < 0.05$). Urine volume and specific gravity at other doses were comparable to controls. At 100 ppm, kidney weights in males and females increased 4.6% and 4.0%, respectively, compared to the controls ($P < 0.05$). Thickened urinary wall (3/60 vs 1/60), congested mucosa (2/60 vs 0/60), nodules (5/60 vs 0/60) masses (6/60 vs 0/60) were observed in high-dose females. Vacoular degeneration of bladder transitional epithelium was seen in both sexes at 40 (M - 1/58 and F - 21/59 vs 0 in control) and 100 ppm (M - 23/59 and F - 26/50 vs 0 in control). Submucosal lymphocytic infiltration was observed in 25% of males and 20% of the females at 100 ppm and 8.5% in females at 40 ppm, compared to controls. Transitional cell hyperplasia of the bladder in males/females at 40 and 100 ppm was 10.3%/49% and 67.8%/80%, respectively, compared to controls. Kidney lesions were dose-related and were confined to 40 and 100 ppm groups and included pyelonephritis (M- 4/60 at 100 ppm), medullary nephrocalcinosis (M - 14/59 at 40 ppm and 18/60 at 100 ppm; F - 12/60 at 100 ppm), and medullary tubular cystic dilatation (M - 3/59 at 40 ppm, and 13/60 at 100 ppm; F - 5/60 at 100 ppm). In addition, at 100 ppm, in males the pelvic transitional hyperplasia increased 10% compared to 0% in controls. At 100 ppm, the

incidence of hyperplasia of epithelium lining renal papilla increased 25% in males and 8% in females compared to controls. A dose-related increase in the height of thyroid follicular epithelium was noted in males at the 10, 40 and 100 ppm and in the females at the 40 and 100 ppm levels. In males, at the 0, 2, 10, 40 and 100 ppm the incidence was 0, 1.7, 6.7, 8.3 and 62%, respectively; and in females 0, 0, 0, 5 and 85%, respectively.

The **systemic toxicity NOAEL = 2 ppm (0.14 mg/kg/day) for males and 10 ppm (0.79 mg/kg/day) for females. The LOAEL = 10 ppm (0.79 mg/kg/day) for males and 40 ppm (3.2 mg/kg/day) for females,** based on increased thyroid follicular epithelial cell height in males and decreased urine specific gravity, and increased follicular epithelial cell height, and urinary bladder lesions (increased vacoular degeneration of transitional epithelium, lymphocytic infiltration, transitional hyperplasia) in females.

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

870.4100b Chronic Toxicity - Dog

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

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

sampling time; also total protein/albumin concentration decreased throughout the study and was 13%/21% at termination of the study ($P < 0.001$). The changes in hematology parameters and protein/albumin levels in high-dose males are consistent with body weight gains and are considered treatment-related, even though it was discounted in the DER. The **Systemic Toxicity NOAEL = 16 mg/kg/day and LOAEL = 40 mg/kg/day, based on salivation, vomiting , diarrhea, and decreased body weight gains (M & F) and decreased HCT%, HgB, RBC counts, and total protein and albumin concentration (M).**

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

4.6 Carcinogenicity

Adequacy of data base for Carcinogenicity: The data base for carcinogenicity is considered complete, although the mouse carcinogenicity study was unacceptable/guideline. The Cancer Peer Review Committee considered the weight-of-evidence on cacodylic acid and concluded that the mouse carcinogenicity study in conjunction with the rat carcinogenicity study provides sufficient information for the carcinogenicity risk assessment, and recommended that there is no need to repeat the mouse cancer study.

870.4200a Carcinogenicity Study - Rat

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

Neoplastic lesions were observed in both sexes at the 100 ppm dose. A transitional cell papilloma was found in one male rat each dosed at 10 and 40 ppm and 0 at 100 ppm. In females, transitional cell papillomas were also observed at 100 ppm only (4/60) which was statistically significant at $P < 0.05$ level. 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, which suggests adequate dosing.

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 vacoular degeneration of transitional epithelium, lymphocytic infiltration, transitional hyperplasia) in females.

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

870.4200b Carcinogenicity [feeding] - Mouse

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

Treatment with cacodylic acid did not affect survival, food consumption, food efficiency, differential cell counts, or organ weights. At 500 ppm, body weight gains decreased 15.5% in males during the study. The urinary system appears to be the target organ for this chemical in both mice and rats. Microscopically, a dose-related, increased vacoular degeneration of bladder epithelium (focal to diffuse) was seen in males at 200 ppm and above and in females at 40 ppm and above. The incidence at the 0, 8, 40, 200 and 500 ppm was 0, 1.8, 0, 94, 100% in males and 2, 1.9, 40.8, 98 and 100% in females, respectively. Progressive glomerulonephropathy and nephrocalcinosis showed a positive trend ($P < 0.05$ and 0.001, respectively) among males; when combined by sex, the trend persisted ($P < 0.05$ and 0.001, respectively). In males, the glomerulonephropathy incidence was 30.3, 41, 32, 57, and 57% at the 0, 8, 40, 200 or 500 ppm, respectively; females were not effected. Eighty-two percent (82%) of 500 ppm males were observed with nephrocalcinosis of the kidney vs 50% in the control group; the incidence at other dose levels was below the control. There was a statistically significant increase ($P < 0.01$) in fibrosarcomas observed in the abdominal cavity of high-dose female (10.7%) mice. In the males there was a non-significant positive trend for fibrosarcomas. 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. No significant result was observed in males. The **systemic toxicity NOAEL = 40 ppm (7 mg/kg/day) for males and 8 ppm (1.7 mg/kg/day) for females and the LOAEL = 200 ppm (35.25**

mg/kg/day) for males and 40 ppm (8.65 mg/kg/day) for females, based on vacoular degeneration of bladder epithelium.

The dosing was considered adequate 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.

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

4.7 Mutagenicity

Adequacy of data base for Mutagenicity: The data base for Mutagenicity is considered adequate based on pre 1991 mutagenicity guidelines. These genetic toxicology studies indicate that cacodylic acid does not present a mutagenicity concern at this time; however, it is noted that other arsenic containing compounds (e.g arsenic acid, arsenic pentoxide, potassium arsenite, sodium arsenate, sodium arsenite) all have been found to produce chromosomal aberrations in cultured mammalian cells.

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; HED Doc. No. 009562).

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; HED Doc. No. 009562).

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; HED Doc. No. 009562).

4.8 Neurotoxicity

Adequacy of data base for Neurotoxicity: Neurotoxicity studies are not required for this class of compounds. However, following on the weight-of-the-evidence considerations, the Hazard ID Committee has determined that developmental neurotoxicity in rats **is required** because of endocrine effects in the reproduction study (decreased ovarian weight and thyroid lesions in females). Acute- and subchronic neurotoxicity studies were also recommended.

4.9 Metabolism

Adequacy of data base for metabolism: The data base for metabolism is considered to be complete. No additional studies are required at this time.

870.7485 Metabolism - Rat

In a general metabolism study (MRID 42341301 & 43005801; HED Doc. No. 010353) [^{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, 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 a single i.v. dose at 5.0 mg/kg.

The 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 ≈ 10% of the i.v. dose was recovered in the blood. The majority of the radioactivity in the blood was associated with 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%; the 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.

870.7600 Dermal Absorption - Rat

In a dermal absorption study(43497401), male rats (28/dose) were administered [^{14}C]cacodylic acid (in the equivalent of 3.25W formulation), at dose levels of 0.90, 9.30 or 91.3 µg/cm2. Four rats/dose were sacrificed 0.5, 1, 2, 4, 10 or 24 hours after application. An additional group of 4 rats/group were exposed for 24 hours and sacrificed at 96 hours.

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

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%

4.10 Special/Other Studies: None

5.0 HAZARD ENDPOINT SELECTION

5.1 Endpoint selection (HAZID)

Table 2. Doses and toxicological endpoints selected for various exposure scenarios

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 fetal weights, shorter crown-rump length, the suggestion of diaphragmatic hernia and delayed/lack of ossification of numerous bones.	Developmental rat MRID 40625701
		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 MRID 40663301
		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 MRID 41862101
		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 MRID 41872801
*Intermediate-Term (Dermal)	Oral NOAEL = 0.4 mg/kg/day	LOAEL = 4 mg/kg/day (male) is based on increased incidence of cuboidal to columnar epithelial lining thyroid follicles and water consumption and urine output; decreased sp.gravity.	13-Week feeding study in rats MRID 42767701
Long-Term (Dermal)	Not required	Not required	Not required
Short-and Intermediate-Term (Inhalation)	NOAEL = 0.01 mg/L (4.38 mg/kg/day adjusted)	LOAEL = 0.034 mg/L (14.95 mg/kg/day adjusted), based on presence of intracytoplasmic eosinophilic granules in the cells of the nasal turbinates.	90-Day Inhalation - Rat MRID 44700301
Long-Term (Inhalation)	Not required	Not required	Not required

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

5.2 Dermal Absorption

Dermal Absorption Factor: 3.5%

Study Selected: Dermal Penetration Study in Rats §85-3

Dermal absorption factor of 3.5% was based on 10 hour exposure period from a dermal absorption study (43497401) in rat.

5.3 Classification of Carcinogenic Potential

5.3.1 Conclusions

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. Based on the weight-of-the-evidence the committee concluded that the chemical is carcinogenic to rodents.

5.3.2 Classification of 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.

5.3.3 Quantification of Carcinogenic Potential

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.

6.0 FQPA CONSIDERATIONS

6.1 Special Sensitivity to Infants and Children

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. 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.

6.2 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; however, no neurotoxicity studies were submitted.

6.3 FQPA Safety Factor Committee Recommendations

1. FQPA Safety Factor Recommendation

The Committee recommended that the FQPA safety factor for protection of infants and children (as required by FQPA) should be retained.

2. Rationale for Requiring the FQPA Safety Factor

The FQPA SFC concluded that the safety factor is required because:

- a quantitative increase in susceptibility of fetuses (compared to dams) is demonstrated in the prenatal rat developmental toxicity study; and
- a developmental neurotoxicity study in rats is required for cacodylic acid based on concerns for endocrine effects observed in the reproduction and other studies.

3. Application of the Safety Factor - Population Subgroups/Risk Assessment Scenarios

Females 13 - 50 Population Subgroup: When assessing **Acute Dietary and Short-term Residential Exposures,** the safety factor should be **retained at 10x** since there is concern for the qualitative increase in susceptibility observed in rat fetuses following *in utero* exposure to rats in the developmental study (which could potentially occur after a single dose); and since there is a data gap for the developmental neurotoxicity study in rats. The developmental neurotoxicity study may further define the neurotoxic potential observed in the developing fetus in the prenatal development study in rats.

All Population Subgroups: When assessing **Acute and Chronic Dietary and Residential Exposures of All Durations,** a safety factor is required since there is a data gap for the developmental neurotoxicity study. However, the safety factor can be **reduced to 3x** since the concern for increased susceptibility seen after *in utero* exposure in the developmental study has no bearing on population subgroups other than females of child-bearing age.

7.0 OTHER ISSUES

None

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9.0 APPENDICES

9.1 Toxicity Profile Summary Tables

9.1.1 Acute Toxicity Table [3.25 Formulation (4.9%, a.i.)]

Guideline No.	Study Type	MRID #(s)	Results	Category
870.1100	Acute Oral	41925601	LD_{50} (M&F) = 2.8 gm/kg	III
870.1200	Acute Dermal	41892701	LD_{50} > 2.0 gm/kg	III
870.1300	Acute Inhalation	41892702	LC_{50} (4 hr):combined = 4.9 mg/L; M = 5.8 mg/L & F = 4.0 mg/L	IV
870.2400	Primary Eye Irritation	41892703	Primary eye irritant - conjunctival redness in 1 hr. In al animals; persisted for 24 hrs. In 1/6 animals.	III
870.2500	Primary Skin Irritation	41892704	Negligible irritation in 0.5 hr. Cleared 24 - 48 hrs.	IV
870.2600	Dermal Sensitization	41892705	Not a sensitizer	N/A

9.1.2 Subchronic, Chronic and Other Toxicity Table

Guideline No./Study Type	MRID No. (year)/Classification/Doses	Results
870.3100 90-Day oral toxicity rodents	42767701(1987) Acceptable/guideline ♂ : 0, 0.4, 4.0, 43.2 mg/kg/d ♀: 0, 0.4, 4.5, 45.7 mg/kg/d	NOAEL = 0.4 mg/kg/d LOAEL = 4 (♂) and 4.5 (♀) mg/kg/d based on ↑ incidence of cuboidal to columnar epithelial lining thyroid follicles and ↑ water consumption and urine output and ↓ specific gravity; and ↓ hematology parameters in females.
870.3200 21/28-Day dermal toxicity	41872801 (1991) Acceptable/guideline 0, 100, 300, 1000 mg/kg/d	NOAEL = 300 mg/kg/day LOAEL = 1000 mg/kg/day based on ↓ body weight gains in females, and ↓ decreased testicular weights, hypospermia and tubular hypolasia in males.
870.3465 90-Day inhalation toxicity	44700301 (1994) Acceptable/guideline 0, 10, 34, 100 mg/m^3	NOAEL = 0.010 mg/L/day LOAEL = 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.
870.3700a Prenatal developmental in rodents	4062701 (1988) Acceptable/guideline 0, 4, 12, 36 mg/kg/d (gavage)	**Maternal** NOAEL = 12 mg/kg/day LOAEL = 36 mg/kg, based on ↓ body weights, body weight gains, food consumption and gravid uterine weight. **Developmental** NOAEL = 12 mg/kg/day LOAEL = 36 mg/kg, ↓ fetal weights, shorter crown-rump length, the suggestion of diaphragmatic hernia and delayed/lack of ossification of numerous bones.
870.3700b Prenatal developmental in rodents	40663301 (1988) Acceptable/guideline 0, 3, 12, 48 mg/kg/d (gavage)	**Maternal** NOAEL = 12 mg/kg/day LOAEL = 48 mg/kg, based on mortality, abortions, body weight loss and reduced food consumption. **Developmental** NOAEL = 12 mg/kg/day LOAEL was not established, since no pregnant rabbit survived to the gestation day 29 scheduled sacrifice.

Guideline No./Study Type	MRID No. (year)/Classification/Doses	Results
870.3800 Reproduction and fertility effects	41059501 (1989) Acceptable/guideline M: 0, 0.31, 2.16, 15.5 mg/kg/d F: 0, 0.38, 2.48, 17.86 mg/kg/d	**Parental/Systemic** NOAEL = M: 2.16, F: 2.48 mg/kg/day LOAEL = M:15.5 mg/kg F: 17.86 mg/kg, based on ↓ absolute and relative ovarian weights and ↑ incidence of thyroid follicles lined with cuboidal to columnar epithelium in females only. **Reproductive** NOAEL = M: 15.5, F: 2.48 mg/kg/day LOAEL was not established **Offspring** toxicity: There was no suggestive evidence of offspring toxicity in either generation.
870.4200a Chronic toxicity rodents	41862101 (1989) Acceptable/guideline M: 0, 0.14, 0.73, 2.80, 7.30 mg/kg/d F: 0, 0.16, 0.79, 3.20, 8.0 mg/kg/d	NOAEL = 0.14 (M) and 0.79 (F) mg/kg/day LOAEL = 0.79 (M) and 3.2 (F) mg/kg/day based on ↑ thyroid follicular epithelial cell height in males and ↓ urine sp. gr., ↑ thyroid follicular epithelial cell height and urinary bladder lesions (↑ vacoular degeneration of transitional epithelium, lymphocytic infiltration and transitional hyperplasia) in females. Kidney, urinary bladder and thyroid gland are the target organs.
870.4200b Chronic toxicity dogs	41490901 (1989) Acceptable/guideline 0, 6.5, 16, 40 mg/kg/d (gavage)	NOAEL = 16 mg/kg/day LOAEL = 40 mg/kg/day based on salivation, vomiting, diarrhea, and decreased body weight gains in males and females; and decreased HCT%, HgB, RBC counts, total protein and albumin in males.
870.4200 Carcinogenicity rats	41862101 (1989) Acceptable/guideline M: 0, 0.14, 0.73, 2.80, 7.30 mg/kg/d F: 0, 0.16, 0.79, 3.20, 8.0 mg/kg/d	NOAEL = 0.14 (M) and 0.79 (F) mg/kg/day LOAEL = 0.79 (M) and 3.2 (F) mg/kg/day based on ↑ thyroid follicular epithelial cell height in males and ↓ urine sp. gr., ↑ thyroid follicular epithelial cell height and urinary bladder lesions (↑ vacoular degeneration of transitional epithelium, lymphocytic infiltration and transitional hyperplasia) in females. Kidney, urinary bladder and thyroid gland are the target organs. **Neoplastic lesions were observed in both sexes at the highest dose tested.** Papillomas sig. increased in high dose females; trend was sig. in both sexes at high dose and exceeded the historical controls. In females papillomas was sig. in pair-wise comparison.

Guideline No./Study Type	MRID No. (year)/Classification/Doses	Results
870.4300 Carcinogenicity mice	41914601 (1990) Unacceptable M: 0, 1.47, 7.0, 35.25, 91.95 mg/kg/d F: 0, 1.7, 8.65, 43.15, 97.0 mg/kg/d	NOAEL = 1.7 (F) and 7 (M) mg/kg/day LOAEL = 8.65 (F) and 35.25 (M) mg/kg/day based on vacoular degeneration of bladder epithelium. **Neoplastic lesions were observed in both sexes at the highest dose tested.** Fibrosarcomas sig. increased in high dose females; there was sig. trend for fibrosarcomas in both sexes.
870.5100 Gene mutation *Salmonella typhimurium* reverse gene mutation	41892706 (1991) Acceptable/guideline Doses: 100 to 10,000 µg/plate in the +/- of S9 activation	Negative in *S. typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100.
870.5300 Gene mutation Mouse lymphoma assay	41892707 (1991) Acceptable/guideline Doses: 1600 to 5769 µg/mL	Doses 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.
870.5385 Chromosomal aberration Mouse micronucleus assay	41892708 (1991) Acceptable/guideline Dose: 147, 293, or 586 mg/kg	Did not induce clastogenic response in the mouse micronucleus assay.
870.7485 Metabolism and pharmacokinetics	42341301 & 43005801 (1992) Acceptable/guideline Doses:0, 5.0 and 50.0 mg/kg	Over a 7-day period 90 - 98% of total dose was excreted. Total radioactivity recovered in the urine, feces and exhiled air was 28 - 82, 4 - 33, and 0 - 0.1%, respectively.
870.7600 Dermal penetration	43497401 (1994) Acceptable/guideline Dose: 0, 0.90, 9.30, or 91.3 µg/cm2	At 10 hours 1.11, 3.51 or 3.0% of the total dose was absorbed at dose levels of 0.9, 9.3, or 91.3 µg/cm2, respectively. Therefore, a dermal absorption factor of 3.5% was established for 10 hour exposure period .

9.2 Summary of Toxicological Dose and Endpoints

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

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF and Endpoint for Risk Assessment	Study and Toxicological Effects
Acute Dietary females 13-50 years of age	NOAEL = 12 mg/kg/day UF = 100 **Acute RfD** = 0.12 mg/kg/day	FQPA SF = 10 **aPAD** = 0.12 / 10 = 0.012 mg/kg/day	Developmental Toxicity - Rat (40625701) 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.
Acute Dietary general population including infants and children	NOAEL= 12 mg/kg/day UF = 100 **Acute RfD** = 0.12 mg/kg/day	FQPA SF = 10 **aPAD** = 0.12 / 10 = 0.012 mg/kg/day	Developmental Toxicity - Rabbit (40663301) LOAEL = 48 mg/kg/day based on mortality, abortions, body weight loss and reduced food consumption.
Chronic Dietary all populations	NOAEL= 0.14 mg/kg/day UF = 100 **Chronic RfD** = 0.0014 mg/kg/day	FQPA SF = 10 **cPAD** = 0.0014 / 10 = 0.00014 mg/kg/day	Two year feeding - Rat (41862101) LOAEL = 0.79 mg/kg/day based on increased thyroid follicular cell height in males.
Short-Term Dermal (1-7 days) (Occupational/ Residential)	dermal study NOAEL= 300 mg/kg/day (dermal absorption rate = 3.5%)	**acceptable MOE** = 100 (Occupational) **acceptable MOE** = 100 X10 (Residential)	21-Day Dermal - Rabbit (41872801) LOAEL = 1000 mg/kg/day based on decreased body weight gain in females, and decreased testicular weights, hypospermia, and tubular hypoplasia in males.
Intermediate-Term Dermal (1 week - several months) (Occupational/ Residential)	oral study NOAEL= 0.4 mg/kg/day (dermal absorption rate = 3.5%)	**acceptable MOE** = 100 (Occupational) **acceptable MOE** = 100 X10 (Residential)	90-Day Feeding - Rat (42767701) LOAEL = 4 mg/kg/day based on increased incidence of cuboidal to columnar epithelial lining thyroid follicles, water consumption and urine output and decreased urine sp. gravity.
Long-Term Dermal (several months - lifetime) (Occupational/ Residential)	Not required	Not required	Not required

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF and Endpoint for Risk Assessment	Study and Toxicological Effects
Short-Term Inhalation (1-7 days) (Occupational/ Residential)	Inhalation study NOAEL= 0.01 mg/L (4.38 mg/kg/day, adjusted)	**acceptable MOE** = 100 (Occupational) **acceptable MOE** = 100 X10 (Residential)	90-Day Inhalation - Rat (44700301) LOAEL = 0.034 mg/kg/L (14.95 mg/kg/day) based on presence of moderate and marked intracytoplasmic eosinophilic granules (IEG) in the nasal turbinate cells of male and female rats.
Intermediate-Term Inhalation (1 week - several months) (Occupational/ Residential)	Inhalation study NOAEL= 0.01 mg/L (4.38 mg/kg/day, adjusted)	**acceptable MOE** = 100 (Occupational) **acceptable MOE** = 100 X10 (Residential)	90-Day Inhalation - Rat (44700301) LOAEL = 0.034 mg/kg/L (14.95 mg/kg/day) based on presence of moderate and marked intracytoplasmic eosinophilic granules (IEG) in the nasal turbinate cells of male and female rats.
Long-Term Inhalation (several months - lifetime) (Occupational/ Residential)	Not required	Not required	Not required
Cancer (oral)	Group B2 - Probable Human Carcinogen	Q1* = 6.23×10^{-2} $(mg/kg/day)^{-1}$ in human equivalents, using Multi-Stage model (Tox-Risk program, version 3.5- K.Crump)	increases in urinary bladder carcinomas (rare tumor type) in both sexes of the Fischer rat and increases in fibrosarcomas (multiple organs) in female B6C3F1 mice.

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

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