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

MEMORANDUM. JUL 13 1983

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

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

THRU: David Ritter, Acting Section Head
Review Section #1
Toxicology Branch/HED (TS-769) DR 7-7-83

SUBJECT: Oryzalin; Request for permanent tolerance at 0.05 ppm on wheat and barley grain
PP#3F2874; Acc. No. 071520; CASWELL#623A

Action Requested:

1. Review and evaluation of the new study on percutaneous absorption of ^{14}C-oryzalin (EL-119, Compound 67109) in monkeys.

2. Request for permanent tolerance at 0.05 ppm of the herbicide oryzalin (3,5-dinitro-N^4,N^4-dipropylsulfanilamide) in or on wheat and barley grain.

Conclusions and Recommendation:

1. Petitioner should be apprised of the deficiencies reported for the percutaneous absorption of ^{14}C-oryzalin in monkeys.

2. The resolution for the data gaps existed in the following toxicological studies must be submitted:

a) Excretion and metabolism of EL-119 by rats, rabbits and ducks (October, 1972).

Because the proper characterization and identification of the metabolites and associated metabolic pathway have not been adequately evaluated in naimals, a general metabolism study requested by TB (1/7/81 and 1/23/81 Quaife) and required to be submitted (letter to company from Mr. Taylor 4/16/81) should be subimitted. (See details also in TB memo - 1/7/83 Jaeger.)

b. Dominant lethal study in Wister rats (Eli Lilly Compound 67019)

The following supplemental information accompanying the report should be submitted:

i. The sufficient procedure details and treatment of results for this study were not given and must be clarified.

ii. The positive control and vehicle control were not included in this study.

iii. No statements justification were made to the selection of two dose levels and the mating ratio per female at weekly cycle.

iv. The interpretation of results was not clear and must be clarified.

(See details also in the previous TB review - 1/20/83 Chen.)

c. Bacterial mutagenic studies (Lilly Compound 67019, Lilly Res. Labs., December, 1979)

The overall results of this study for the test compound in accordance with the modification of the Ames test for detecting bacterial mutagens by R.E. McMahon, J.C. Cline and C.Z. Thompson (Cancer Research 39, 682-93, March, 1979) are acceptable. (Two submissions were evaluated by TB - 1/23/81 and 1/5/82). However, some reporting deficiencies related to performing this test must be clarified.

i. Raw data representing exact counts of revertant colonies, spontaneous mutation rates, and solvent control must be included in the report.

ii. Only a single data summary sheet was presented. One plate per treatment was employed.

iii. There are no cytotoxicity screen study to determine the proper range of concentration for the test.

(See details also in the previous TB review - 1/5/82 Mauer.)

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3. Residues of oryzalin have already established under 40 CFR 180.304 in Almond hulls, Avacodos, Citrus fruits, Cottonseed, Figs, Kiwifruits, Nuts, Olives, Pistachios, Pome fruits, Pomegrantes, Small fruits, Stone fruits at 0.05 ppm and Soybean at 0.1 ppm. Under the proposed tolerance, the TMRC (resulting 58.3% increase in TMRC) due to wheat and barley at 0.05 ppm will have no appreciable toxicological increment. Toxicology Branch has no objection to add the requested use to the use pattern contingent upon concurrance by RCB. The summary of available toxicological data considered in support this request is attached.

Percutaneous Absorption of ^{14}C-Oryzalin (EL-119, Compound 67019) in Monkeys. Toxicological Division, Lilly Res. Labs., Greenfield, Indiana 46140.

Procedures:

Both of the intravenous administration and the dermal application were used in this study. The study consisted of four Rhesus monkeys (2 male and 2 female young adults) from the Charles River Breeding Laboratories, Key Lois, FL. The mean body weight of the females 5.7 $\pm$ 0.4 kg to 5.8 $\pm$ 0.15 kg. The intravenous study and dermal study were conducted approximately six weeks apart.

1. Intravenous Study:

Each monkey was injected into the sephenous vein with a single intravenous dose of 2 mg/kg ^{14}C-oryzalin equivalent to approximatley 10 uci per animal. Immediately after dosing, the monkeys were placed in individual aluminum metabolism cages for collection of serum, urine and feces samples.

2. Dermal Study:

Approximately six weeks later, the right ventral forearm of each monkey was shaved. A volume of 0.05 ml of ^{14}C-oryzalin solution/kg of body weight (2 mg/kg and 10 uci/animal) was applied to a six cm^2 area on the forearm of each animal and the area was covered with a gauze dressing for 24 hours. Serum, urine, and feces samples were collected similarly to the intravenous study.

In each study, blood samples were collected at 0, 0.25, 0.5, 1, 2, 4, 6, 24, 48, 72, 96, 120, 144 and 168 hours after dosing. Total urine and feces samples were taken for 24 hours prior to dosing and at 24, 48, 72, 96, 120, 144 and 168 hours after dosing. All samples (radioactivity) were counted in a Packard Model 3330 liquid scientillation spectrometer. The behavior and physical appearance, and food consumption of each monkey were observed and recorded daily.

Results:

1. All monkeys survived the test period of both study. (Monkey, IV or Topical, Male & Female LD_{50} > 2 mg/kg)

2. Clinical Observations: No abnormal clinical signs were observed during the test period of both studies. There were also no treatment-related changes in food consumption.

3. Serum Levels of Radiocarbon: The highest serum level (An average value of 0.8 ug equivalent/ml) was obtained at 15 minutes after intravenous injection of ^{14}C-oryzalin. However, the peak serum levels of radiocarbon after topical application occurred from 2 hours to 3 days and values ranged from 2.4 to 7.3 ng equivalent/ml. Although some variability was observed between monkeys, these low levels are definitely indicative of poor absorption. (The numbers of ug or ng equivalent per ml for the intravenous and dermal studies were converted from the sample DPM's through Quench correction by the channels-ratio method.)

4. Excretion of Radiolabelled Oryzalin:

a) Intravenous Administration: Forty-three percent of radiolabelled oryzalin was collected in the urine with 36% present with the first 24 hours. Forty-one percent of ^{14}C-oryzalin was collected in the feces with 30% occurring with the first 24 hours.

b) Dermal Application: One percent of radiolabelled oryzalin was found in the urine and 0.6% of ^{14}C-oryzalin in the feces. Approximately 73% of the topically applied dose was recovered in the dressing, wash water, and acetone wipe obtained 24 hours after application.

5. Biochemical Toxicology:

a) Applied to a two-compartment open model, serum level data from the intravenous study indicated that oryzalin was rapidly distributed to a second compartment with a half-life of 2.5 hours. The half-life for the terminal phase of the serum disappearance was 92.8 hours.

b) Using a comparison of total excretion data (a ratio of the percent excreted after 7 days from topical versus intraveous administration - Felman and Maibach, 1969 and 1970), 1.9% of topically applied ^{14}C-oryzalin was absorbed systemically.

c) Comparison of area under the intravenous serum level-time curve (AUC) to that obtained from topical application (Wagner, 1975) indicated that 1.6% of topically applied ^{14}C-oryzalin was absorbed through the skin.

Conclusions:

1. The following deficiencies in reporting of this study are noted:

a) The raw data (radioactivity) from serum, urine, feces samples for both study were not presented with the report. The method described for converting sample DPM's to ug or ng equivalent per ml for the intravenous and dermal studies was not clear and must be clarified.

b) The details of serum level-time curve (AUC) determined by the trapezoidal method should be provided.

c) Age of Rhesus monkeys was not given. The body weight and signs of erythema and edema of individual monkeys were not recorded during the test period of these studies.

2. Classification of Data: Supplementary; may be upgraded with submission of requested additional information.

Toxicological data considered in support request:

90-day feeding - rat Lilly Res. Labs #R-1077	Oryzalin	NOEL = 750 ppm LEL = 2250 ppm (HDT) depressed Hct, Hb and RBC's
90-day feeding - dog Lilly Res. Lab #D-100-67	Oryzalin	NOEL = 750 ppm LEL = 2250 ppm reduced Hb, Hct and RBC's increased BUN, alkaline phosphatase and sedimentation rate increased blood sugar and SGPT hyperplastic bone marrow splenic hematopoiesis, anemia, hepatic changes
51-day - chicken Lilly Res. Labs #16-0-4-68; 6/17/68	Oryzalin	NOEL = 0.05% LEL = 0.2% decreased food consumption increased mortality
2-year feeding - rat Eli Lilly; 3/80 Acc.#099517 & 099518	Oryzalin	NOEL = 300 ppm (LDT) LEL = 900 ppm decreased RBC's Hct, Hb increased mean leukocyte counts increased BUN increased liver and kidney weights inhibition of growth decreased survival
2-year feeding/oncogenic - mouse Eli Lilly (replicat #'s M-9087 & M-9097 Acc.#244746, #244747, #244748)	Oryzalin Tech.	Negative for oncogenicity at 3650 ppm (HLF). Systemic NOEL = 500 ppm LEL = 1350 ppm decreased wt. of uterus plus ovary, which is dose-related, in female mice
Pilot reproduction - rabbit Lilly Res. Labs #B-7326; 8/11/76	Oryzalin	Maternal NOEL = 75 mg/kg Maternal LEL = 225 mg/kg reduced body weight gain fetotoxic NOEL = 225 mg/kg (HLT)

3-generaion reproduction - rat #R1226, R-327 and R-647 1/80 Acc. No. 241742	Oryzalin 99%	Reproduction NOEL = 2250 ppm (HLT) fetotoxic NOEL = 250 ppm (LDT) fetotoxic LEL = 750 ppm depressed growth
Teratology - rat Lilly Res. Labs #R-22, 8/72	Oryzalin EL-119	NOEL = 2250 ppm (HLT) not teratogenic
Teratology - rabbit Eli Lilly #B-7366 10/13/76	Oryzalin Compound 67019	NOEL = 125 mg/kg not teratogenic
Teratology - rat Elanco Prod. Co. #R-1186; 11/5/76 Acc.#241232	Oryzalin	Teratogenic/fetotoxic NOEL = 225 mg/kg Some conclusion reached by OSHA (2/1/80)
Teratology - rabbit Study#B-7526 Eli Lilly 12/16/76	Oryzalin Compound 30545	Teratogenic NOEL = 225 mg/kg/day Some conclusion reached by OSHA (2/1/80)
Teratology - rat Eli Lilly Study #R-1166 12/21/76	Oryzalin Compound 30545	Teratogenic NOEL = 225 mg/kg Some conclusion reached by OSHA (2/1/80)
A Replicated Teratology Study in Dutch Belted Rabbits Eli Lilly Study#B-7281 & B-7291; 12/16/81	Oryzalin 67019, EL-919	Teratogenic NOEL = 125 mg/kg/day
Mutagenicity - Unscheduled DNA Repair. Rat hepatocytes KS Lilly 810217-337-UDS 6/81	Oryzalin Tech.	Negative (at up to and including 100 nanomoles per ml)
Mutagenicity - Sister Chromatid Exchange in Bone Marrow of Chinese Hamster Lilly Res. Labs Study#810601SCE, 810707SCE, & 810720SCE; 12/14/81	Oryzalin 67019, EL-919	Negative (200 mg through 500 mg/kg)

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File last updated 5/23/83

ACCEPTABLE DAILY INTAKE DATA

DOG mg/kg	NOEL ppm	S.F.	PADI mg/kg/day	HPI mg/day(60kg)
18.750	750.00	2000	0.0094	0.5625

Published Tolerances

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Soybeans (oil)(146)	0.100	0.92	0.00138
Cottonseed (oil)(41)	0.050	0.15	0.00011
Avocados(6)	0.050	0.03	0.00002
Citrus Fruits(33)	0.050	3.81	0.00286
Figs(57)	0.050	0.03	0.00002
Kiwi Fruit(204)	0.050	0.03	0.00002
Nuts(101)	0.050	0.10	0.00008
Olives(104)	0.050	0.06	0.00005
Pistachio nuts(210)	0.050	0.03	0.00002
Pome Fruits(126)	0.050	2.79	0.00209
Pomegranates(186)	0.050	0.03	0.00002
Small Fruit,berries(146)	0.050	0.83	0.00062
Stone Fruits(151)	0.050	1.25	0.00094
Sweet Potatoes(157)	0.050	0.40	0.00030
Peas(117)	0.050	0.69	0.00052
Peppermint(119)	0.050	0.03	0.00002
Spearmint(149)	0.050	0.03	0.00002
Potatoes(127)	0.050	5.43	0.00407

HPI	THRC	% ADI
0.5625 mg/day(60kg)	0.0132 mg/day(1.5kg)	2.34

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Current Action 3F2674

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Barley(8)	0.050	0.03	0.00002
Wheat(170)	0.050	10.36	0.00777

HPI	THRC	% ADI
0.5625 mg/day(60kg)	0.0210 mg/day(1.5kg)	3.73

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