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

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Oryzalin Registration Standard: Need for Worker Safety Risk Assessment. CASWELL #623A

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

FROM: R. Bruce Jaeger, Section Head
Review Section #1
Toxicology Branch/HED (TS-769) 6/21/85

The following explanation is provided to address the concern of Ms. Susan Wells (OPPE) with regard to risk assessment for worker/applicator exposure.

The toxicology data base for oryzalin contains substantial information pertaining to the absence of toxicity associated with dermal contact to technical oryzalin and/or the various formulations of oryzalin. The acute dermal LD_{50} in rabbits is > 2 g/kg; it is not a dermal sensitizer; 2 separate subchronic dermal studies using Surflan 75W and Surflan 4AS demonstrated no adverse effects to rabbits when applied to intact or abraded skin at concentrations of 4.8% for 6 hrs. per day; a pecutaneous absorption study using monkeys demonstrated that dermal absorption is poor (@ 1.6% of applied dose) and that the rate of excretion is high compared to the rate of absorption. Furthermore, the basis of concern for oryzalin has been the oncogenic response which was observed in rats following oral exposure. There was no oncogenic potential in mice at dietary doses up to and including 3650 ppm for 2 years, and there was no mutagenic activity in a complete battery of mutagenicity tests.

Epidemiology data which have been provided on worker exposure have not identified compound related effects associated with such worker or applicator situations. All of these data, in addition to others summarized in the Reg. Standard, demonstrate the absence of any significant concern for dermal exposure. Toxicology Branch believes the present labeling for formulations of oryzalin is adequate and provides an added measure of safety to the users.

There are, in addition, a few factual errors in our TOX Chapter (dated 2/12/85) which need to be noted and corrected. The corrections are attached.

Attachment

TS-769:JAEGER:s11:X73710:6/21/85 Card 5

dose solution were injected into the saphenous vein (9 mg oryzalin/animal and 9 uCi/animal). The blood concentrations of ^{14}C decreased rapidly after intravenous administration of ^{14}C-labeled oryzalin. The initial half-life of disappearance was 1.6 hours. At 48 hours less than 10% of the ^{14}C was present. Within 24 hours after intravenous administration of ^{14}C-labeled oryzalin, nearly 60% of the dose was excreted in the urine and feces (23% in urine and 35% in feces). Approximatley 74% of the dose was excreted within 96 hours. In the dermal absorption study in monkeys, single 250 ul aliquots of the ethanol solution containing ^{14}C-labeled oryzalin (ca 8.6 uCi) was applied to each monkey. After the dermal application of ^{14}C-labeled oryzalin, the serum concentration of 14C was nearly constant from 4 to 96 hours. These data indicated that blood concentrations of ^{14}C obtained after dermal application were much lower than those obtained after intravenous administration although the doses were similar (8.6 uCi dermally and 9 uCi intravenously). The data also showed that the rate of excretion was high compared to the rate of absorption. Only 9.7% of the dermal dose was excreted into the urine and feces in 96 hours (5.1% in urine and 4.6% in feces). The amount of the dermally applied radioactivity absorbed was ~~10~~ 1.6 percent (24).

Domestic Animal Safety

In an acute oral toxicity study with oryzalin in female cats, vomiting was observed within a few hours after the compund was administered. Urine and feces also contained much of the administered oryzalin. The acute oral LD_{50} in cats for technical oryzalin is greater than 1 g/kg body weight. In chickens, the LD_{50} was greater than 1 g/kg. The birds lost weight during the first week of observation and death was recorded between days 2 and 9 post-treatment (25, 28, 69).

Human Exposure

Extensive field and occupational exposure investigations have not demonstrated any toxic response associated with the use of oryzalin (21, 63, 64, 65, 70).

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	Tox Category	Core Grade Doc. No.
3 Month feeding - rat; Lilly Research Labs; #R-1077; 1971	Oryzalin	MRID# 00038669 00106669 00026759 00106683 00106674	Levels tested: 250, 750, and 2250 ppm NOEL = 750 ppm LEL = 2250 ppm (HDT) (Depressed Hct, Hb and RBC's)		000958
3 Month feeding - dog; Lilly Research Labs; #D-100-67; 1968	Oryzalin	MRID# 00106670 00026760 00106666 00038668 00026757	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.) Levels tested: 250, 750, and 2250 ppm		000958
51 Day feeding - chicken; Lilly Research Labs; H-0-4-68; 06/17/68	Oryzalin	MRID# 00109908 00094415 00085530	NOEL = 0.05% LEL = 0.2% (Decreased food consumption. Increased mortality.)		000958
2 Year feeding/oncogenic - rat; Eli Lilly; #R167 & R177; 03/80	Oryzalin 96%	ACC# 099517 099518 MRID# 00044332 00070569 00026779	NOEL = 300 ppm (LDT) LEL = 900 ppm (Decreased RBC, Hct, Hb - increased mean leukocyte counts. increased BUN. Increased liver and kidney wts, inhibition of growth, decreased survival. Oncogenic potential still undetermined however, an increase in skin tumors is seen in both sexes. The increase in thyroid tumors was found not to be significant.) Levels tested: ~~500, 1350 and 3650~~ ppm 300, 900 And 2700		Minimum 000959 000961

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	Tox Category	Core Grade Doc. No.
Percutaneous absorption - monkey; Lilly Res. Labs; 2/16/84 AND 3/22/83 ; #P03382 and P04082	Oryzalin Compound 67019 (STET)	ACC# 252490 ~~MRID# 00098463~~ AND 071520	Results are indicative of poor absorption in monkeys under the test conditions. (0.8 ug equivalent/ml of serum level radiocarbon was obtained after intravenous injection of 14C-oryzalin (2 mg/kg). 43% and 41% of 14C-oryzalin were also collected in urine and feces respectively after intravenous administration). 1.6% of topically applied 14C-oryzalin was absorbed dermally.	NA	Acceptable 003915 003073
Dermal sensitization - guinea pig; Lilly Research Labs; #G-D7-72; 08/72	Oryzalin in alcohol	MRID# 00026762	Not a sensitizer		000957
Acute oral LD_{50} - dog; Elanco Prod. Co.	Oryzalin	MRID# 00026592 00106667	LD_{50}>1 g/kg - Vomiting	III	000958
Acute oral LD_{50} - chicken Elanco Prod. Co.	Oryzalin	MRID# 00026592 00106667 00106666 00038668	LD_{50}>1 g/kg - weight loss, anorexia	III	000958
Acute oral LD_{50} - rat; Eli Lilly Co; 12/12/79	Oryzalin in 5% acacia	MRID# 00026592 00026084 00106667 00106666 00038668 00026757	LD_{50} > 10 g/kg -ptosis	IV	000958
Acute oral LD_{50} - rat Eli Lilly Co.	Oryzalin in DMSO		LD_{50} > 5 g/kg - ptosis	IV	000958
Acute oral LD_{50} - gerbil Eli Lilly Co.	Oryzalin in 5% acacia	MRID# 00106667 00106666 00038668 00026757	LD_{50}> g/kg - ptosis	IV	000958

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	Tox Category	Core-Grade Doc. No.
Acute oral LD_{50} - rat; Lilly Research Labs; #R-O-457-78 and R-O-456-78	EL-5219 EC (trifluralin 17.2% and oryzalin 17.2%)	MRID# 00056713 00105788	$LD_{50} > 500$ mg/kg	III	Minimum 000953
Acute dermal LD_{50} - rabbit; Lilly Research Labs; #B-D-210-78	EL-5219 EC	MRID# 00056713 00105788	$LD_{50} > 2$ g/kg	III	Minimum 000953
Primary eye irritation - rabbit; Lilly Research Labs; #B-E-20678	EL-5219 EC	MRID# 00056713 00105788	Conjunctivitis in 1/6 for 7 days corneal opacity in 1/6, cleared by day 7	II	Minimum 000953
Primary dermal irritation - rabbit; Lilly Research Labs; #B-D-210-78	EL-5219 EC		Slight erythema and edema within 24 hr. At day 14, all normal except slight desquamation in 4/6	III	Minimum 000953
Acute inhalation LC_{50} - rat; Lilly Research Labs; #R-H-155-78	EL-5219 EC	MRID# 00056712 00105788	$LC_{50} > 38$ mg/L nominal concentration	IV	Minimum 000953
Dermal absorption - monkey; Lilly Research Labs; #M6231, and M6012 ; 3/82	EL-119 Compound 67019 (97% Pure)	ACC# 247229	Data inconclusive with respect to absorption and excretion of dermally applied concentrations of 14C-Oryzalin to the forearm of Rhesus monkeys		Supplementary 002143
Percutaneous absorption of 14C-oryzalin in monkeys; Lilly Research Labs; #P03382 &P04082; 3/22/83	Compound 67019 EL-119	ACC# 071520	Monkey, IV or Topical M/F $LD_{50} > 2$ mg/kg	N/A	Supplementary 003073
Acute oral LD_{50} - rat; Lilly Research Labs; #R-O-125-83; 9/83	Balan/Surflan 2G Formulation	ACC# 251712	$LD_{50} > 3750$ mg/kg	III	Minimum 003649
Acute dermal LD_{50} - rabbit; Lilly Research #R-D-122-83; 9/83	Belan/Surflan 2G Formulation	ACC# 251712	$LD_{50} > 2000$ mg/kg	III	Guideline 003649