UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: MAY 02 1980

SUBJECT: EPA Reg.#1016-EUP-LE; Larvin; PP#9G2152; CASWELL#900AA; Acc.#099378, 099377

FROM: William Dykstra
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WRD 4/29/80

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Recommendations:

1) The submitted rat teratology study is acceptable as Core-Minimum Data. The results show UC51762 is not teratogenic at dosages up to 100 mg/kg/day. The NOEL for fetotoxicity is 3 mg/kg/day.

2) The signed report of the mouse teratology study is acceptable. This study was reviewed in memo of 2/21/80 from William Dykstra to Charles Mitchell (12).

3) The EUP and temporary tolerances are not toxicologically supported. A repeat of the acute delayed neurotoxicity study is required. The exposure data provided to EFB by Union Carbide was considered inadequate by EFB (Memo of 4/28/80 from Abe Mittleman to William Dykstra attached).

Review:

1) Rat Teratology Studies with UC51762 (Carnegie-Mellon Institute for Research, Project Report 42-48, June 1, 1979).

Test Material: UC51762, 99+% A.I.

One hundred-sixty Fisher 344 rats of each sex, 43 days of age, were used in the stduy. The rats were mated 1 male to 1 female in sufficient numbers to acheive a goal of at least 10 pregnant females per treatment. Vaginal plugs were used as evidence that mating had occurred.

UC51762 was administered to each group of female rats at each of two dosage regimens at each of 4 dosage levels.

The two dosage regimens were as follows: (1) UC51762 was fed from day of vaginal plug (day 0) to day 20; (2) UC51762 was fed from days 6 to 15 after appearance of a vaginal plug.

UC51762 was added to the chow at dosage rates of 100.0, 3.0, 1.0 and 0.5 mg/kg/day.

A positive control group received 625 mg/kg of Aspirin on gestation day 10. The aspirin was suspended in 0.2% carboxymethyl cellulose and administered by gavage.

The females were assigned randomly to treatment groups after observation of vaginal plugs. All females were weighed on the day of mating and on gestation day 12. The male rats were not dosed at any time during the study nor were they randomized. The rats were approximately 100 days of age when first mated on November 7, 1977.

Treatment effects were evaluated by statistical comparisons of the following: fetal weights, fetal crown-rump lengths, maternal weight gain (day 0 to day 12 of gestation, number of corpora lutea, live fetuses and metrial glands per pregnant rat, pre-implantation loss, per percentage of resorptions (early, late and total) per litter, percentage of litters with one or more resorptions or dead fetuses per litter (for each abnormality), and percentage of litters having one or more abnormal fetus (for each abnormality).

Results:

Statistically significant reductions in dam body weight gain were observed in all UC51762 - treated groups. This reduction was particularly severe in the 100 mg/kg groups where the weight gain was approximately 25% of that observed in the controls. UC51762 treatment from days 6 through 15 of gestation did not affect fetal weight or length. However, treatment from days 0 through 20 did result in statistically significant reduction in fetal weights and lengths in the 100 mg/kg group. Aspirin treatment resulted in statistically significant reductions in fetal weight and length.

Ingestation of UC51762 did not significantly affect the number of implantations, resorptions or live fetuses per litter. Pre-implantation loss was also unaffected by UC51762 ingestion. However, the data suggest a possible increase in resorption frequency in rats which received 100 mg/kg of UC51762 on days 6 through 15 of gestation. The increase is evident both in the percentage of affected litters (78% vs. 50% in the negative controls) and especially in the percentage of resorptions per litter, which estimates the "average effect" within litters. The median percentage of resorptions per litter in the 100 mg/kg group was six-fold higher than that of the negative controls (23.1% vs. 3.8%).

Aspirin treatment did not result in statistically significant embryolethal effects. However, the data suggest a possible increase in frequency of resorptions both in terms of the percentage of litters affected (83% vs. 50% in the negative controls) and especially in the percentage of resorptions per litter in which the median of the aspirin group was four-fold higher than that of the negative control.

Ingestion of UC51762, even at 100 mg/kg/day, did not alter the frequency of visceral anomalies as compared to those of the control animals. Similarly, aspirin treatment (625 mg/kg on day 10) did not increase the freqency of visceral anomalies.

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A variety of skeletal variations were observed in the control and UC51762 - (100 mg/kg) treated fetuses including a substantial number of bilobed thoracic vertebral centra and poorly ossified sternebrae. These findings are not unusal for 20-day rat fetuses (Kimmel and Wilson, Teratology, 8: 309-316, 1973).

Statistical comparisons between the UC51762 - treated and control fetuses revealed a significant difference in only one parameter; i.e., bilobed vertebral centra.

There was a statistically significant ($p < 0.05$) increase in the percentage of live fetus per litter which showed this variation in rats treated throughout gestation but there was little difference in the percentage of litters affected (100% of U51762 litters vs. 86% of negative control litters). This increase was not observed in rats which received the same dose (100 mg/kg/day) of UC51762 throughout organogenesis (days 6 through 15). Examination of the fetuses which received 3.0 mg/kg/day revealed no significant difference from controls in the incidence of bilobed centra.

Bilobed thoracic vertebral centra are anatomical variants found frequently in untreated 20-day rat fetuses. The increased incidence over the control level may indicate delayed maturity of the affected fetuses.

The 100 mg/kg dams received a dose of UC51762 which resulted in a severe reduction in weight gain and a decrease in fetal size (weight and length). The fetotoxic effects and increased incidence of bilobed centra were observed only in the rats which were exposed throughout gestation.

The aspirin - treated fetuses exhibited increased incidences of several skeletal variations and anomalies including split and missing vertebral centra, extra vertebrae, extra ribs and misshapen (fused, wavy) ribs. These results indicate the rats were sensitive to the teratogenic action of aspirin. The skeletal findings and their interpretation have been substantiated by an independent expert teratologist, Dr. James J. Wilson; his report is presented in Appendix III of the submission.

Conclusion:

UC51762 was not teratogenic at dosages up to 100 mg/kg/day given during days 6-15 or days 0-20. The fetotoxic NOEL is 3 mg/kg/day.

Classification: Core-Minimum Data

TOX/HED:th:CFRICK:4-29-80

C. Frick 4/29/80
M 6/3/80

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