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

MEMORANDUM JAN 18 1983

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

TO: Robert J. Taylor, Product Manager #25
Registration Division (TS-767)

SUBJECT: EPA Reg. No. 241-243. Review of Rabbit Teratology Study with AC 92,553 (Pendimethalin), the Active Ingredient of the Herbicide PROWL.

TOX Chem. No. 454BB

Background:

The American Cyanamid Company has submitted a rabbit teratology study with their herbicide AC 92,553, the active ingredient of their product PROWL®, to support registrations and tolerances for this chemical.

Recommendations and Comments:

The study was reviewed and it was concluded that AC 92,553 is not teratogenic at doses up to and including 60 mg/kg/day.

A preliminary range finding study indicated that dose levels of 125 mg/kg/day were toxic to the dams and resulted in deaths.

Review of Study

A. Pilot Teratology Study in Rabbits AC 92,553 Technical - Revised Final Report

Hazleton Labs, #362-163, May 6, 1982, EPA Acc. NO. 248659

1. The substance tested was AC 92,553 (Lot No. AC 3528-129-1, HM-Lot 1-096, Drum #3A-9). The purity was 92.2% and was adjusted to 100% for dosing purposes. The compound was dissolved in corn oil and administered by gavage on days 6 through 18 of gestation.

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2. New Zealand White rabbits were used. Six groups of 5 females were artificially inseminated and dosed with 0, 31.25, 62.5, 125, 250 or 500 mg/kg /day. They were sacrificed on day 29 of gestation by using T-61 Euthanasia solution and the fetuses were delivered by Cesarean section.

3. Maternal Effects - The treated groups were associated with deaths. For example, there were 0 for the control group and the group receiving 62.5 mg/kg. There were 1, 3, 5, and 4 deaths among the rabbits dosed with 31.25, 125, 250 or 500 mg/kg/day. Signs of reaction were most prevvalent in the higher dose groups and included depression, coldness, cyanosis, and paleness. Body weight gain was also adversely affected. Gross necropsy of the dams revealed the presence of a yellow tinge (test substance) in several organs. A higher incidence of thin/vascular stomach walls was evident in the two highest dosed groups.

4. Uterine Data - The high rate of deaths at dose levels of 125 mg/kg and above limited the usefulness of this study. There was a possible increased incidence of resorptions at 62.5 mg/kg but other signs of uterine effects at 32.25 or 62.5 mg/kg were not evident.

5. Fetal Data -

   a. Fetal viability, size and sex were not affected at 31.25 or 62.5 mg/kg/day.

   b. Visceral examination - several types of soft tissue abnormalities were reported but not in sufficient frequency to draw a conclusion that a teratogenic effect was induced by the test chemical.

   c. Skeletal abnormalities were not evaluated.

Conclusion:

Supplementary Data. Information important for the selection of doses for a definitive teratology study was generated.

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B. Teratology Study in Rabbits AC 92,553 Technical - Final Report

Hazleton Laboratories, Inc., Pro. No. 362-164, May 11, 1982. EPA Acc. No. 248659

1. Substance tested - The test material was AC 92,553 and was stated as being 92.2% pure. The dose was corrected to 100% purity. A data sheet accompanied the report which described the composition of the impurities.

2. Test animals - New Zealand White female rabbits were obtained from Dutchland Lab Animals, Inc., Denver, Pa. They were artificially inseminated with sperm from bucks of the same strain. Four groups of 20 inseminated females were selected and dosed with 0, 15, 30 or 60 mg/kg of AC 92,553 per day by gavage on days 6 through 18 of gestation. The rabbits were sacrificed on day 29 of gestation. The test material was disolved in corn oil and the control group received corn oil. No positive control group was included in this study.

3. Maternal effects - Deaths (a total of 5) were noted but no definite relationship to the presence of the test chemical was apparent. Higher incidences of anorexia and adipsia were reported for the high dose test groups. No treatment related effects on body weight gain were noted. Uterine weights were also reported as not being affected. Necropsy revealed the presence of "compound like" material in several organs. The animals which died in the mid and high dose test groups had some evidence of liver damage.

4. Fetal data: Visceral examination - There were 111, 106, 118, and 107 fetuses examined and 104, 94, 111, and 96 of these were normal for the control, low, mid and high dose test groups respectively. No single type of variant was predominatly found in the high dose test groups to indicate a teratogenic effect of AC 92,553.

Skeletal examination - There were 111, 106, 118 and 107 fetuses examined and 76, 78, 93 and 82 of these were normal for the control, low, mid and high dose test groups respectively. There were thus 35, 27, 23 and 22 fetuses with variants for the control, low, mid and high dose test groups respectively.

The high dose test group was clearly associated with signs of anomalies in the ribs. There were 0, 0, 2 and 11 incidences reported for the control, low, mid and high dose test groups. These included "ribs-less than 12 pairs" and "missing incomplete vertebrae -lumbar, sacral, or caudal". Less evident was an effect on the sternebrae - "small, incomplete non fused." In contrast, the control group had many more incidences of "thoracic centra - incomplete /nonfused.

Conclusion:

This study is Core Minimum. AC 92,553 was shown not to be teratogenic at doses up to and including-60 mg/kg/day. The slight effects noted on the rib and skeletal system are considered to be only possibly a fetotoxic response. No positive control was run concurrently.

John D. Doherty, Ph.D. Jan 14, 1983
Toxicology Branch
Hazard Evaluation Division (TS-769)

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