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

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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

SUBJECT: Supplemental Acute Oral and Inhalation Information for Prometon
ID#: 80804-0001000
Submission: S434795
DP Barcode: D187728
Tox Chem: 096

FROM: Vivian A. Williams, M.S.
Toxicology Section II
Toxicology Branch I
Health Effects Division (H7509C)

TO: Thomas Luminello, PM Team #52
Special Review and Reregistration Division (H7508W)

THRU: Melba Morrow, D.V.M.
Acting Chief
Toxicology Section II
and
Karl Baetcke, Ph.D.
Chief
Toxicology Branch I
Health Effects Division (H7509C)

Registrant: Ciba-Geigy

Action Requested: Review the supplemental information on prometon in an effort to upgrade the acute oral and inhalation studies (MRID's 421321-03 & 04) which were classified as unacceptable. These studies lacked information on purity and composition and there was no justification for the administration of a 25% w/v concentration of prometon technical instead of a more highly concentrated dose in the acute oral study.

Conclusion: The acute oral and inhalation studies have been upgraded to **acceptable** based on the following rationales which were provided:

1) The purity of the prometon technical used in these studies is 98.5% a.i.; this information was "inadvertently not provided to the laboratory and therefore not included in the final reports".

2) Excessive thickening was observed in the suspensions initially prepared as 40 % w/v concentrations. The testing laboratory concluded that the suspensions were too thick to provide an accurate measurement of dose

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and they reduced the concentration accordingly.

The results of the acute oral LD50 study demonstrate that the 25% w/v concentration that was utilized was sufficient for evaluating the dose response relationship in this study.

Amended DER's are attached for your reference.

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Reviewed by: Vivian Williams, MS 3/2/93
Section II, Tox. Branch (H7509C)
Secondary Reviewer: Melba Morrow, D.V.M. 3/3/93
Toxicology Branch I

DATA EVALUATION REPORT

STUDY TYPE: Acute Inhalation Study in Rats TOX. CHEM NO: 096

MRID NO.: 421321-03

TEST MATERIAL: Prometon; 2,4-bis (isopropylamino)-6-methoxy-s-triazine

SYNONYMS: Pramital

STUDY NUMBER: 7306-90

SPONSOR: Ciba-Geigy Corp.

TESTING FACILITY: Stillmeadow, Inc.

TITLE OF REPORT: Acute Inhalation Study in Rats

AUTHOR(S): M.S. Holbert

REPORT ISSUED: September 11, 1990

CONCLUSION: Prometon, a fine powder, was tested in an acute inhalation rat study using only one level, 0.52 mg/l, the maximum attainable concentration. None of the male or female rats died during this study. Toxicologic signs noted during the study in both sexes were decreased activity, nasal discharge, piloerection, ptosis and salivation. Polyuria was seen only in the females. No observable abnormalities were seen in any animals at the gross necropsy examination. The acute LC50 for prometon technical (FL 892529) is greater than 0.52 mg/l when administered undiluted to albino rats.

Toxicity Category: III

Classification: Acceptable

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A. MATERIALS:

1. Test compound:

Chemical Name: Prometon Technical, FL 892529
Description - Fine Powder;
Batch # GP 012601
Purity and other composition: 98.5% a.i.

2. Test animals: Species: Rat (5/sex);
Strain: HSD:(SD);
Age: Young adult;
Weight: Males (210-252 g)
Females (202-221 g) when tested

Source: Harlan Sprague Dawley, Inc.; Houston, Texas

3. Procedure:

a. Atmosphere Generation: The report stated that the animals were exposed to aerosol generated from the undiluted test material (fine powder) for four hours. The aerosol was generated with a Gem T Trost Air Mill coupled with a motor driven revolving disc delivery system. The concentrated aerosol was then diluted with filtered air and drawn into the exposure chamber. Air flow into the chamber was then maintained through the use of a calibrated critical orifice. Air flow was recorded at 30 minute intervals during the exposure period, and was sufficient to ensure adequate oxygen content of the exposure atmosphere. Temperature and humidity were recorded at 30 minute intervals during the exposure period from a wet bulb/dry bulb hygrometer located in the exposure chamber. Also cited in the report was information on the concentration of the test material in the exposure atmosphere being determined gravimetrically twice/hour (taken from the breathing zone of the animals), and nominally at the end of the exposure. The gravimetric concentration was determined by passing a known volume of exposure air through a pre-weighed filter and dividing the amount of test material deposited on the filter by the volume of air which passed through the filter. The nominal concentration was determined by dividing the loss in weight of the test material after the exposure by the total volume of air which passed through the chamber. Particle size determinations were made using an Andersen cascade impactor.

As noted in the submission, 0.52 mg/L was the only level to which the animals were exposed and this level was cited as being the highest attainable test level. Several runs were conducted which did show that higher concentrations could be generated, but in doing so, the particle size would drop below the EPA recommendation for having 25% of particles less than 1.1 um. (EPA's recommendation at the time the study was conducted).

b. Exposure System: The animals were exposed to the aerosol while individually housed in stainless steel cages within a 500 L New York University design, stainless steel, dynamic flow inhalation chamber. Because of the chamber design, only 4 animals (2/sex) could be observed during the exposure period. The mean temperature during this exposure was 22.7°C. The mean relative humidity during exposure was 71%; this value is greater than the Agency's suggested range of 40-60% for acute inhalation tests. This deviation is not thought to have adversely affected the outcome of this study. As for the chamber air flow dynamic, the number of air changes was not cited in the data (the EPA acceptance criteria calls for at least 10 air changes/hour). However, utilizing the available information, there were approximately 16 air changes/hour in the exposure chamber based on the following calculation:

Chamber size (volume) = 500 liters
Total air flow thru chamber = 133.1 liter/minute (lpm)
133.1 lpm X 60 min = 7986 Liters
7986 L/500 L = 15.97 # of Air Changes

c. Animal assignment: The test group consisted of 5 male and 5 female rats exposed to one level of 0.52 mg/L. This amount was stated as being the highest attainable aerosol concentration for this test chemical. No control animals were utilized in this study.

d. Protocol: The animals were individually housed in stainless steel cages within the dynamic flow inhalation chamber during the exposure period. They were returned to their stock laboratory cages at termination of the exposure. Observations for mortality and pharmacologic and/or toxicologic signs were made on the day of exposure and at least once daily thereafter for 14 days. The day of exposure was considered as day 0. Due to chamber design, only 2 animals/sex could be observed during the exposure period. Individual body weights were recorded just prior to inhalation exposure and on days 7 and 14. A gross necropsy examination was conducted on each animal at termination of the study.

e. Clinical Examination and Mortality: Observations for mortality and pharmacologic and/or toxicologic signs were made frequently during the study.

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f. Body Weight Determinations:
Animals were weighed on day 0 (day of exposure), day 7 and day 14.

g. Terminal Procedure: No information was provided concerning the method of sacrifice and no details were provided concerning the necropsy procedure. Only the abbreviated statement of "no observable abnormalities" was provided.

B. Results:
The nominal chamber concentration of the test compound was calculated to be 0.72 mg/L. The actual chamber concentration over the exposure period was 0.5 mg/L. Particle size distribution is shown in the attached table, reproduced from the original report. The mass median aerodynamic diameter of the particles collected was 1.686 μm, with a geometric standard deviation of 3.209. Particles < 1.1 μm comprised 32% of the particles collected. The maximum attainable concentration of the test compound was 0.52 mg/L, based on the guideline requirement for at least 25% of the particle concentration used in these studies be in the submicron range for acute and repeat exposure studies.

All animals exposed for 4 hours to an aerosol of prometon at a level of 0.52 mg/L survived through the 14 day observation period. Observations noted during the study were decrease in activity, nasal discharge, piloerection, polyuria, ptosis and salivation. All animals gained weight in a normal manner. The gross necropsy examination conducted on each animal at termination of the study revealed no observable abnormalities.

C. Quality Assurance: A signed and dated statement of GLP compliance was provided.

D. Discussion: The study appears to have been well run.

It should be noted that contrary to the EPA recommendation that the dose levels which are tested be sufficient to determine a toxicity category or a limit dose (5 mg/L actual concentration of respirable substance), only one dose level was utilized in this study. Since 0.52 mg/L was the highest attainable concentration, it is acceptable that a range of dose levels not be incorporated into this study.

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Reviewed by: Vivian Williams, MS 3/2/93
Section II, Tox. Branch (H7509C)
Secondary Reviewer: Melba Morrow, D.V.M. 3/3/93
Toxicology Branch I

DATA EVALUATION REPORT

STUDY TYPE: Acute Oral Toxicity in Rats TOX. CHEM NO: 096

MRID NO.: 421321-03

TEST MATERIAL: Prometon technical FL 892529

SYNONYMS: Pramital

STUDY NUMBER: 7171-90

SPONSOR: Ciba-Geigy, Inc.

TESTING FACILITY: Stillmeadow, Inc.

TITLE OF REPORT: Acute Oral Toxicity Study in Rats

AUTHOR(S): J.O. Kuhn

REPORT ISSUED: August 21, 1990

CONCLUSION: Prometon technical was tested in an acute oral study in rats of both sexes at the following concentrations: 1000 mg/kg, 1400 mg/kg and 1800 mg/kg. An additional group of male rats only was tested at dose levels of 2500 mg/kg, 4000 mg/kg, 4200 mg/kg, 4500 mg/kg and 5050 mg/kg. Clinical signs of toxicity were decrease in activity, ataxia, chromodacryorrhea, diarrhea, lacrimation, piloerection and salivation. In the females, death occurred at each of the three dose levels. In males, death occurred in the 4200 mg/kg, 4500 mg/kg and the 5050 mg/kg dose levels. Unusual findings that were common to both sexes were found in the gastrointestinal tract (discolored contents) and liver (discoloration). In addition to those findings, the lungs of male rats were discolored and they had testes which were drawn into the abdominal cavity.

The male LD50 = 4345 mg/kg with 95% confidence limits of 4060 to 4650 mg/kg.

The female LD50 = 1518 mg/kg with 95% confidence limits of 1107 to 2080 mg/kg.

Toxicity Category: III

Classification: Acceptable

A. MATERIALS:

1. Test compound: Prometon Technical FL 892529
Description - Powder; Batch # - GP-012601;
Purity and composition: 98.5% a.i.

2. Test animals: Species: Rat;
Strain: HSD:(SD); Age:Young Adult;
Weight: Males (185-285 g) & Females(180-222 g) when tested
Source: Harlan Sprague Dawley, Inc.; Houston, Texas

B. STUDY DESIGN:

1. Animal assignment

Animals were assigned randomly to the following test groups:

Test Group	Dose in diet (mg/kg)	male	female
1	1000	5	5
2	1400	5	5
3	1800	5	5
4	2500	5	0
5	4000	5	0
6	4200	5	0
7	4500	5	0
8	5050	5	0

2. Experimental Design:

Sprague Dawley rats were divided by sex into groups of five animals for each of three dose levels. Five additional groups of males (5 animals each) were selected for testing at higher dose levels. All animals were fasted for at least 16 hours prior to dosing. All animals were treated with a 25% w/v concentration of prometon technical in deionized water. The selected dose was administered by oral intubation using an appropriately sized syringe and stainless steel ball tipped intubation needle. Following treatment, the animals were immediately returned to their cages; they were housed 2-3 per cage.
Food was made available for the duration of the study, post treatment. Observations for pharmacologic and /or toxicologic signs were made frequently throughout the study. A gross necropsy examination was conducted on each animal which died on test and each animal which survived through the terminal sacrifice.

3. Statistics - To determine the LD50 the following source was utilized: "A Simplified Method of Evaluating Dose effect Experiments" By Litchfield and Wilcoxon (J. Pharm. & Ther., 96, 99-115, 1949).

4. Results: Common signs which were seen in both sexes, at all dose levels were piloerection, increased activity, and salivation.

Of the five females administered the 1000 mg/kg dose, one died on day one. That animal displayed signs of salivation and had white slurry in the stomach and orange slurry in the small intestine. The other female animals at this 1000 mg/kg level survived until the terminal sacrifice and had no observable signs of abnormalities at necropsy.

Of the five females administered 1400 mg/kg, one died on day one. That animal displayed signs of salivation and chromodacryorrhea, had a black mottled liver, white slurry in the stomach and orange slurry in the gastrointestinal tract. The other females dosed at this level survived until terminal sacrifice and had no observable signs of abnormalities at necropsy.

Of the five females administered the 1800 mg/kg dose, 3/5 died on day 1, showing signs of salivation black mottled livers and orange slurry throughout the intestinal tract. One female died on day 3 and the same findings were observed. Only one female at this dose level survived until termination and it was the only female at this level which had no observable abnormalities.

None of the males treated at the 1000 mg/kg, 1400 mg/kg, 1800 mg/kg, 2500 mg/kg, or 4000 mg/kg dose levels died during the study or had abnormal findings at the terminal sacrifice. At the 4200 mg/kg dose, 2/5 males died on day one. Those animals showed signs of salivation, nasal discharge and diarrhea. The necropsy examination revealed discolored material in the stomachs and intestines and the testes were withdrawn into the abdominal cavity. The other three animals survived until the sacrifice; they had no observable abnormalities.

All males (5/5) administered the 4500 mg/kg dose died on day one. They showed signs of red nasal discharge, diarrhea, lacrimation and salivation. The necropsy examination revealed white spots on the liver, discolored material in the stomachs and intestines, black spots on the lungs and testes drawn into the abdominal cavity.

Four of the five males administered the 5050 mg/kg dose died on day one. These animals showed signs of salivation. The

necropsy examination revealed the same findings in the stomach, intestines, liver and lungs as previously cited. The fifth male in this group survived until the sacrifice on day 14; white spots on the liver were the only adverse effects noted in this animal.

5. A signed and dated statement of GLP compliance was submitted.

6. DISCUSSION: This acute oral study was adequately run. Sufficient justification was provided for administering the test substance as a 25% w/v concentration rather than a more highly concentrated dose. (When initially prepared as a 40% w/v concentration, the suspension was too thick to provide for accurate measurements; the concentration was reduced, accordingly)