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MAR 24 1993

OFFICE OF  
PREVENTION, PESTICIDES AND  
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Propachlor - Developmental Toxicity Study in Rabbits; Additional Historical Control Data

TO: Susan Cerrelli  
Product Manager (71)  
Reregistration Branch, SRRD (H7508C)

FROM: Linda L. Taylor, Ph.D. *Linda Taylor 3/19/93*  
Toxicology Branch II, Section II,  
Health Effects Division (H7509C)

THRU: K. Clark Swentzel *K. Clark Swentzel 3/23/93*  
Section II Head, Toxicology Branch II  
Health Effects Division (H7509C)

and

Marcia van Gemert, Ph.D. *Marcia van Gemert 3/23/93*  
Chief, Toxicology Branch II/HFAS/HED (H7509C)

Registrant: Monsanto Company  
Chemical: 2-chloro-N-isopropylacetanilide  
Synonym: Propachlor  
DP Barcode: D185895  
Submission No.: S432251  
Caswell No.: 194  
Case: 818640  
Identifying No.: 019101  
Shaughnessy No.: 019101  
MRID No.: 425847-01

Action Requested: These data are a follow-up to your October 20, 1992 FAX requesting historical control data. Determine if 83-3(b) is satisfied.

Comment: The Registrant has submitted supplemental information related to the rabbit developmental toxicity study with Propachlor (Study # SB-91-86; MRID # 423480-02) in response to the Agency's request for additional historical control data on post-implantation loss and bent hyoid arches.

In the rabbit developmental toxicity study (DER dated 8/20/92), there was a dose-related increase in the number of resorptions, # resorptions/does, and the % of does with resorptions at the mid- and



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high-dose levels, with a comparable increase in post-implantation loss at these two dose levels compared to the control. Although there were no statistically significant differences in the incidence of any fetal malformation (external, visceral or skeletal) that could be attributed to treatment, there was a statistically significant increase in the number of high-dose litters with fetuses with bent hyoid arch(es). A meeting was held with the Registrant on October 13, 1992 to discuss what additional historical control data should be submitted to upgrade the study.

The historical control data requested have been submitted. The data represent 10 studies conducted within a 12-months period of the Propachlor study, using the same strain of rabbit from the same supplier as the Propachlor study. With regard to the percent of litters with resorptions, two of the 10 studies display a higher incidence (63.2% and 66.7%) than that observed in the Propachlor study (60%) at the high dose. The number of resorptions per litter at the mid- and high-dose level was increased (dose-related) compared to the concurrent control group, but the incidence observed at each dose level was displayed in one historical control study each. With respect to resorptions on a mean litter % basis, when all litters are considered and when only those with resorptions are considered, the incidence at the high-dose level exceeds that of the historical control data.

With regard to the mean post-implantation loss per group data (last row of table on page 5), no units are presented, and the numbers in the 10 studies range from 0.2 to 1.4 (mean 0.56). It appears that the numbers listed for the mean post-implantation loss per group were obtained by dividing the # of resorptions by the # of litters in the group. In the original study report, it appears that the same type of calculation was made. The mean post-implantation loss per group in the Propachlor study was listed as 0.39, 0.35, 1.0, 1.4 for the control, low- mid-, and high-dose groups, respectively. Although there is one historical control study with a loss of 1.1 (comparable to the mid-dose value) and one with a loss of 1.4 (equal to the high-dose value), the other 8 studies show a loss of 0.7 or less (mean 0.39). As calculated for the Propachlor study by this reviewer, the post-implantation loss on a percent basis 5.7, 5.0, 13.5, and 19.8 for the control, low-, mid-, and high-dose groups. No data were provided as to the number of implantations and live/dead fetuses observed in the 10 historical control data studies; therefore, a similar calculation of the historical control data on a % basis could not be run for comparison. Given the dose-related increase in females with 100% intrauterine deaths, the 2- and 3-fold increase in the total number of resorptions at the mid- and high-dose levels, and the fact that the incidences of post-implantation loss at the mid- and high-dose levels are at the high end of the historical control values, both dose levels are viewed as effect doses.

With regard to bent hyoid arches, the highest % of litters with

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this observation in the historical control data is 52.6, which is greater than that observed in the high-dose group (46.1%) of the Propachlor study. Not provided by the Registrant but calculated by this reviewer is the incidence of bent hyoid arches on a mean litter % basis. The highest observed in the historical control data was 39.2%, which exceeds the highest observed in the Propachlor study (13.9%). Based on the historical control data, there is no evidence that the incidence observed in the Propachlor study is related to treatment with Propachlor.

#### CONCLUSION

The maternal NOEL can be set at 5 mg/kg, the LOEL at 50 mg/kg, based on the apparent increase in resorptions/postimplantation loss compared to the concurrent control. This study is classified Core Minimum, and it satisfies the guideline requirement [83.3(b)] for a developmental toxicity study in rabbits.

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