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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

DATE: November 2, 1981

SUBJECT: EPA Reg.#100-524, 100-565 and 100-577; Diazinon Rabbit
Teratology Study. CASWEL#342 Acc.#245728

FROM: William Dykstra, Toxicologist
Toxicology Branch/HED (TS-769) WAD JOC 11/2/81
df/ul/B

TO: George LaRocca (15)
Registration Division (TS-767)

Pat Critchlow (43)
Registration Division (TS-767)

Recommendations:

1. The pilot rabbit teratology study is acceptable as Supplementary Data.
2. The teratology study in rabbits with Diazinon is acceptable as Core-Minimum Data. Diazinon was not teratogenic or fetotoxic at dosages up to 100 mg/kg/day during days 6-18 of gestation.
3. The rabbit teratology study fulfills the data gap for PP#OE2388; Diazinon in/on Winter Wheat. This petition can now be toxicologically supported.
4. In reference to our previous request for raw data relative to the rat teratology study (No. 22741301), Ciba-Geigy supplied transcribed and tabulated data on July 2, 1980 and not raw data for the study. In their letter of September 23, 1980, Ciba-Geigy indicated that this was the "only available information." Since no individual raw data, i.e., skeletal, was made available to the Agency, the study is regarded as Supplementary Data and needs to be repeated.

Review:

1. A dose range-finding teratology study of Diazinon in New Zealand White Rabbits including a positive control group administered 6-aminonicotinamide (Science Applications, Inc. study No. 280007; July 28, 1981)

Groups of six pregnant rabbits were administered Diazinon to determine dose levels for the definitive teratology study. The compound was orally administered via gavage at 0 (control), 7, 25, 100, 200, 300, and 400 mg/kg/day from days 6-18 of gestation. All does were weighed on the day of insemination, daily throughout dosing, on day 25 of gestation, and prior to laparohysterectomy on day 30 of gestation. Fetuses were weighed and evaluated for external abnormalities only. A positive control agent, 6-aminonicotinamide, was given orally to 10 pregnant rabbits at 2.5 mg/kg on day 9 of gestation, to demonstrate the sensitivity of this species to a known teratogen.

Results:

Significant maternal mortality was observed at 100 (16.7 percent), 200 (83.3 percent), 300 (33.3 percent), and 400 (50.0 percent) mg/kg. Because the 200, 300, and 400 mg/kg dose levels produced substantial maternal toxicity, these treatment groups were discontinued. Neither embryotoxicity nor frank external malformations were seen as a result of Diazinon exposure. The positive control agent (6-aminonicotinamide) elicited a characteristic embryotoxic response, which included increases in embryoletality, malformations, and decreased fetal weights.

Conclusion:

In conclusion, these results indicate that the maximum tolerated dose that could be used in the definitive teratology study was 100 mg/kg.

Classification: Supplementary Data

2. A teratology study of Diazinon in New Zealand White Rabbits (Science Applications, Inc., Study No. 281005; 7/28/81)

The compound was orally administered by gavage at 0 (control), 7, 25, and 100 mg/kg from days 6-18 of gestation as shown below:

<u>Group No.</u>	<u>No. Bred</u>	<u>Dose (mg/kg)</u>	<u>Day of Compound Administration</u>
I	19	0.0 (0.2% CMC)	6-18
II	18	7.0	6-18
III	19	25.0	6-18
IV	22	100.0	6-18

All does were weighed on the day of insemination, daily throughout dosing, on day 25 of gestation, and prior to laparohysterectomy on day 30 of gestation. Fetuses were weighed, sexed, and evaluated for external, visceral, and skeletal abnormalities and variations.

Results:

At the dose of 100 mg/kg, Diazinon produced a biologically significant, but not statistically significant, increase in maternal deaths. Doe mortality was seen only at the 100 mg/kg dose which was lethal to 9 of 22 (40.9 percent) of the females exposed. This effect is statistically significant ($p < .005$) in conventional Chi-Square analysis and approached statistical significance ($p < .07$) when analysis is done by Fisher's Exact Test. Seven of the nine females that died exhibited lesions characteristic of gastrointestinal toxicity. No gross lesions were observed in the remaining two females that died on study. The remaining doses of 7 and 25 mg/kg caused no maternal deaths.

There were no statistically significant differences among the groups regarding the mean number of implantation sites, proportions of live, dead, or resorbed fetuses per litter. Similarly, fetal weights were not significantly different among groups. Furthermore, no alterations in fetal sex ratio were observed.

A small number of miscellaneous malformations were observed in this study that included: Control - one fetus was considered a runt by the definition of a runt being < 30 percent of its mean litter weight, one fetus with a common truncus arteriosus and ductus arteriosus arising from the left pulmonary artery, three fetuses with fused sternbrae, one fetus with small clavicles, and one fetus with scoliosis; 7 mg/kg - four fetuses were runts, one fetus had fused sternbrae, and one fetus had small clavicles; 25 mg/kg - one fetus was a runt, one fetus had a common truncus arteriosus with two lumens and an interventricular septal defect, five fetuses had fused sternbrae, and one fetus had fused ribs; 100 mg/kg - one fetus was a runt. There were no significant differences among control and treated groups and none of the observed malformations were determined to be related to treatment.

A variety of skeletal variations were observed among experimental and control litters but not at a statistically significantly greater incidence among groups. The most frequent skeletal variations were the number of fetuses with either 12 or 13 pairs of ribs and incomplete ossification of either the fifth or sixth sternbrae.

Conclusion:

Significant maternal toxicity was observed only in the highest dose group (100 mg/kg). There were no indications of prenatal toxicity/teratogenicity at any of the dose levels studied. Because 100 mg/kg Diazinon approached the maternal multiple-dose LD50 (40.9 percent mortalities) and produced no signs of fetotoxicity, it is inferred that maternal rabbits were more sensitive to the test article than rabbit embryos or fetuses. These findings demonstrated that Diazinon was not fetotoxicity or teratogenic in rabbits at dosages of 100 mg/kg or less.

Classification: Core-Minimum Data

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