UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

000716

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EPA Reg. No. 100 - 443 Pramitol 25E Herbicide Caswell #96

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Registrant: Ciba - Geigy Corp.
Greensboro, North Carolina 27409

Action Requested: An expeditious review to change the signal word from Danger to Warning and a change in precautionary statements.

Recommendation: Acute oral LD_{50}, acute dermal LD_{50}, acute inhalation LC_{50} and the skin irritation study support toxicity categroy III precautionary labeling. This formulation is moderately irritating to the rabbit eyes and permits a change in the signal word from Danger to Warning. The precautionary labeling proposed by the registrant appears adequate for protection of the public.

Active ingredient: 2,4 - bis (isopropylamimo)-6-methoxy-5-triazine 25%

Discussion: In an effort to register a product that is less irritating to the eyes and skin, a new formulation was developed through changes in the solvent system and emulsifers in this product. No changes are proposed in the concentration of active ingredient.

Review of Toxicity Data on the Formulated Product - Pramitol 25E

I. Acute Rat Oral Toxicity (Stillmeadow Inc., Biological Testing Lab. No. 1055-79 for Ciba - Geigy, March 27, 1979, Acc. No. 238509)

A. Procedures: Twenty-five male (200-270 grams) and 25 female (200-240 grams) Sprague - Dawley rats were divided into five groups of five males and 5 females each. Animals were fasted for approximately 16 hours prior to treatment with water available adlibitum. Dosages of 1983, 2498, 3147, 3967 and 5006 mg/kg were administered by gavage to the respective five groups. The animals were observed three times during the day of the treatment and at least twice daily for 14 days. Body weight was recorded prior to treatment and on days 7 and 14. Gross necropsy was conducted on each animal at the termination of the study or at the time of death.

B. Results:

	(1) LD_{50}	95% Confidence limits (mg/kg)	Slope function	95% Confidence limits
Male	3290	2762-3919	1.22	1.08-1.37
Female	2600	2078-3253	1.29	1.06-1577
Combined	2900	2441-3445	1.41	1.15-1.73

(2) Pharmacotoxic signs include: piloerection, salivation hypoactivity, lethargy, ptosis, polyuria, exophthalmia, lacrimation, epistaxis, difficult and labored breathing, chromodacryorrhea and constricted pupils.

(3) Necropsy: discoloration of gestrointestinal and urinary systems pronounced serosal blood vessels, and agonal changes.

C. Conclusion:

1-Classification of data - Guideline

2-Toxicity Category - III

I. Acute Rabbit Dermal Toxicity (Stillmeadow Inc., Biological Testing Lab. No. 1056-79 for Ciba - Geigy, March 22, 1979, Acc. No. 238509.)

A. Procedure: Five male and five female New Zealand white rabbits weighing betwen 2.2 and 2.6 kg were abraded and wrapped with polyethylene film. The undiluted test material was applied under the wrapped area at 2003 mg/kg and remained in contact for 24 hours. The animals were observed at least three times in the day of treatment and at least once daily for 14 days. Gross necropsy was conducted on each animal on day 14. Observations for skin irritation were made after the 24 hours exposure and daily for 14 days.

B. Results:

(1) No mortality observed at 2003 mg/kg (2.1 ml/kg) of undiluted material.

(2) Pharmacotoxic sign included: Rapid breathing, hypoactivity, diarrhea and reduced urinary and fecal output.

(3) Necropsy: Urine retention in one male and discoloration of the liver in one female.

(4) Irritation: Erythemia through day 12 with a score average of 0.89. Edema through day 13 with an average score of 0.99.

C. Conclusion:

1-Classification of data - Guideline
2-Toxicity category III

III Acute Rat Inhalation Toxicity (International Research and Development Corp. for Ciba - Geigy March 14, 1979, Acc. No. 238-509)

A. Procedure:

Six male and six female Charles River CD rats weighing from 242 to 266 grams were exposed to a nominal concentration of 21.78 mg/l for four hours. The animals were observed for pharmacotoxic signs and mortality during the four hours exposure and twice daily for 14 days. All animals dying during the study were necropsied as well as all survivors at the end of the 14 day observation period. Four aerosol samples of chamber atmosphere were taken at one hour intervals for concentration analyses. Particle size distribution of the aerosol was determined. The equivalent aerodynamic diameter and the percent of respirable particles were determined graphically by interpolation.

B. Results:

(1) One male rat found dead on day 1 postexposure and one female rat was found dead on day 2 postexposure. The LD_{50} was determined to be greater than 2.36 mg/l air (analytically).

(2) Observation: Slight body weight loss on day 1 post-exposure. During exposure preening, nasal discharge, salivation and dyspnea were observed in all animals, Dyspnea persisted in three male and three female rats from 1-4 days postexposure. All rats exhibited a urine stained abdomen, dried blood around eyes and nares for 1-4 days postexposure.

(3) Necropsy of the two rats that died revealed dark pink lungs and red or black pin points on the stomach mucosa. No gross pathological lesions in the surviving animals at the end of the observation period.

(4) Particle size distribution: 96% of the particles were seven micrometers and smaller. The calculated aerodynamic mean diameter was 2.25 micrometers with a geometric standard deviation of 1.88.

C. Conclusion:

(1) Classification of data - Guideline

(2) Toxicity category III

IV. Eye Irritation - rabbit (International Research and Developement Corp. for Ciba - Geigy, January 29, 1979, Acc. No. 238-509)

A. Procedure: The eyes of five male and four female New Zealand white rabbits were examined with ultraviolet light following instillation of one drop of 2% sodium flourescein solution prior to the study and at 3,7 and 14 days. The animals weighed between 2275 and 2950 grams. The undiluted test material (0.1 ml) was placed in the conjunctival sac of the right eye. The eyelids were gently held together for one second. The left eye served as the untreated control. The eyes of six rabbits were not washed. These rabbits received a one minute wash with distilled water commencing 30 seconds following instillation. The treated eyes were graded according to Draize at 24, 48, 72 hour at 4,7 and 14 days.

B. Results (1) Unwashed Eye – groups average

	24hr	48hr	72hr	4day	7day	14day
rnea	9.0	14.4	17.6	18.9	0	0
is	5.0	4.0	1.0	1.0	0	0
njunctivae	13.4	10.2	8.8	7.4	0.4	0
tal	27.4	28.6	27.4	27.3	0.4	0

servations: Purulent discharge lasting 72 hours with corneal ithelial damage, peeling lasting 4 days.

(2) Washed Eye – Group Average

	24hr	48hr	72hr	4day	7day
rnea	0	0	0	0	0
is	1.5	0	0	0	0
njunctivae	6.0	2.6	2.6	2.0	0
tal	7.5	2.6	2.6	2.0	0

servations: Purulent discharge at 24 hours for one animal.

C. Conclusion:

1-Classification of data – Guideline
2-Toxicity categroy II
Unwashed: Moderate irritation
Washed: Mild irritation

Skin Irritation - Rabbit (Stillmeadow Inc., Biological Testing Lab. No. 1057-79 for Ciba - Geigy March 22, 1979, Acc. No. 238-509)

A. Procedure: The undiluted test material (0.5 ml) was applied to an intact and an abraded sites on each of three male and three female New Zealand White rabbits. The test site was occluded for 24 hours. Animals were observed and graded according to Draize for irritation at 24 and 72 hours after treatment.

B. Results (1)

Exposure Area	Mean Irritation Score
Intact	3.0
Abraded	3.5

(2) Observations: No signs of ulceration, necrosis or other dermal defects.

C. Conclusion:
1-Classification of data - Guidelines
2-Toxicity category III Moderately irritating

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