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

003661

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Review of Rabon teratology study as an IBT replacement. CASWELL No. 217A. EPA Reg. No. 677-Q

TO: George LaRocca, PM #15
Insecticide Branch/RD (TS-767)

THRU: Robert B. Jaeger, Section Head
Review Section #1
Toxicology Branch/HED (TS-769)

FROM: Henry W. Spencer, Ph.D.
Review Section #1
Toxicology Branch/HED (TS-769)

Recommendations and Conclusions:

1. TOX Branch recommends the study, Rabbit Teratology with Rabon be added to the files in support of Rabon uses.

2. TOX Branch concludes that Rabon is not a teratogenic agent in the rabbit.

Study:

A Teratology study in Rabbits with DS-36779 (Rabon), by WIL Research Laboratories, Inc., for Diamond Shamrock Corp., dated Sept. 21, 1982.

Material Tested:

Rabon, technical (T-142-3) as a white powder, 98% purity as a suspension in 1% aqueous CMC.

Animals Studied:

New Zealand white rabbits from Langshaw Farms, Augusta, Michigan. Sexually mature.

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Methods:

After 64 days of acclimating, 72 of 90 rabbits were used in groups containing 18 per dosage. Feed in the form of Purina® Certified Rabbit Chow #5322 pellets and water was provided ad libitum. Temperature was maintained at 70 ± 3°F for the individually caged animals. Humidity ranged from 40%-60% and a 12 hr. diurnal cycle was maintained.

Individuals weighed from 3.2 to 4.8 kg after artificial insemination, followed by an iv injection of HCG (100 USP Units).

Dosages of 0, 150, 375 or 750 mg/kg were given by gavage as 5 ml/kg in 1% CMC suspension on days 6 through 19 of gestation. Controls received only the CMC.

Observations:

Twice daily general clinical evaluation for behavior, toxicity signs, appearance, and for mortality and morbundity were made. Body wts. were determined on 0, 6, 9, 12, 15, 19, 24 and 29 days of gestation. Number of total implantations, viable and dead/fetuses, and early and late resorptions were recorded. Each fetus was visually examined. Internal and skeletal findings were also recorded after sacrifice of the dam on day 29 of gestation. Several protocol amendments were made, none of which altered the validity of the study. Statistical evaluation methods were listed by the registrant in the following format:

"1. The fetal sex ratios were compared by Chi-square test (6) with Yeates' correction factor.

2. The number of litters with malformations and genetic and developmental variations were compared by Fisher's Exact Test (6).

3. The number of early and late resorptions, dead fetuses and post-implantation losses were compared by the Mann-Whitney U-Test (6).

4. Mean number of corpora lutea, total implantations, viable fetuses, mean fetal and maternal body weight at each interval and maternal body weight gain data was analyzed by a one-way analysis of variance, and Dunnett's test (7)."

Results: Clinical Observations

Several treated dams died prior to the end of study (one each of the low and middle dosage and 2 at the highest dosage) None of the controls died.

Three aborted at the highest dosage and 1 aborted at the lowest treatment level. Red vaginal fluid was passed by 8 of 11, at the high dose, and 1 each in the middle and low dose groups. Nasal discharges and lacrimation and decreased defecation were noted but not dose related.

Body wts.	Wt. Changes in grams w/o + S.D. of Gravid Does.			
Day	Controls	150 mg/kg	375 mg/kg	750 mg/kg
0	30	47	76	27
6	-20	-15	-36	-148
9	18	-3	4	-89
12	63	22	-30	-11
15	16	34	60	-34
19	17	23	50	3
24	-4	33	48	88
29	120	212	164	90

Pup wts. were not markedly reduced from control at any treatment level. No increase in numbers of pups with markedly lower body wts. (runts) was noted. Mean numbers of viable fetuses per litter were reduced at 375 and 750 mg/kg to 6.9 ± 2.7 and 5.8 ± 3.0 SD respectively compared to 7.7 ± 1.5 SD for controls and 7.8 ± 2.3 SD for Group I (150 mg/kg) dams. The SD for dose related trend of reduced litter sizes was increasing only slightly and fetotoxic effects are obvious at 750 mg/kg coinciding with maternal toxicity. Early resorptions were increased only at the highest dosage while late resorptions were not effected by treatment. No increase in dead fetuses was noted, while implantations were slightly reduced in both group 3 (375 mg/kg) and group 4 (750 mg/kg) compared to controls and the 150 mg/kg treatment group.

Soft tissue and skeletal variations and malformations seen in the study with the exception of a single case of fused ribs and missing gall bladders do not significantly excede the rates reported by the laboratory for historical controls. Only single cases of absence of kidneys are noted at the top two treatment levels.

No consistent dose related increases in any-anomalies or malformations were noted. The top dose level is a maternally toxic dose LEL = 750 mg/kg
NOEL = 350 mg/kg

The material is not considered to be teratogenic at 750 mg/kg, (NOEL). A fetotoxic LEL is 350 mg/kg based on the number of viable fetuses per litter. A NOEL is 150 mg/kg.

Core Evaluation:

Minimum.

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