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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: December 22, 1977

SUBJECT: Pramitol 25E-Update Files
Caswell #96

EPA Registration #100-443
Shaughnessy #080804

FROM: Toxicology Branch
Registration Division

TO: Robert Taylor
Product Manager#25

Thru: Acting Branch Chief, Toxicology E for GEW 1/8/78

Recommendation: Acute oral LD_{50}, acute dermal LD_{50}, acute inhalation LC_{50}, eye irritation, skin irritation, and subacute dermal LD_{50} data adequately support the TOX Category I label proposed by the registrant. Recommended changes in the Precautionary Statement are as follows:

Hazard Human and Domestic Animals
Corrisive-Causes eye damage. Wear goggles or face shield and rubber gloves when handling. Causes skin irritation. Harmful if swallowed, inhaled or absorbed through the skin. Avoid breathing spray mists. Do not get in eyes, on skin or on clothing. Avoid contamination of food.

First Aid
In case of contact with eyes, immediately flush with plenty of water for 15 minutes and get medical attention; with skin, wash immediately with plenty of soap and water. If swallowed, drink promptly a large quantity of milk, egg whites, gelatin solution or if these are not available drink large quantities of water. Avoid alcohol. Call a physician immediately In case of inhalation exposure remove from contaminated area. Wash thoroughly after handling and before eating and smoking. Remove and wash contaminated clothing before reuse.

Note to Physician
Probable mucosal damage may contraindicate the use of gastric lavage. Measures against circulatory shock, respiratory depression and convulsions may be needed.

The rest of the label (attached) is adequate.

*No RPAR criteria have been exceeded.
**Results from Industrial Bio-Test Laboratories are included in submitted data. When data are validated, statistical analyses should be done as appropriate.

Review

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I. Acute Toxicity Studies on Prometone 25E (Industrial Bio-Test Laboratories, Inc., IBT, 5/21/65, submitted nu Cina-Geigy Corp., 9/7/77, Acc.#231816).

A. Acute Oral Toxicity

1. Procedure

a. Young, albino rats (Sprague-Dawley), 160g av. wt., were divided into 4 groups of 4 animals each (2 males and 2 females) which were administered 1.4, 2.0, 3.0, or 4.5 g/kg of undiluted test material by gavage. Animals were housed individually and were permitted food and water ad libitum until 16 hours prior to gavage. Onservations of mortalities and reactions were recorded during 14 days post-treatment. Necropsies were done on animals which died during the study.

2. Results

a). Mortalities

Dose(g/kg)	Deaths
1.4	0/4
2.0	1/4
3.0	3/4
4.6	4/4

LD_{50} = 2.5 ± 0.4 (S.D.) g/kg

b). Toxic Symptoms: Hypoactivity, ptosis, muscular weakness, ruffed fur, emaciation, loss of righting reflex, dyspnea, hemorrhagic rhinitis, sedation.

c). Necropsy: No gross pathological abnormalities in decedents were reported.

3. Conclusions

a). Classification: Supplementary. Only 2 animals/sex/dose were used.
b). Tox. Cat.: III

II. Acute Toxicity Studies on Pramitol 25E (Industrial Bio-Test Laboratories, Inc., IBT#A1228, 3/29/72, submitted by Ciba-Geigy Corp., 9/7/77, Acc.#231816).

A. Acute Oral Toxicty

1. Procedure

a). Young albino rats (Charles River), 147-225g, were divided into 5 groups of 10 animals each (5 males and 5 females) which were administered 900, 1350, 2025, 2500, or 3038 mg/kg of undiluted test material by gavage. Animals were housed individually and were permitted food and water ad libitum until 16 hour prior to gavage. Observations of body weight changes, mortalities, and reactions were recorded during 14 days post-treatment. Necropsies were done on all animals.

2. Results

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a). Mortalities

Dose (mg/kg)	Deaths
900	0/10
1350	0/10
2025	3/10
2500	8/10
3038	8/10

LD_{50} = 2,276 (1953-2653) mg/kg

b). Toxic Symptoms: Hypoactivity, ruffed fur, atoxia, ptosis, salivation, muscular weakness, emaciation, hemorrhagic rhinitis, labored breathing. All survivors gained weight (7/35g), but weight changes were unaffected by test material.

c). Necropsy: Hemorrhaged stomachs in decedents.

3. Conclusions

a). Classification: Core Guidelines
b). Tox. Cat.: III

III. Acute Oral Toxicity Study on GAZ-525 Pramitol 25E (Food and Drug Research Laboratories, Inc., FDRL, OE No. 3772-530, 10/15/73, submitted by Ciba-Geigy Corp., 9/7/77, Acc.#231816).

A. Acute Oral Toxicity

1. Procedure

a). Albino rats (Sherman-Wistar), 200-300g, were divided into 5 groups of 10 animals each (5 males and 5 females) which were administered 1500, 2,000, 2500, or 3000 mg/kg of test material in CMC or 30 ml/kg CMC (control) by gavage. Animals were permitted food and water ad libitum until 16 hrs. before dosing. Mode of housing was not stated. Observations of mortalities and toxic symptoms were recorded during 14 days post-treatment. Necropsies were done.

2. Results

a). Mortalities:

Dose (mg/kg)	(male) Deaths	(female)
Control		
1500	0/5	0/5
2000	0/5	1/5
2500	0/5	2/5
3000	3/5	3/5
		4/5

males: LD_{50} > 2500 mg/kg Females: LD_{50} = 2100 (1600-2800) mg/kg

b). Toxic Symptoms: Belly-drag, salivation, lethargy, atoxia (1 male and 1 female) piloerection (1 female).

c). Necropsy: Unremarkable

3. Conclusions

a). Classification: Core-Minimum Guidelines. Although body weights were not recorded, results support Tox. Cat. III

b). Tox. Cat.: III

IV. Acute Toxicity Studies on Prometone 25E (Industrial Bio-Test Laboratories, Inc., IBT, 5/21/55, submitted bu Ciba-Geigy Corp., 9/7/77, Acc.#231815)

A. Acute Dermal Toxicity

1. Procedure

a). Animals were housed individually and were permitted food and water ad libitum. Backs were shaved 24 hours prior to application of test material. Young adult albino rabbits (New Zealand), 2.5 kg.av.wt., were divided imto 4 groups of 4 animals each (2 males and 2 females) which received dermal application of 1.4, 2.0, 3.0, or 4.5 g/kg of undiluted test material. Application sites were occluded with impervious plastic sheeting. Sheeting was removed 24 hours post-treatment. Observations of behavior, local reactions, and mortalities were recorded during 14 days after treatment. Necropsies were done.

2. Results

a). MOrtalities

Dose (g/kg)	Deaths
1.4	0/4
2.0	1/4
3.0	4/4
4.5	4/4

LD_{50} = 2.2 $\pm$ (S.D.) g/kg

b). Toxic Symptoms: Salivation, tremors, convulsions, hyperthermia, lethargy, emaciation, diarrhea. All deaths occurred within 24 hours except for 1 animal in the 4.5 mg/kg group. Moderate to severe erythema and edema were evident for all groups. Skin was stated to have appeared normal by 14 days post-treatment in survivors, but in a subsequent study (V) severe desquamation was evident at the end of the observation period.

c). Necropsy: Unremarkable

3. Conclusions

a). Classification: Supplementary. No animals with abraded test sites were used.

b). Tox. Cat. III

V. Acute Toxicity Studies on Pramitol 25E (Industiral Bio-Test Laboratories, Inc., IBT#A1228, 3/29/72, submitted by Ciba-Geigy Corp., 9/7/77, Acc.#231816

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A. Acute Dermal Toxicity

a). Animals were housed individually and were permitted food and water ad libitum. Backs were shaved 24 hours prior to application of test material. Young adult albino rabbits (New Zealand), 2.12-2.3Kg, were divided into 3 groups of 4 animals each (2 males and 2 females) which received dermal applications of 1000,2000, or 3000mg/kg of undiluted test material. Animals were fitted with collars, and test sites were occluded with imprevious plastic sheeting. Sheeting and residual test material were removed 24 hours post-treatment. Observations of behavior, local reactions, body weight changes, and mortalities were recorded during 14 days after treatment. Necropsies were done.

2. Results

a). Mortalities:

Dose (mg/kg)	Deaths
1000	0/4
2000	2/4
3000	4/4

LD_{50} = 2000 mg/kg

b). Toxic Symptoms: Diuresis, hypoactivity, salivation, rhinitis, and dyspnea. Local reactions included red, well-defined erythema, severe edema, superficial escharosis, cracking, and severe desquamation. Weight changes were slight.

c). Necropsy: Unremarkable

3. Conclusions

a). Classification: Supplementary. No animals with abraded sites were used.
b). TOX. Category: III Although the LD_{50} = 2000 mg/kg, results of other studies support the selection of III.

VI. Acute Dermal Toxicity Study on GA2-525 Pramitol 25E (Food and Drug Research Laboratories, Inc., FDRL, OE No. 3772-530, 10/15/73, submitted by Ciba-Geigy Corp., 9/17/77, Acc. #231816).

A. Acute Dermal Toxicity

1. Procedure

a). Animals were housed individually and were permitted food and water ad libitum. Backs were shaved 24 hours prior to application of test material. Young adult albino rabbits (unspecified strain), about 2.5kg, were divided into 4 groups of 8 animals each (4 males and 4 females) which received dermal applications of 1500,2000,2500 or 3000 mg/kg of undiluted test material. Backs of 2 males and 2 females in each group were abraded. Application sites were occluded with imprevious rubber sheeting. Sheeting was removed, and test sites were cleansed with warm water 24 hours post-application. Observations of toxic symptoms, local reactions, mortalities, and body weight changes were continued during 14 hours post-application. Necropsies were done.

2. Results

a). Mortalities

Dose (mg/kg)		1500	2000	2500	3000
Males:	Intact	1/2	2/2	2/2	2/2
	Abraded	0/2	2/2	2/2	2/2
Females:	Intact	0/2	0/2	0/2	2/2
	Abraded	0/2	1/1	1/2	2/2
	Total	1/8	5/8	5/8	8/8

LD_{50} = 1500-2000 mg/kg

b). Toxic Symptoms: Decreased activity, withdrawal, ataxia, head drop, unconsciousness. All mortalities arose within 30 hours post-application. Weight changes were slight. Local reactions included moderate to severe erythema without edema. By the end of the 14 day observation period, most eschar formation had been shed, but in a previous study (V) severe desquamation was evident by the e of the observation period.

c). Necropsies: Unremarkable

3. Conclusions

a). Classification: Core-Guidelines

b). Tox. Category: III. The LD_{50} appears to be borderline at 2000 mg/kg, and other studies support Tox. Category III.

VII. Acute Dermal Toxicity Study on GA-20525 Pramitol 25E (Industrial Bio-Test Laboratories, Inc., IBT No. 601-04656, 3/8/74, submitted by Ciba-Geigy Corp., 9/17/77, Acc. #231816).

A. Acute Dermal Toxicity

1. Procedure

a). Animals were housed individually and were permitted food and water ad libitum. Backs were shaved 24 hours prior to application of test material. Young adult albino rabbits (New Zeland), 2.4-2.8kg, were divided into 8 groups of 4 animals each (2 males and 2 females) which received dermal applications of 500, 1000, 1500, 2000, 2500, 3000, 3500 or 4000 mg/kg of undiluted test material. Backs of 1 male and 1 female in each group were abraded. Another group of 1 male (abraded) and 1 female received 10000 mg/kg applications. Animals were collared, and test sites were occluded with impervious plastic sheeting. Rabbits were kept under a fume hood 1.5 hours post-treatment. Sheeting and residual test material were removed 24 hours after application. Observations of mortalities, local reactions, body weight changes, and behavior were recorded during 14 days post-treatment. Necropsies were done.

2. Results

a). Mortalities

Dose (mg/kg)	Deaths
500	0/4
1000	0/4
1500	0/4
2000	0/4
2500	3/4

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a). Mortalities:

Dose (mg/kg)	Deaths
3000	1/4
3500	3/4
4000	4/4
10000	2/2

LD_{50} = 2820 (2495.5-3186.6) mg/kg

b). Toxic Symptoms: Hypoactivity, vasodilation, hypothermia, iritis, rapid respiration, rhinitis, white nasal discharge, lacrimation, muscle weakness, tremors, ataxia, analgesia, and, in rabbits dosed erythema, moderate with edema, desquamation, escharosis, necrosis, second degree chemical burns. Survivors lost weight (0.08-0.70 Kg) by 7 days post-treatment, but by 14 days post-treatment all survivors except 2 regained weight (0.14-0.44Kg) above 7 day values.

c). Necropsy: Examination of 3 decedents and 3 survivors revealed retroperitoneal hemmorhages in the lumbar area adjacent to the perirenal fat. These findings were not dose-related. No other gross pathological changes were found.

3. Conclusions

a). Classification: Core-Minimum Guidelines. Although only 2 animals/sex/dose level/(intact and abraded sites together) were used, nine dose levels were used to enhance the acceptability of the study.

b). Tox. Category: III

VII. Acute Toxicity Studies or Prometone 25E (Industrial Bio-Test Laboratories, Inc., IBT, 6/12/65, submitted by Ciba-Geigy Corp., 9/7/77, Acc.#231816).

A. Acute Aerosol Inhalation Study

1. Procedure

a). Young adult albino rats (Sprague-Dawley), 250 g aw.wt., were divided into 2 groups of 10 animals each (5 males and 5 females). Each group was exposed separately in a 38 L inhalation chamber, and aerosols (0.5-3.0 μ particles) of test material were generated with an OHIO rebulizer in a medium of dried metered (4.0 L/min av.) air. Aerosol concentration was calculated by dividing total weight of test material by total volume of air.

Exposures were of 1 group to undiluted test material (46.3 mg/L air) and of the other group to a 30% (v/v, 36.0 mg/ L air) aqueous solution of test material. Exposure lasted 4 hours. Observations of body weight changes, toxic symptoms, and mortalities were recorded during 14 days post-treatment. Necropsies were done.

2. Results

a). Mortalities:

Exposure	Deaths
Undiluted	8/10
30%	0/10

(Undiluted) LC_{50} < 46.3 mg/L air

(30%) LC_{50} > 36.0 mg/L air (12 mg. equiv. of undiluted).

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b). Toxic Symptoms: General inactivity, hyperpnea, lacrimation, conjunctivitis, salivation, rhinitis, ataxia. Animals exposed to undiluted test material were comatose and dyspneic. Body weight changes were slight.

c). Necropsy: Moderate lung hemorrhages and mild small intestinal hemorrhages were found in decedents. Observations on survivors were unremarkable.

3. Conclusions

a). Classification: Core Minimum ~~Guidelines~~. Although only 2 dose levels were used, the levels were sufficiently high to determine the low toxicity of the test substance. These conclusions are supported by results of a second study (IX).

b). Tox. Category: IV

IX. Acute Aerosol Inhalation Toxicity Study or GA-2-395 Pramitol 25E (Industrial Bio-Test Laboratories, Inc., IBT No. N1229, 4/4/72, submitted by Ciba-Geigy Corp., 9/17/77, Acc. #231816).

A. Acute Aerosol Inhalation Study

1. Procedure

a). Young adult albino rats (ARS/Sprague-Dawley), 155 g av. wt., were divided into 3 groups of 10 animals (5 males and 5 females). Each animal was caged separately in a 70 L inhalation chamber during exposure to an aerosol of undiluted test material generated with an OHIO Ball-Jet nebulizer in a medium of dried, metered air. Average aerosol concentrations were calculated by nebulizer weight loss by total volume of air. Experimental condition were outlined as follows:

Group	Exposure Duration (Min)	Air Delivery Rate (L/min)	Average Aerosol Concentration (mg/L
I	240	16.5	15.9
II	240	9.2	33.6
III	130	5.1	55.2

Observations of body weight changes, toxic symptoms, and mortalities were recorded during 14 days post-exposure. Necropsies were done.

2. Results

a). Mortalities:

Dose (mg/L air)	Deaths
15.9	3/10
33.6	9/10
55.2	10/10

LC_{50} = 19.5 (13.7-27.7) mg/L air

b). Toxic Symptoms: Salivation, nasal discharge, lacrimation (bloody in 1 rat), ataxia, tremors, hyperpnea, clonia, prostration, unconsciousness. In Table III of the report, body weight changes were reported as gain (20-60g), but in the summary rats were stated to have lost weight.

c). Necropsy: Lung hyperemia was found in all animals except 1 survivors.

3. Conclusions

a). Classification: Core Guidelines
b). Tox. Category: III

X. Acute Toxicity Studies on Prometone 25E (Industrial Bio-Test Laboratories, Inc., IBT, 6/21/65, submitted by Ciba-Geigy Corp., 9/7/77, Acc.#231816).

A. Eye Irritation Test-Albino Rabbits

1. Procedure

a). Five young adults albino rabbits (New Zealand) were used. Into each right eye was instilled 0.1 ml of test material. Untreated left eyes were controls. Cornea, iris, and palpebral conjunctiva were examined 1,23,48,72, and 96 hours and 7 days post-instillation, and injuries were scored according to Draize et al. (1944). Eyes were unwashed after treatment.

2. Results

a). Time	1 hour	24 hours	48 hours	72 hours	96 hours	7 days
Total/110	51.5/110	52.0/110	50.0/110	41.4/110	29.4/110	10.6/

Scores were obtained for cornea, iris, and conjunctiva throughout the 7 day observation period. Corneal injury was evident in rabbit at day 7 post-treatment

3. Conclusions

a). Classification: Core Minimum Guidelines. Although only 5 animals were used, eye damage was clearly defined.
b). Tox. Category: I

XI. Acute Toxicity Studies on Pramitol 25E (Industrial Bio-Test Laboratories, Inc., IBT#A1228, 3/29/72, submitted by Ciba-Geigy Corp., 9/7/77, Acc.#231816

A. Eye Irritation Test-Albino Rabbits

1. Procedure

a). Two groups of 6 albino rabbits (New Zealand) each were used. Into each right eye was instilled 0.1 ml of undiluted test material. Untreated left eyes were controls. Exposure to test substance was 4 second followed by washing with water for 1 group and an unlimited period for the other group. Injuries were scored according to Draize et al. (1944) 1,24, and 72 and 7 and 14 days post-treatment.

2. Results

a). Group	1 hour	24 hours	72 hours	7 days	14 days

Unlimited	39/110	39/110	62.5/110	56.5/110	56.8/110	54.5/1
4 second	19/110	19.4/110	19.4/110	20.4/110	8.5/11-	2.7/11

Unlimited contact yielded corneal opacities, iritis, and conjunctivitis throughout 14 days post-treatment. Corneal injury and conjunctivitis were evident at 14 days after application in 1 rabbit exposed 4 seconds to test material.

3. Conclusions

a). Classification: Core Minimum Guidelines. Washed eyes were exposed to test substance less than 20 seconds.

b). Tox. Category: I

XII. Rabbit Eye Irritation Study on GA-2-525 Pramitol 25E (Food and Drug Research Laboratories, Inc., FDRL, CE No. 2772-530, 10/15/73, submitted by Ciba-Geigy Corp., 9/7/77, Acc. #231816).

A. Rabbit Eye Irritation

1. Procedure

a). Nine albino rabbits of unmentioned weight and strain were used. Into each right eye was instilled 0.1 ml of undiluted test material. Untreated left eyes were controls. Eyes of 6 animals remained unwashed, but eyes of 3 animals were washed after a 30 second exposure to test material. Cornea, iris, and conjunctiva were examined 1 hour and each day for 7 days post-application. Injuries were scored according to Draize et al. (1944).

2. Results

	Time					
a). Group	1 hr	1 day	2 days	3 days	4 days	7 days
Unwashed		33-57	33-53	31-53	49-53	20,45,71-
Washed	18-25	37	57	57-77		71-73

Corneal damage, iritis, and conjunctivitis were evident in both treatment groups throughout 7 days post-application. Washing was not beneficial.

3. Conclusions

a). Classification: Core-Guidelines
b). Tox. Category: I

XIII. Acute Toxicity Studies on Prometone 25E (Industrial Bio-Test Laboratories, Inc., IBT, 6/21/65, submitted by Ciba-Geigy Corp., 9/7/77, Acc.#231816).

A. Primary Skin Irritation Tests-Albino Rabbits

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1. Procedure

a). Four albino rabbits of unmentioned weight and strain were used. To both

intact and abraded sites on the clipped back of each rabbit was applied 0.5 ml of undiluted test material under occlusive dressing. Plastic wrappings and patches were removed 24 hours post-treatment. Injuries were scored according to Draize et al. (1944) 24 and 72 hours post-treatment.

2. Results

a). P. I. Index = 5.2/8.0

3. Conclusions

a). Classification: Supplementary. Only 4 animals were used.
b). Tox. Category: II

XIV. Acute Toxicity Studies on Pramitol 25E (Industrial Bio-Test Laboratories, Inc., IBT#A1228, 3/29/72, submitted by Ciba-Geigy Corp., 9/7/77, Acc.#231816).

A. Primary Skin Irritation Test-Albino Rabbits

1. Procedure

a). Six young rabbits (New Zealand) were used. To both intact and abraded sites of the clipped back of each rabbit was applied 0.5 ml or 0.5g (moistened with water) of undiluted test material under occlusive dressing. Plastic wrappings and patches were removed 24 hours post-treatment. Injuries were scored according to Draize et al. (1944) 24 and 72 hours post-treatment.

2. Results

a). P. I. Index = 1.2/8.0. Erythema was evident on all test sites. Edema was apparent on both sites on 1 rabbit.

3. Conclusions

a). Classification: Core Guidelines
b). Tox. Category: III

XV. Primary Skin Irritation Study on GA2-525 Pramitol 25E (Food and Drug Research Laboratories, Inc., FDRL OE No. 3772-530, 10/15/73, submitted by by Ciba-Geigy Corp., 9/17/77, Acc. #231816).

A. Primary Irritation Study

1. Procedure

a). Six albino rabbits of unmentioned weight and strain were used. To both intact and abraded sites on the clipped back of each rabbit was applied 0.5 ml of test material inder occlusive dressing. Wrappings were removed 24 hours after application. Injuries were scored according to a scale of 0-4, 24 and 72 hours post-treatment.

2. Results

a). P. I. Index = 6.29/8.0. Severe erythema and moderate edema were evident at all test sites.

3. Conclusions

a). Classification: Core Guidelines
b). Tox. Category: II

XVII. 21-Day Subacute Dermal Toxicity Study on Prometone 25E (Industrial Bio-Test Laboratories, Inc., IBT, 10/5/65, submitted by Ciba-Geigy Corp., 9/17/77, Acc.#231816).

A. 21-Day Subacute Dermal Toxicity

1. Procedure

a). Methodology was based on that of J.S. Leary. Animals were housed individually and were permitted food and water ad libitum. Backs were shaved 24 hours prior to application of test material. Adult albino rabbits (New Zealand), 2-3 Kg, were divided into groups and treated as follows:

	Males	Female	Skin Condition	Dose g/kg/day	Applications
Control	5	5	Intact	Water	15
T-I	5	5	Intact	0.22	15
T-II	5	5	Abraded	0.22	15
T-III	5	5	Intact	0.45	15
T-IV	5	5	Abraded	0.45	15

Test material was in contact with skin 7 hours/day, 5 days/week, 3 weeks under occlusive dressing. At the end of each 7 hours contact period, coverings were removed, and test sites were cleansed with soap and water. Observations of body weight changes, mortalities, behavior, local reactions, hematology, blood chemistry, and urine analyses were recorded during 3 weeks post-treatment. Necropsies were done.

2. Results

a). Mortalities: None
b). Body Weight: Weight gain was reduced in a dose-realted manner as follows over 3 weeks post-treatment:

Group	Weight Gain (kg) Males	Females
Control	0.58	0.60
T-I	0.39	0.41
T-II	0.50	0.48
T-III	0.39	0.22
T-IV	0.35	0.09

c). Behavior: Unremarkable

d). Local skin reactions: Erythema and dryness was slight in T-I and T-II animals and moderate in T-III and T-IV animals after the second application. Desquamation was noted after the sixth application.

e). Hematology: Blood analyses were done at the beginning of the study and at 3 weeks post-treatment and included hemoglobin concentration, hematocrit value, erythrocyte count, and total and differential leukocyte counts. Percent hematocrits of T-IV males was slightly decreased below control values.

f). Blood chemistry: Analyses included determination of urea nitrogen concentration (BUN) and alkaline phosphatase activity (SAP) and were conducted at the beginning and the end of the 3 weeks test period. Results were unremarkable.

g). Urine analyses: Analyses including determinations of reducing substances albumin, macroscopic elements, and pH were conducted at the beginning and the end of the 3 week test period. Tests were done on pooled urine from 3 males and 3 females, separately, from each group. Results were stated to have been unremarkable, but no datea of analyses were submitted for review.

h). Necropsies: At the conclusion of the 3 weeks test period, all rabbits were sacrificed and were subjected to gross pathological examination. At the time of gross pathological examination, the following tissues and organs were fixed in formalin and examined:

Heart	Aorta
Trachea	Lungs
Liver	Gall bladder
Pancreas	Esophagus
Stomach	Small intestine
Colon	Spleen
Lymph nodes	Kidneys
Urinary bladder	Gonads
Prostate	Seminal vesicles
Uterus	Pituitary
Adernal glands	Salivary glands
Thyroid gland	Parathyroid glands
Skeletal muscle	Sternum
Perioheral nerves	Brain
Skin from application sites	

Additionally, weights of the following organs were taken:

Liver	Kidneys
Spleen	Heart
Brain	Gonads
Thyroid gland	Adrenal glands

With the exceptions of aforementioned local skin reactions, no significant gross pathological changes were stated to have been found. No statistically significant differences were found among organ weights, organ/body weight ratios, and organ/brain weight ratios. However, increases of gonad weight, gonad/body weight ratios and gonad/brain weight ratios in group IV females and of brain weights in group III females were evident but, since histopathological changes were not found, the significance of these findings is unclear.

Microscopic examinations were done on tissues and organs subjected to gross pathological study which were taken from all control, T-III and T-IV animals. Only skin was processed from T-I and T-II animals.

Skin of all animals was characterized by minimal chronic inflammatory infiltrate. Symptoms of lung pneumonitis, liver hepatitis, and hyperemia of lung, liver, spleen, kidney, and adrenal glands were rated slight or mild for all control, T-III and T-IV rabbits.

3. Conclusions

a). Classification: Core-Minimum Guidelines. Only 5 animals/sex/dose and only 2 dose levels were used. Food consumption was not recorded. Organ weights were not obtained for lungs. Eye, thymus, bone with marrow, and mammary glands were not histopathologically examined.

b). NEL: A NEL could not be determined based on the evidence showing dose-related body weight loss.

XVII. Conclusions

Results of reviewed studies indicate the following toxicity categories:

Hazard Indicator	Toxicity Category
Oral LD_{50}	III
Inhalation LC_{50}	III
Dermal LD_{50}	III
Eye	I
Skin	II

Although disparity exists among the 3 primary skin irritation studies, total evidence suggests the Tox. Category II rating on the side of safety.

Larry Anderson