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

MAR 30 1984

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Poast®, EPA Reg. No. 7969-58. Eye Irritation Study (Accession No. 250966) and Re-review of Dermal Irritation Study (Accession No. 243319)

Tox. Chem. 72A

TO: Robert Taylor, PM#25
Registration Division (TS-767)

FROM: Minnie Sochard, Ph.D.
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Hazard Evaluation Division (TS-769)

Minnie Sochard 3/23/84

THRU: Albin Kocialski, Acting Section Head
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Hazard Evaluation Division (TS-769)

ABK 3/23/84

3/30/84

Registrant: BASF Wyandotte Co.
Parsippany, N.J.

Action Requested:

The registrant proposes that the toxicity Category for Poast® herbicide be changed from Category I to Category II for eye and skin effects. In support of this proposal, BASF Wyandotte has submitted a third eye irritation study in rabbits with a more extended observation period than in previously submitted studies and has requested a re-evaluation of the previously submitted acute skin irritation study in rabbits. The submission includes a statement by the study director which points out that the persistent skin scaling in the rabbits does not indicate necrosis, and does not justify placement in Toxicity Category I.

Recommendations:

1. A review of the present study indicates that the Toxicity Category for the formulated product (Poast®, BAS 90520H, 20% a.i.) should be downgraded from Category I to Category II for eye effects (corneal involvement or ocular irritation clearing in 21 days or less). (Refer to Detailed Review of this study and copies of two previous studies, attached.)

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2. A re-review of a previous dermal irritation study (copy attached) and consultation with Toxicology Branch pathologist L. Kasza, D.V.M., has indicated to this reviewer the following conclusions: (1) since no necrosis was involved in the scaling that was observed, and (2) only one small spot of necrosis was seen in an abraded skin site, the Toxicity Category for Poast® (BAS 90520H) should be downgraded from Category I to Category II, (severe skin irritation).

3. A summary of toxicity data is attached, with revisions indicated.

Detailed Review of Study

Eye Irritation Study in White Rabbits, Using BAS 90520H. Aktiengesellschaft Department of Toxikologie. Dated February 1, 1983. No study number, 6 pp. report. Accession No. 250966.

Protocol: 0.1 ml of undiluted Poast® (BAS 90520H, 20% a.i., substance #82/377) was applied to the conjunctival sac of one eyelid of 3 male and 3 female White Vienna rabbits. The untreated eyes served as controls. Observations were carried out for 15 days. The Draize method was used to measure eye effects.

Results: A primary eye irritation index of 35 was determined. At the 15th day all animals showed small retractions of the treated eyelids but no ocular irritation. One animal showed loss of hair around the eyelid margin of the treated eye. Since all corneal involvement or irritation was absent by day 15, Toxicity Category II is considered appropriate for this chemical. (Observations and procedures were similar in the second eye study, but observations were not done beyond 7 days, leading to the conclusion that Toxicity Category I was appropriate at that time - refer to copies of 2 previous studies, attached).

PIS index = 35

Toxicity Category = II (corneal involvement or irritation clearing in 21 days or less).

Core Classification - Guidelines.

Attachments

Results - There were no mortalities. Symptoms among experimentals included discharge from eyes and nose; lid closure; dyspnea; staggering gait; crouching posture; apathy; ruffled and slightly sticky fur. No symptoms were seen after 6 days. Body weight gain of males was retarded in comparison with controls; this was not seen with females. No abnormalities were seen at necropsy. The LC50 (4 hours) was calculated to be greater than 7.64 mg/L at the 1% level of significance.

LC50 (4 hours), male and female rats = > 7.6 mg/L

Toxicity Category III, Core Study - Guidelines

10. Report on the Study of the Primary Irritation of "BAS 9052 OH" on the Eye of White Rabbits. Report C10, BASF Gewerbehygiene und Toxikologie; Tab. C10 ; pp. 1-3 (in German); August 15, 1980, Accession No. 099536; In English 6 pp. Accession No. 243319. (First Eye Study) (20% a.i.)

Protocol - 0.1 ml of undiluted "BAS 9052 OH" was applied to the conjunctival sac of the lower right eyelid of three male and three female (3.55 and 3.39 kg mean weights) White Vienna rabbits. Eyes of the animals were not washed after treatment. Animals were observed for eye irritation and scored according to the Draize method at 24, 48 and 72 hours and 8 days following treatment. Observation were not made beyond 8 days.

Results - The primary eye irritation average indexes were 32, 35 and 29 at 24, 48 and 72 hours respectively. At 8 days redness was observed in the conjunctivae of all animals, discharge in one animal and very slight corneal opacity in one animal. In addition, scarring was seen in 5 of 6 animals at 8 days.

P.I. Index = 32 (24 hours); 35 (48 hours) and 29 (72 hours).

Toxicity Category I (scarring in 5/6 animals at 8 days; persistence of very slight corneal opacity in one animal at 8 days), Core study - Minimum data.

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11. Report on the Study of the Primary Skin Irritation of "BAS 9052 OH" on the Dorsal Skin of White Rabbits, Report C11; BASF Gewerbehygiene und Toxikologie; Tab. C11; pp. 1-3 (in German) August 15, 1980, Accession No. 099536; In English, 5 pp. Accession No. 243319.

Protocol - 0.5 ml of BAS 9052 OH was placed on intact and abraded dorsal skin of 4 female and 2 male White Vienna rabbits (mean weight 3.53 and 3.58 kg, respectively). Application sites were 2.5 X 2.5 cm; exposure was for 24 hours. Observations for erythema and edema were made at 24 and 72 hours and at 8 days. Reactions were scored according to Draize. Necrotic changes were confirmed by gross pathology.

Results - Erythema and edema were observed in all abraded animals at 24 and 72 hours on all intact animals at 24 hours and on 5 of 6 intact animals at 72 hours. Severe scaling was observed at 8 days in 4 of 6 intact and 3 of 6 abraded animals. Confirmed necrosis (millet-seed size) was seen at 8 days in one animal. It was concluded however, that "...8 days after application... erythema and severe scaling indicated severe skin irritation". The primary irritation index was 4.0.

P.I. Index = 4.0 (moderately irritating. However, despite the numerical score which indicates "moderately irritating" the finding of one animal with necrosis and 5/6 with severe scaling at 8 days necessitates upgrading of the toxicity category to Toxicity Category I).

Toxicity Category I, Core Study - Minimum.

Subchronic and Chronic Studies, Technical NP-55 (BAS 9052 H)

12. Subacute Feeding Study of NP-55 in the Mouse, Report C12, Nisso Institute; Tab C12, pp. 1-140; December 18, 1978, Accession No. 099536.

Protocol - Five groups of six week old ICR mice, each group consisting of 20 males and 20 females were fed a diet containing technical NP-55 dissolved in acetone to make the following doses administered for 14 weeks: 2700 ppm, 900 ppm, 300 ppm, 100 ppm and 0 ppm. Mean NP-55 intakes over the study period in mg/kg/day were as follows for males and females, respectively: 373.6 and 486.3 (2700 ppm group), 137.1 and 164.4 (900 ppm group), 45.6 and 52.7 (300 ppm group), 15.4 and 17.2 (100 ppm group). The 0 ppm group was the vehicle control (acetone added to diet). Animals were observed daily for pharmacotoxic symptoms, mortalities, physiological changes, central nervous system effects. Body weights were measured weekly. Estimates of food consumption were made weekly for 4 weeks and biweekly thereafter. Estimation of water intake were made at the termination of feeding. At the termination of the experiment, hematology, urinanalysis, blood chemistry, gross necropsies, organ weight measurements and histopathology were performed on each animal.

Detailed Review of Studies

Acute Study Formulation

1. Primary Eye Irritation Study of NP-55, 20% EC in Rabbits. Report No. 0056, November 27, 1981. Nisso Institute for Life Science pp. 1-11. Accession No. 070820. (Second Eye Study).

Protocol:

0.1 ml of undiluted NP-55 (BAS 9052) formulated to contain 20% a.i. was placed on the everted right lids of 9 Japanese white male rabbits aged 3-4 months old (averaging 3-4 kg). Eyelids of treated eyes were held together for one second and released. Untreated eyes served as controls. Eyes of 3 treated animals were flushed with lukewarm water for one minute; the remaining 6 animals were not further treated. Observations and scoring according to the Draize method were done at 1, 2, 3, 4, and 7 days after treatment. Readings were discontinued after 7 days.

Results:

Mean Primary Irritation (PI) scores were 6.0, 6.0, 1.3, 0.7 and 0.0 at respectively, 1, 2, 3, 4 and 7 days for washed eyes. Values for unwashed eyes for the same reading days were 32, 31, 28, 17.6 and 7.7. These latter values were similar to those obtained in an earlier study with the same formulation, (memo of August 31, 1981 M. Sochard, Ph.D.) which were 32, 35 and 29 at respectively 24, 48 and 72 hours, with corneal and conjunctival damage persisting through day 8 (observations not made beyond 8 days). In that study, there was no group of "washed eyes" for comparison. In the present study washed eyes exhibited no eye injuries persisting beyond day 4. Unwashed eyes showed corneal and conjunctival injury through day 7.

PI Index: Washed eyes: 6.0 (24 hrs); 6.0 (48 hrs); 1.3 (72 hrs); 0.7 (4 days); 0 (7 days).

Toxicity Category = I (Corneal and conjunctival injury present in 3/6 unwashed eyes at 7 days.)

Core Category = Minimum data

Summary of Toxicity Data and Eight Point Free Standing Summary

1. Summary of selected toxicology data considered for these actions:

a) Data on Technical NP-55

STUDY	RESULTS	TOX CATEGORY	CORE CLASSIFICATION
Acute Oral LD50, Rat	3.125 gms/kg - males 2.676 gms/kg - females	III	Guidelines
Acute Dermal LD50, Rat	> 5.0 gms/kg, males & females	III	Guidelines
Acute Inhalation LC50, Rat (4 hours)	6.03 mg/L, males 6.28 mg/L, females	III	Guidelines
Primary Eye Irritation, Rabbit	No irritation	IV	Guidelines
Primary Dermal Irritation, Rabbit	No irritation	IV	Guidelines
Dermal Sensitization, Guinea Pig	Negative	-	Minimum
14-Week Mouse Feeding Study	NOEL = 300 ppm	-	Minimum
14-Week Rat Feeding Study	NOEL = 300 ppm	-	Guidelines
Six Month Dog Feeding Study	NOEL = 20 mg/kg/day (males and females) LEL = 177 mg/kg/day - males 223 mg/kg/day - females (values based on analysis of diet and food) Non-specific anemia, liver effects, possible kidney effects.	-	Guidelines

...Y	RESULTS	TOX CATEGORY	CORE CLASSIFICATION
2-Year Mouse Chronic Feeding/Oncogenicity Study	NOEL = 120 ppm (=18 mg/kg/day) LEL = 360 ppm (non-neoplastic liver lesions) Not oncogenic in BDF1 mice.	-	
	As a chronic feeding study	-	Guidelines
	As an oncogenic study	-	Guidelines
2-Year Rat Chronic Feeding/Oncogenicity Study	NOEL $\geq$ 360 ppm (highest dose tested, (= 18 mg/kg/day)	-	
	As a chronic feeding study	-	Guidelines
	As an oncogenic study	-	Guidelines
Teratology Study, Rats	Teratogenicity NOEL: 250 mg/kg/day (highest dose tested) (Maternal NOEL = 40 mg/kg/day Maternal LEL = 100 mg/kg/day, [significantly decreased adrenal weight]).	-	Guidelines
Teratology Study, Rabbits	No terata up to and including 160 mg/kg/day. Effects observed at 480 mg/kg/day (increased number of a variety of random effects including skeletal, visceral abnormalities, reduced fetal weight, changes in male/ female ratios) considered due to extreme toxicity in dams and not to test material. Maternal NOEL = 160 mg/kg/day. Maternal LEL = 480 mg/kg/day (severe weight loss, 5/16 deaths, 6/16 abortions, reduction in number of litters and viable fetuses).	-	Minimum

STUDY	RESULTS	TOX CATEGORY	CORE CLASSIFICATION
Two Generation Reproductive Study, Rats	No reproductive effects. NOEL = 360 ppm	-	Guidelines
Mutagenicity Studies:			
i. Rec-assays and forward mutations, B. subtilis, E. coli, S. typhimurium	Negative at concentrations of chemical to 100%	-	Minimum
ii. Mouse host-mediated assay - S. typhimurium	Negative at up to 2.5 gms/kg bw/day of chemical.	-	Minimum
Metabolism Study - Rats	Tissue accumulation of chemical negligible and excretion extremely rapid, assuming DMSO vehicle doesn't affect storage or excretion of the chemical.	-	Guidelines
b) Data on Formulated Product - BAS 9052 OH (EPA #7969 - LI)			
Acute Oral LD50, Rat	4918.7 mg/kg	III	Guidelines
Acute Dermal LD50, Rat	>4000 mg/kg	III	Guidelines
Acute Inhalation LC50, Rat	>7.6 mg/L	III	Guidelines
Primary Eye Irritation, Rabbit Study No. 1	P.I. = 32 (24-hrs.); 35 (48-hrs.); 29 (72 hrs.) (scarring in 5/6 animals at 8 days, corneal opacity, in one animal at 8 days).	I	Minimum
		TOX	CORE
Primary Eye Irritation, Rabbit Study No. 2 (~~present review~~)	P.I. indexes - Washed eyes = 6.0, 6.0, 1.3, 0.7 and 0.0 at respectively 24, 48, 72 hrs. and 4 and 7 days.	I	Minimum
Primary Eye Irritation.	P.I. = 35 (unwash_ 1 eyes)	II	Guidelines

STUDY	RESULTS	TOX CATEGORY	CORE CLASSIFICATION
	Unwashed eyes = 32.0, 31.0, 28, 17.6, 7.7 at respectively, 24, 48, 72 hrs and 4 and 7 days.		
Primary Dermal Irritation, Rabbit ~~Re-review 3/84~~	P.I. = 4.0 Tox. Category I (numerical score indicates moderately irritating but 1 animal with necrosis & 5/6 with severe scaling at 8 days upgrades category to I).	I	Minimum
Re-review 3/84	Severe skin Irritation	II	minimum

2. Summary of Data Considered Desirable But Lacking for This Action:

Additional toxicity studies using hydroxylated metabolite(s) as test material. See # 3 and 8 under recommendations.

3. Action being taken to obtain the lacking information or other additionally needed information.

See # 3 under recommendations.

STUDY	RESULTS	TOX CATEGORY	CORE CLASSIFICATION

4. A summary of other permanent tolerances granted for this herbicide.
None.

5. See attached computer printouts (an following pages) for:

   a. soybeans (oil) at 3.0 ppm (plus secondary residues in meat, milk, poultry and eggs), and

   b. soybeans (oil) at 10.0 ppm (plus secondary residues in meat, milk, poultry and eggs)

Note: - RCB has informed TB (on 3/2/83) that increasing the soybean tolerance from 3.0 to 10.0 ppm will not alter the secondary residue levels in meat, milk, poultry and eggs.

6. The 2-year rat chronic feeding/oncogenicity study with a NOEL of 360 ppm (or 18.0 mg/kg/day) was used to set the ADI. The safety factor employed was 100. The ADI is 0.18 mg/kg/day. The MPI is 10.8 mg/day (for a 60 kg person).

7. There are at this writing no pending regulatory actions against the registration of this pesticide.

8. Other relevant considerations in setting these tolerances.

See recommendations #1 through #8.