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DATA EVALUATION REPORT

STUDY TYPE: Teratology Dose Range Finding Study (Rabbits) TOX. CHEM. NO.: 320

MRID NO.: 139985 REPORT NO.: 682R-277/4

TEST MATERIAL: 2,4-DP ("pinkish feathery powder"); purity unspecified.

SPONSOR: Boots Company Ltd.

TESTING FACILITY: Hazleton Laboratories Europe Ltd., England

CITATION: Tucker, M. (1978) 2,4-DP Oral Teratogenicity Dose Range Finding Study in Rabbits: Report No. 682R-277/4. (Unpublished study received Mar 28, 1979 under 264-222; prepared by Hazleton Laboratories Europe Ltd., Eng., submitted by Union Carbide Agricultural Products Co., Inc., Greensboro, NC; CDL:237981-A)

CONCLUSION: This study was previously evaluated by James Holder (Tox. Doc. No. 001995; attached). This reviewer, in general, agrees with the conclusions arrived at by the previous reviewer except the following points:

(1) The incidence of major defects (1 fetus with omphalocele & 1 fetus with displaced kidney) observed in the fetuses of 25 mg/kg females was within the range of the historical control data, and this observation would not be considered as compound related effect.

(2) In 25 mg/kg group, one female prematurally littered 4 dead fetuses. In addition 2 early intra-uterine deaths were observed in this rabbit. These results might be due to the maternal toxicity.

(3) There were decreases in the mean fetal weight and mean crown/rump length in fetuses of 25 mg/kg females relative to the controls. Although these decreases are not statistically significant, they provide additional evidence for the compound-related effects in 25 mg/kg rabbits. Thus, the NOEL could not be established.

(4) The death of two control females was due to mechanical errors because one was diagnosed as died of pneumonitis and other as lung dosing. These two animals and the dead fetuses from these two controls should be excluded from the calculation. In addition, the report should present the data of certain parameters on the basis of observations/ litter.

Classification: This study is a dose-range finding study, which provides useful information in selecting the dosages for the primary teratology study, and the study will not be classified.

ATTACHMENT

§5.0 Dutch Belted Rabbit Range-Finding Teratology Study

001995

5.1 Conclusions of the Rabbit Teratology Study

5.11 The control rabbits exhibited normal nest sizes with normal newborn weights and newborn sizes.

5.12 At 25 mg/kg, the NOEL is exceeded with two major birth defects - congenitally ruptured umbilical cord and 13 ribs on one side - and some fetuses born dead all to one doe (2 died early and 4 just before or during parturition). So, NOEL < 25 mg/kg, but the specific level is undetermined by this experiment.

5.13 At 100 mg/kg, one doe did not conceive, 3 died early bearing dead fetuses, and one bore 7 smaller (in size) newborn bunnies. Definite signs of maternal toxicity were observed at this higher dose.

§6.0 Methods of Rabbit Teratology Study

Rabbits were dosed at 0, 25, and 100 mg/kg just as in the previous rat study. The protocol was virtually the same between the two studies except: (1) rabbits were artificially inseminated and (2) dosing was done by gavage from one day after artificial insemination to day 27 of the 28 gestation period. Examinations followed the protocol (which was almost the same as the rat study) and the rabbit study was conducted using GLP.

§7.0 Results of the Rabbit Teratology

The high dose (100 mg/kg) group showed definite signs of maternal toxicity in the does. All high dose rabbits showed unsteadiness in gait, reduced food intake, and some loss in weight gains leading to weight loss. Two rabbits in the high dose group were sacrificied on day 22 because of poor health conditions. One more rabbit was sacrificed on day 23 for the same reason. All these animals that were sacrificed were gravid, but were bearing dead fetuses. Of the two remaining rabbits only one rabbit produced a litter of normal size (7 bunnies) but with 46% reduction in fetal weight and 18% reduction in crown-to-rump distance.

The mid-dose (25 mg/kg) group showed 4 of 5 pregnant does with one of the four prematurely delivering on day 25 with normal weight newborn, but all newborn were dead (2 early in pregnancy and 4 late or during pregnancy). Only the mid-dose group showed major birth defects (two). The first bunny with major birth defects had omphalocele (plus displaced kidney), and the second with omphalocele, displaced kidney, and 13 ribs on one side.

The study does not demonstrate a NOEL in so far as teratogenic effects were observed in the low dose group (25 mg/kg). At 100 mg/kg pronounced maternal toxicity was observed leading to moribundity. At the high dose group, the MTD is exceeded for 2,4 DP in rabbits.

§8.0 Classification of Study: Not Classified