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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

AUG 4 1982

MEMORANDUM AUG 4 1982

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

SUBJECT: Oryzalin; Replicated Rabbit Teratology Study;
Percutaneous Absorption of ^{14}C-Oryzalin in Monkeys;
EPA Reg. Nos. 1471-96 and 1471-112. CASWELL #623 A

Submitted studies are reviewed and commented on as follows:

1. Study:

A Replicated Teratology Study on Oryzalin (EL-119, Compound 67019) By the Oral Route in Dutch Belted Rabbits. [Acc. #247229] Studies: B7281 and B7291 (Replicates). Date: March 1982. Lab: Lilly Research Laboratories.

Conclusion:

Oryzalin was not teratogenic to Dutch Belted Rabbits when administered, via gavage, at doses up to and including 125 mg/kg; NOEL = 125 mg/kg.

Method:

Two replicate studies were performed; each containing 75 virgin female Dutch Belted Rabbits which were randomly distributed among 5 experimental groups per study (15 rabbits per group). Animals were acclimated for a 2 week period and given physical/eye examinations prior to group assignment. Each female was artificially inseminated followed by an injection of chorionic gonadotropin. Environmentally controlled room conditions were: temp - 21±3°C; rel. hum. - 45%; 12 hr. light cycle; 12 air changes/hr. Animals were housed individually and received rabbit chow/tap water ad libiturm.

Oryzalin, (97% pure) was administered orally via gavage in doses of 0, 10, 25, 55 and 125 mg/kg/day on gestation days 6-18. Doses were based on gestation day 6 and adjusted on day 13 body weights.

Observations:

Daily for overt toxic signs
Body wt. - days 0, 6, 13, 19, 24 and 28
Food Consump. - daily
Gross necropsy - on all animals at day 28 and all animals that died prior to terminus.

Parents:

Uterus and ovaries
° # and distribution of implantations
° live fetuses
° dead fetuses
° # resorptions

Fetuses:

external anatomical anomalies
body wt.
skeletal/visceral exam.
sex

Analsysis of Data:

Data pooled from both replicates.

Results:

Survival - No compound related effects
Body wt. - No compound related effects
Food Consumption - No compound related effects

Accumulated Data:
Replicate B7281/B7291

Dose (mg/kg)	0	10	25	55	125
#Animals	15/15	15/15	15/15	15/15	15/15
#Pregnant	10/4	8/11	11/9	9/10	7/7
#Aborted	0/0	0/0	1/0	0/0	1/0
%Fertility	66%/27%	53/73	73/60	60/66	46/46
(pooled)	(47)	(63)	(67)	(63)	(46)
Corpora Lutea	7.1/6.8	9.1/7.9	5.9/8.4	8.0/6.5	7.7/7.9
Implantations	5.9/5.3	6.3/7.5	4.8/6.1	5.2/5.6	3.7/5.3
Live Fetuses (%/Litter)	94/93.8	91.9/95.8	95.8/89.4	83.8/94	94.5/97.1
(#/Litter)	5.5/4.8	5.7/7.2	4.6/5.6	4.6/5.3	3.5/5.1
Resorptions (%/Litter)	6/6.3	8.1/4.2	4.2/10.6	16.2/6	5.6/2.9
%Males/Litter	56.5/64.6	49.6/50	63.1/43.4	55.9/51.5	46.7/58.7
Fetal Wt.	35/35	34.5/32.5	37.5/34	36.2/37.2	40.6/37.2
Fetuses Examined	55/19	45/79	46/50	41/53	21/36
# Fetuses w/ Anomalies	25/8	19/31	23/12	13/29	10/20
(%/Litter)	44/42	44/41	49/30	44/56	55/57
Exencephaly (# fetuses)	0/0	*1/0	0/0	0/0	0/0
Cleft Palate	0/0	*1/0	0/0	0/0	0/0
Hypoplastic kid.	0/0	*1/0	0/0	0/0	0/0
Displaced kid.	0/0	0/0	0/0	0/1	0/0
Malformed Sternebrae	1/0	*1/0	1/0	0/2	1/0
" Vertebrae	0/0	*1/0	1/0	0/1	0/0
Incompl. Closure of Vertebral centra	0/0	0/0	0/0	0/1	0/0

NOTE: *Same fetus (rabbit #6292, 1 of 4 fetuses)

Administration of oryzalin to rabbits during gestation days 6-18 did not adversely effect fetal viability, fertility rates, or prenatal mortality. Skeletal and visceral examinations did not reveal any treatment related effects. Oryzalin was not evidenced to be teratogenic to Dutch Belted Rabbits at doses up to and including 125 mg/kg.

It should be recognized that the fertility rates for both replicates were extremely low (e.g. 27 to 73%). However, there was no apparent dose-related trend in these fertility rates. Because of this, it was apparently necessary to combine the results from both studies in order to provide sufficient data on pups, and in fact may be the reason for a second or replicate study (B7291) started 2 weeks after the first study (B7281). In either event neither study provides adequate information when viewed as a separate study. However, when considered collectively, as submitted by the registrant, the replicate studies are considered CORE Minimum data and provide evidence that Oryzalin is not teratogenic or fetotoxic to Dutch Belted Rabbits under the conditions of the study.

2. Study:

Percutaneous Absorption of ^{14}C-Oryzalin in Monkeys. [Acc. #247229]. Studies: M-6231 and M-6012. Date: March 1982. Lab: Lilly Research Laboratories.

Conclusion:

Data presented are inconclusive with respect to absorption and excretion of dermally applied concentrations of ^{14}C-Oryzalin to the forearm of Rhesus Monkeys.

Method:

Two male and two female Rhesus Monkeys were given I.V. and percutaneous doses of ^{14}C-Oryzalin in ethanol and the rate of excretion via urine, blood and feces was measured for 96 hours after dosing. The same monkeys were used in both studies (M-6231 and M-6012). The studies were conducted 2 months apart.

Lab conditions temp = 22±1°c; Rel. humid = 45%; 12 hr. light/dark cycle.

Dose Administration:

a. Dermal - 250 ul of ^{14}C-oryzalin (ca 8.6 u Ci) were applied to 6 cm^2 area on the shaved ventral forearm (shaved 24 hrs. prior to administration). Solution applied slowly and evaporated with a hair dryer. After 24 hrs., application area was washed and the wash water saved and analyzed. During the test, monkeys were placed in metabolism chains for the first 24 hrs., arms restrained for the first 4 hrs. Afterwards they were placed in metabolism cages. Sampling: Blood- 0.5, 1, 2, 4, 6, 24, 48, 72 and 96 hrs. Urine/feces - 6, 24, 48, 72 and 96 hrs.

b. Intravenous - 1 ml (ca 9 mg oryzalin/animal or 9 u Ci/animal) injected into the saphenous vein. Animals placed in metabolism cages immediately after dosing. Sampling: Blood - 0.25, 0.5, 1, 2, 4, 6, 24 and 48 hrs. after dosing; urine/feces- 6, 24, 48, 72 and 96 hrs. [Bechman LS 9000 liquid scintillation spectrometer used for sample analysis].

Results:

After I.V. administration ^{14}C-oryzalin is apparently rapidly eliminated from the blood, with approx. 74% excreted in urine/feces within 96 hrs. The fate of oryzalin via dermal application is less accurately determined from the data presented. ^{14}C Oryzalin appears in the blood following application and attains a steady state for the duration of monitoring (96 hrs.), but shows no sign of decreasing (DPM/ML). The statement that "these data indicate that the rate of excretion was high compared to the rate of absorption", in my opinion, cannot be determined from the data (graphs) presented. The accum. % excretion (Figure 2) demonstrates an increase with time, as does the blood level DPM/ML (Figure 1). [Correction to report: Figure 3 does not contain excretion information for dermal dose, as stated on page 10, "RESULTS" of subject report.] Without actual data from which these figures were made it is difficult to determine how much of the dermal dose was absored. Furthermore, excretion via urine and feces may not be the only route of elimination, in which case the determination of % absorbed based upon such data may not be completely accurate.

It would appear that oryzalin is poorly absorbed via the forearm of Rhesus Monkeys, however, this can only be verified with submission of the data upon which these figures and general statements are based.

Robert B. Jaeger 7/30/82

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8/4/82

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