UNITED STATES ENVIRONMENTAL PROTECTION AGENCY 000712

DATE: February 1, 1978

SUBJECT: Technical Prometon-Update Files.
Caswell #96

EPA Reg. No. 100-544
Shaughnessy # 080804

FROM: Toxicology Branch
Registration Division

TO: Robert Taylor
Product Manager #25

Thru: Acting Branch Chief 2/13/78

Recommendation: Acute oral LD_{50} dermal LD_{50}, inhalation LC_{50}, eye and skin irritation, teratologic, and skin sensitization studies are adequate. The test material is not a teratogen or skin sensitizer. The Tox. Cat. III label, proposed by the registrant, requires changes in the First Aid statement which should read:

First Aid

If swallowed, induce emesis, give saline laxative and supportive therapy. Do not induce emesis or given anything by mouth to an unconscious person. Barbiturates may be used to control convulsions. In case of contact; for skin, wash with soap and water; for eyes, flush with plenty of water for at least 15 minutes. Seek medical attention if irritation persists.

The rest of the label (attached) is adequate.

* No RPAR criteria have been exceeded.

** Results of studies done by Industrial Bio-Test Laboratories are included in the submission. Studies must be validated by registrant.

Review

A. A Four-Week Range-Finding Study with Technical Prometon in Rats (Bio/dynamics, Inc., Project No. 76-1445, December 9, 1976, submitted by Ciba-Geigy Corp., September 15, 1977, Acc # 231815.

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EPA FORM 1320-6 (REV. 3-76)

1. Procedure

a) Young albino rats (Long-Evans), 108-159g, were randomly divided into 10 groups of 10 animals each (5 males and 5 females) and were administered 1, 10, 30, 100, 300, 600, 1000, 3000, 6000, or 10000 ppm of solid test material in the diet. Test substance was mixed with fresh diet weekly. Administration of test compound occurred daily for 29 days. Observations of toxic symptoms, body weight changes, food consumption, and mortalities were recorded throughout the 29 day experimental period. Necropsies were done.

2. Results

a) Mortalities: One male in the 10000 ppm dosage broup died on day 13.

b) Toxic symptoms: Unremarkable except for body weight changes

c) Body weight changes: Significant ($p \leq 0.05$) dose-related reductions of weight gain occurred in females and males given 1000 ppm of test material. A slight reduction was indicated in females given 1000 ppm.

d) Food Consumption: Mean food consumption of males and females given 6000 or 10000 ppm of test material was significantly ($p \leq 0.01$) decreased below control levels at week 1. This decreased consumption was suggested to be due to an adverse flavor imparted by the test substance in the diet. Four scattered significant ($p \leq 0.05$) differences from control levels were evident but were not dose-related. Five food consumption levels for individual females were not recorded due to spillage.

e) Necropsy: Although isolated macroscopic pathologic abnormalities in survivors occurred, no dose-related effects were evident.

3) Conclusions:

a) Classification: Supplementary. Dose-related effects on body weight were evident.

B. A Four-Week Range-Finding Study with Technical Prometon in Beagle Dogs (Bio-dynamics, Inc., Project No. 76-1446, November 29, 1976, submitted by Ciba-Geigy Corp,. September 15, 1977, Acc. # 231815).

1. Procedure

a) Six mouth old beagles, o.9-8.7 kg. were divided into 4 groups of 2 dogs each (1 male and 1 female) and were administered 0, 100, 300, or 3000 ppm of solid test material in the diet. Test substance was mixed with fresh diet weekly. Administration of test compound occurred daily for 4 weeks, but during weeks 3and 4, 100 and 300 ppm doses were increased to 1000 and 2000 ppm, respectively. Observations of toxic symptoms, body weight changes, food consumption and mortalities were recorded. Necropsies were done.

2. Results

a) Mortalities: None

b) Toxic Symptoms: Unremarkable. Loose stool was observed in the male receiving 100 ppm once during week 2 and 1000 ppm once during week 3 and in the male receiving 3000 ppm once during week 2 and once during week 3. Emesis was detected in the female given 2000 ppm once during week 3.

c) Body Weight Changes: Weight losses were observed in the male given 3000 ppm (0.9 kg., 4 weeks) and females given 1000 ppm (0.5 kg., 2 weeks), 2000 ppm (0.7 kg, 2 weeks) or 3000 ppm (0.8 g/kg/day, 4 weeks).

d) Food Consumption: Food consumption decreases were observed in the male given 3000 ppm (13.3 g/kg/day, 4 weeks) and in females given 2000 ppm (5.8 g/kg/day, 2 weeks) or 3000 ppm (12.2 g/kg/day, 4 weeks). Decreased food consumption was suggested to be due to adverse flavor imparted by the test material to the food.

e) Necropsies: Unremarkable.

3. Conclusions

a) Classification: Supplementary. An effect of the test material on body weight was evident. Particularly because of weight reductions recorded for females, a lowest effect level (LEL) of 1000 ppm is suggested.

C. Teratogenic Study with Prometon Technical in Albino Rats (Industrial Bio-Test Laboratories, Inc., IBT No. B904, March 28, 1972, submitted by Ciba-Geigy Corp., September 15, 1977, Acc. #231815).

1. Procedure

a) Femal : albino rats (Charles River) were bred at Charles River Breeding Laboratories, Inc., and were confirmed as pregnant by sperm-positive results of vaginal examinations. Day 0 was the time of insemination. Animals were shipped to the laboratory on day 1 of gestation.

b) Dosage groups of 0 (control), 25, and 50 mg/kg/day consisted of 17, 18, and 15 females/group , respectively. One percent Prometone Technical (W/V) in corn oil was administered by gavage inclusively from days 6-15 of gestation. Controls received corn oil. Mortalities, reactions, and body weights, at days 6, 9, 12, 15 and 20 (sacrifice) of gestation, were recorded.

c) Animals were sacrificed on day 20 of gestation, uterine horns were fully exposed. Fetal sites, implantation sites, uterine abnormalities, and number of corpora lutea were reported. The number of viable fetuses was determined by spontaneous movement and enhanced ruddy color. Fetuses were examined for external abnormalities. Skeletal and internal developments of fetuses were evaluated according to Hurley (1965) and Wilson and Warkany (1965), respectively, and, when possible, equal numbers of each sex from each litter were evaluated.

2. Results

a) Body Weight Changes (Maternal): Slight dose-related weight gain reductions were evident. Gains were control, 133g; 25 mg/kg/day, 126g; 50 mg/kg/day, 106g.

b) Mortalities (Maternal): None.

c) Toxic Symptoms (Maternal): Unremarkable other than body weight changes.

d) Reproductive Effects (Material)

e) Body Weight Changes (Fetal): Unremarkable.

f) External Development. (Fetal): In the 25 mg/kg/day groups were 1 runt fetus and 1 fetus with a hematoma.

g) Skeletal Development (Fetal): No remarkable differences of incidences of incomplete sternum ossification, non-ossified sternum, and abnormal and normal fetuses between groups were found, but the percent of fetuses exhibiting non-ossified sternum decreased in dose-related manner.

h) Internal Development (Fetal): No remarkable differences of incidences of small and large atria and abnormal and normal fetuses between groups were observed, but the percent of fetuses with small atria or which were abnormal decreased a dose-related manner. One of 68 fetuses in the 50 mg/day group had an enlarged bladder.

3. Conclusions

a) Classification: Core Minimum Data. Although food consumption data were not reported, the study shows that the test compound is not a teratogen.

b) Teratogenic NEL is greater than or equal to 50 mg/kg/day (highest level tested).

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Part II

I. Acute Toxicity Studies with Prometon Technical (97%) (Industrial Bio-Test Laboratories, Inc., IBT No. 8530-09308, September 27, 1976, submitted by Ciba-Geigy Corp, September 15, 1977, Acc # 231815).

A. Acute Oral Toxicity Study Albano Rats

1. Procedure

a) Young albino rats (Sprague-Dawley), 154-268g, were divided into 8 groups of 4 animals each (2 males and 2 females) and were administered 177.8, 600, 1350, 2025, 3038, 4556, 6834, or 10250 mg/kg of test compound in corn oil by gavage. Body weight changes, mortalities, and reactions were recorded during 14 days post-treatment. Necropsies were done.

2) Results

a) Mortalities: LD_{50} = 3000 (1973-4560) mg/kg.

b) Body Weight Changes: Unremarkable.

c) Toxic Symptoms: Hypoactivity, salivation, muscular weakness, labored breathing, prostration, diarrhea.

d) Necropsy: Survivors - Unremarkable. Decendents - Red lungs, pale kidneys, distended stomach, pale livers, chemical burn on 1 liver. Autolysis of organs occurred in 5 rats.

3. Conclusions

a) Classification: Core Minimum Data. Although only 2 rats/sex/dose were used, the 9 dose levels employed allowed an acceptable study.

b) Tox. Cac.: III

B. Acute Dermal Toxicity Study - Albino Rabbits.

1. Procedure

a) Four (2 males and 2 females) young adult albino rabbits (New Zealand), 2.48-3.36 kg, were used. Backs were shaved 24 hours before treatment. Test sites of 1 male and 1 female were abraded. To test sites was dermally applied 2000 mg/kg of test material as aqueous slurry. Animals were collared, and test sites were occluded with impervious plastic sheeting. Sheeting and residual test material were removed 24 hours post-treatment. Observations for mortalities, local reactions, behaviour, and body weight changes were recorded during 14 post-treatment. Necropsies were done.

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2. Results

a) Mortalities: None. LD_{50} > 2000 mg/kg

b) Body Weight Changes:

	Male	Female
Intact	+ 0.24 kg	+ 0.32 kg
Abraded	+ 0.10 kg	- 0.12 kg

Body weight gain was lowered in rabbits with abraded test sites possibly due to greater absorption of test material.

c) Toxic Symptoms: Unremarkable except for weight changes. Local reactions included pale red erythema, mild edema, and slight desquamation.

d) Necrospy: Unremarkable.

3. Conclusions

a) Classification: Core Minimum Data. Only 2 animals/sex and 1 dose were used, but the classification was selected on the basis of no mortalities at 2000 mg/kg.

b) Tox. Cat.: III

C. Primary Skin Irritation Test Albino Rabbits

1. Procedure

a) Six albino rabbits, unspecified weight and strain, were used. Backs were shaved, and test sites were premoistened prior to application of test material. To 1 abraded and 1 intact test site on each animal was applied 500 mg of test material under occlusive dressing. Dressing and residual test material were removed 24 hours after application. Inquiries were scored according to Draize et al. (1944) 24 and 72 hours post-treatment.

2. Results

a) P. I. Index = 0.2/8.0. Barely perceptible erythema and no edema were recorded.

3. Conclusions

a) Classification: Core Guidelines.

b) Tox. Cat.: IV

D. Skin Sensitization Test-Albino Guinea Pigs

1. Procedure

a) The procedure was based on that of Buehler (1965). Albino guinea pigs of unspecified sex and weight were used. An irritation range-finding test was done in which 3 groups of 2 animals each were exposed for 5 hours to single closed patches containing 0.5 ml of 10%, 1.0% or 0.1% (W/V) test material in propylene glycol. Subsequently, 10 guinea pigs were insulted with single closed patches containing 0.5 ml of 10% (W/V) test material in propylene glycol 9 times, 5 hours. each time. Two weeks after the last exposure, test animals and 4 control animals from the same population were challenged with duplicate patches. Injuries were scored 24 and 48 hours after inital insult, 24 hours after each intermediate insult, and 24 and 48 hours after challenge.

2. Results

a) No injuried were observed in the range-finding and skin sensitization studies.

3. Conclusions

a) Classification: Core Guidelines.

b) Not a sensitizer.

II. Acute Dust Inhalation Study with Prometon Technical (FL-761144) in Albino Rats (Industrial Bio-Test Laboratories, Inc., IBT No. 8562-09297, August 13, 1976, submitted by Ciba-Geigy Corp., September 15, 1977, Acc. # 231815).

A. Acute Inhalation Toxicity Study in Rats.

1. Procedure

a) Ten (5 males and 5 females) young adult albino rats (Charles River), unspecified weight, were placed into an 30 l inhalation chamber, and test material, as dust, was introduced into the chamber as a suspension in clean, dry air (4.62 l/min=flow). Exposure lasted 4 hours. Atmospheric dust concentraion, 3260 mg/m^3 air, was estimated by dividing total dust weight on a glass filter by total volume of air drawn through the filter. Particle sizes were estimated to be 1-30 μ with 34.75% estimated to be less than or equal to 10 μ. Observations of mortalities, reactions, and body weight changes were recorded during 14 days post-exposure. Necrpsies were done.

2. Results

a) Mortalities: None. LC_{50} t = 4 is greater than 3.26 mg/1 air

b) Body Weight Gain: Males, 113g; females. 30g

c) Toxic Symptoms: Ptosis, salivation.

d) Necropsy: Unremarkable.

3. Conclusions

a) Classification: Core Minimum Data. Although only 1 dose was used, it was sufficiently high to yield results indicating low inhalation toxicity of the test material, particularly since exposure lasted 4 hours.

b) Tox. Cat.: III

III. Eye Irritation Test with Prometon Technical (99.5%) in Albino Rabbits.(Industrial Bio-Test Laboratories, Inc., IBT No. 601-04656; March 9, 1974, submitted by Ciba-Geigy, September 15, 1977, Acc. # 231815).

A. Eye Irritation Test

1. Procedure

a) Six young albino rabbits (New Zealand), unspecified weight, were used. Into each right eye was instilled 100 mg of undiluted test sample. Untreated left eyes were control. Eyes were unwashed after treatment. Injuries were scored according to Draize et al. (1944) 1, 24, 48, and 72 hours and 7 days post-treatment.

2. Results

a) Average scores post-instillation were 15/110 at 1 hour, 3.5/110 at 24 hours and 0.110 at 48 and 72 hours and 7 days. Corneal damage was not observed. Iritis and conjunctivitis were not observed beyond 24 hours post-treatment.

3. Conclusions

a) Classification: Core Minimum Data. The effect of washing eyes after treatment was not evaluated.

b) Tox. Cat.: III

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IV. Hazard indicators support the Tox. Cat. conclusions of the registrant to use the signal word Caution.

Hazard Indicator	Tox. Cat.
Oral LD_{50}	III
Inhalation LC_{50}	III
Dermal LD_{50}	III
Eye Effects	III
Skin Effects	IV

Larry Anderson

1/13/78

JM