UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

003531

DATE: January 3, 1978

SUBJECT: Pramitol 80 WP EPA Registration #100-536
Caswell#96

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TO: Robert J. Taylor, (25)

Action Type: Updating of files and approval of signal word and precautionary statements.

Ciba-Geigy Corporation submitted 5 acute toxicity studies in support of the safety of the herbicide Pramitol 80 WP, an 80% formulation of prometon. These studies and their toxicity classification form the basis for determining the appropriate signal word, warning and precautionary statements for the product label. The studies are summarized below.

Study	Animals	Dose Levels	Exposure Hrs.	Observation, Days	LD_{50}	Toxicity Category
Acute Oral	50 rats	500,1000, 2000, 3000 mg per kg	-	14	2100 M 930 F	III
Acute Dermal	32 rabbits	1000,2500, 5000, 10000 mg per kg	24	14	>10000 mg per Kg	III
Eye Irritation	3 rabbits 6 rabbits	100 mg 100 mg	30 sec. 24	7	-	II
Skin Irritation	6 rabbits	0.5 ml	24	3	-	III
Inhalation *	10 rats	3260 mg per m^3.	4	14	>3.26 mg per liter	III

*Conducted by the Industrial Bio-Test Laboratories, Incorporated.

All of these studies but one, the inhalation study, were initially submitted to the EPA on 12/18/73, in order to support the registration of Pramitol 80 W, another prometon formulation. A product identified as GA-2-522 Pramitol 80 W was the test compound in these studies. A product identified as Prometon Technical (FL-761144) 97% (ARS 1899/76) was the test compound in the currently-submitted inhalation study.

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

The inhalation study (report dated 8/13/76), conducted by the Industrial Bio-Test Laboratories, conforms to the core-minimum data requirements. Since prometon, 2,4-bis(isopropyl-amino)-6-methoxy-s-triazine, is an active ingredient and a major constituent of Pramitol 80 WP, this reviewer accepts the study with prometon for Pramitol 80 WP. The four remaining studies (report dated 10/15/73), conducted by the Food and Research Laboratories, meet the requirements of the core-guideline category. The RPAR criteria were not exceeded in any of these studies.

Pramitol 80 W formulation is an eye irritant (toxicity category II) and the label proposed by Ciba-Geigy for Pramitol 80 WP contains the appropriate word, WARNING. The formulation is moderately toxic (category III) when ingested, inhaled (Prometon Technical used) or when it comes in contact with skin, and this is reflected in the precautionary statements. These statements list numerous hazards to humans, domestic animals and environment. A first aid treatment is alo included.

Both the signal word and the precautionary statements are acceptable as proposed by Ciba-Geigy. In regard to the precautionary statements, the following additions are suggested:

A. Under Hazards to Humans and Domestic Animals.

Wash clothing before reuse.

Studies

1. Acute Oral Toxicity (50 rats). Procedure

Four groups of Sherman-Wistar rats (weighing 200-300 g), 5 males and 5 females per group, received single doses of Pramitol 80 W at the following dose levels (mg/kg of body weight): 500, 1000, 2000 and 3000. The formulation was given as a 10% (w/v) suspension in 1% aqueous carboxy-methylcellulose (CMC), in volumes ranging from 5 ml to 30 ml/kg of body weight. The controls (5 males and 5 females) received CMC, 30 ml/kg of body weight. The rats were observed continuously during the first 4 hours after dosing and once daily thereafter for a total of 14 days. All of the animals were necropsied shortly after death or at the end of the observation period. Mortality data were evaluated according to the method of Litchfield and Wilcoxon.

Results

None of the male rats died at the 1000 mg/kg dose level, whereas all of them died at the 3000 mg/kg level. The mortality in the female rats occurred at all levels of dosing, with all of the animals dying at the 2000 mg/kg level. All of the deaths occurred within 24 hours after dosing. The following toxic symptoms were noted:

a) Belly-drag, in both sexes.
b) Lethargy and pilo-erection, in females only.

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c) Prostration, salivation, writhing, tremors, muscular spasm and convulsions, in females only at the 3000 mg/kg dose level.

Necropsy on the non-surviving animals revealed a gastrointestinal inflammation, whereas no abnormalities were detected in the survivors of the Pramitol treatment. The LD_{50} values and the 95% confidence limits, both expressed as mg/kg of body weight, were as follows:

Rats	LD_{50}	Confidence Limits
Males	2100	1500-3000
Females	930	600-1450

Comment

Based on the LD_{50} values, Pramitol 80 W falls into the toxicity category III. This study meets the requirements of the core-guideline category.

2. Acute Dermal Toxicity (32 rabbits). Procedure

A 50% (w/w) suspension of Pramitol 80 W in 0.5% CMC was applied to the hairless backs of rabbits, using 4 males and 4 females per dose level. Four levels were used (mg/kg of body weight): 1000, 2500, 5000 and 10000. Each rabbit weighted about 2.5 Kg. The skin of 2 male and 2 female rabbits was abraded. After a 24-hour exposure, the skin was cleansed with water and the animals were observed for 14 days.

Results

None of the rabbit died and all of them gained weight. No abnormal behavior or toxic symptoms were noted during the exposure or after its termination. There was no edema and no abnormalities in the internal organs were detected at necropsy. A moderate genralized erythema, noted immediately after exposure, disappeared within 48 hours after discontinuing the exposure.

Comment

Since the rabbits survived the 10000 mg/kg dose level and the 14-day observation period, the acute dermal LD_{50} is, therefore, $>$10000 mg/kg of body weight. The compound falls into the toxicity category III. The study meets the requirements of the core-guideline category.

3. Eye Irritation Study (9 rabbits).

In this study Pramitol 80 W was tested as supplied, in the form of a gray powder. The formulation, 100 mg, was placed into the conjunctival sac of the right eye of 9 rabbits. The eyes of 6 rabbits were then left unwashed (Geoup I), whereas the eyes of 3 rabbits were washed with water after 30 seconds of exposure (Group II). The eyes of all animals were examined at 1, 23, 48 and 72 hours, and then daily, for 7 days after treatment. The appearance of eyes was evaluated by the Draize procedure.

Results

In the case of Group I (long exposure), the initial symptoms (corneal opacity, conjunctival redness, chemosis, discharge) disappeared within the 7-day observation period. In the case of Group II (short exposure), all of the symptoms disappeared with 24 hours of the termination of the exposure. It was concluded that Pramitol was an eye irritant and that flushing the eyes with water alleviated damage to ocular tissues.

Comment

Pramitol 80 W falls into the toxicity category II. This study conforms to the core-guideline data requirements.

4. Primary Skin Irritation (6 rabbits).

Procedure

Pramitol 80 W, 0.5 ml of a 50% (w/w) suspension in 1% CMC, was applied to the hairless backs of 6 rabbits for 24 hours. One of the test sites on each rabbit was abraded. The unwashed skin was then examined for both erythema and edema at 24 hours and 72 hours after exposure.

Results

At 72 hours, no irritation was found on the intact skin. At the abraded skin, pale-red erythema was noted in all of the animals and a slight edema was observed in 4 out of the 6 abraded sites. Based on an index of 2.16, obtained for both intact and abraded skin, Pramitol was considered a mild skin irritant. However, it was concluded that Pramitol was not a primary irritant of sufficient magnitude to require cautionary labeling.

Comment

Pramitol falls into the toxicity category III. This study can be accepted as the core-guideline data.

5. Acute Inhalation Study (10 rats).

This study was conducted by the Industrial Bio-Test Laboratories, Inc. (IBT No. 8562-09297; 8/13/76).

Procedure

Five male and 5 female young adult rats of the Charles River strain were continuously exposed to a dust aerosol of Technical Prometon*, in an 80-liter chamber. The determined concentration of Prometon in the vicinity of the animals was 3260 mg/m^3. The size of Prometon dust particle was 1-10 microns (34.75%) and 11-30 microns (65.25%). Following the 4-hours exposure, the animals were observed for 14 days and then they were necropsied.

*The compound used was identified as Prometon Technical (EL-761144) 97% (ARS 1899/76). Prometon (e) is another name for Pramitol (Ciba-Geigy trademark), according to Pesticide Index (1975).

Results

Salivation was noted in all of the animals, nut it disappeared within 18 hours after termination of the exposure. Ptosis, observed in 5 animals, subsided immediately after removal of the animals from the chamber. There were no deaths and no pathologic alterations were found at necropsy. The body weight gain was 113 f for male and 30 g for female rats, respectively. The LC_{50} value is 3.26 mg/liter, based on gravimetric determination of the aerosol sampled in the immediate vicinity of the animals and the fact that none of the animals died.

Comment

Prometon falls into the toxicity category III. This study meets the core-minimum data requirements.