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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

Subject: Benefin: 1471-71 (Record Number 212720): Registrant's Reply to the Previous Toxicology Branch Review Comments Concerning the Rat Teratology Study with Benefin Caswell Number 130

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Hazard Evaluation Division (TS-769C) 5/5/88

Review of the Registrant's Response to the Previous TB Review Comments Concerning the Rat Teratology Study with Benefin (TB Memo 9/8/86 J. Chen)

1. High Incidence of Male Fetuses with Unossified Sternebrae at the 225 mg/kg/day Dose Level

Registrant's Response:

"... The occurrence of male fetuses with unossified sternebrae at the 225 mg/kg/day dose level was statistically greater than the concurrent control group but this finding did not occur in a dose-response manner across the benefin treatment groups. The proportion of female fetuses with unossified sternebrae at the 225 mg/kg/day dose level was similar to the proportion of male fetuses affected but was not statistically different from the concurrent control group. These data indicated that the occurrence of unossified sternebrae was not a sex-linked event. Hazleton historical control data from teratology studies conducted during the two-year period encompassing study 6180-101 reported minimum and maximum incidences of fetuses with unossified sternebrae of 18.4% and 29.4% respectively. The incidence observed at the 225 mg/kg/day dose level was well within the range for historical control fetuses. However, the concurrent control incidence for male fetuses was lower than all studies

conducted over the preceding two-year period. Based on these data, the occurrence of a statistically significant increase in male fetuses with unossified sternebrae at the 225 mg/kg/day dose level appeared to be the result of antypically low incidence in the concurrent control group and was not considered to be toxicologically significant. "

Reviewer's Comments:

The submitted historical control data provide adequate information for the spontaneous incidences of fetuses with unossified sternebrae in the rat teratology study. Registrant's explanation for the statistically increased incidences of fetuses with unossified sternebrae found at the 225 mg/kg/day dose level is considered to be reasonable.

2. High Incidence of Dark Brown-Red Diffuse Areas on the Liver at the 225 mg/kg/day Dose Level

Registrant's Response:

"... Contrary to the EPA's comments, the original report cited only the litter incidence of dark brown-red diffuse areas on the liver at the 225 mg/kg/day dose level to be statistically greater then the concurrent control group. The numbers of litters affected were 0, 0, 5, 1 and 4 from the 0, 50, 225, 475 and 1000 mg/kg/day dose levels respectively and did not indicate a pattern related to benefin treatment. It should be noted that no gross morphological changes in the liver were observed in conjunction with these dark brown-red areas. In the teratology segment of a rat multigeneration reproduction study with benefin, liver anomalies were not observed in fetuses from rats that received 0, 1000 and 5000 ppm benefin in the diet (ca. 0, 100 and 500 mg/kg/day) throughout gestation (Adams et al., 1973). Based on these data, the sporadic occurrence of fetuses with dark brown-red areas on the liver was not considered to be toxicological significant. "

Reviewer's Comments:

The provided information and explanation for the statistically increased litter incidences of dark brown-red diffuse areas of the liver at the 225 mg/kg/day dose level are considered to be reasonable.

3. Tabulation Errors

Registrant's Response:

"... The numbers and percentages of abnormal and normal fetuses were derived from data in Table A-7 (Individual Fetal Skeletal Observations) on pages 54-67, and Table A-8 (Individual Fetal Soft Tissue Observations) on pages 68-73. Subsequent to receiving comments from the EPA, a review of study 6180-101 was conducted by Lilly scientists. Tabulation errors were discovered in the reported values for the numbers of fetuses examined and the numbers and percentages of abnormal and normal fetuses presented on page 9. Although the occurrence of these tabulation errors was regrettable, they were not of sufficient magnitude to affect the conclusions of this study. The corrected values for these parameters are shown below:

	Mg Benefin 54521/Kg				
	0	50	225	475	1000
No. of Fetuses Examined	353	349	353	324	385
No. of Abnormal Fetuses (%)	65(18)	93(27)	89(25)	74(23)	90(23)
No. of Normal Fetuses (%)	288(82)	256(73)	264(75)	250(77)	295(77)

In addition, a dose group heading for Table A-8 on page 73 of the original report was incorrectly identified as "225 mg Benefin 54521/kg (continued)"; the dose group identification should read "475 mg Benefin 54521/kg (continued). A report amendment correcting these errors was prepared by Hazleton Laboratories, Inc. and was submitted to EPA by Lilly Research Laboratories (Byrd., 1986). "

Reviewer's Comments:

The corrected Table (Total Number of Abnormal and Normal Fetuses) ia considered to be acceptable and should replace the same table summarized in the original Toxicology Branch review of this study (TB Memo 9/8/86 J. Chen).

4. Methodology for Visceral and Skeletal Examination Used by Hazleton Laboratories, Inc.

Registrant's Response:

" Copies of standard operating procedures for visceral and skeletal examination techniques were requested and received from Hazleton Laboratories, Inc. These standard operating procedures have been included in this document as Appendix C. "

Reviewer's Comments:

The provided details of visceral and skeletal examination techniques used by the Hazleton Laboratories, Inc. are considered to be acceptable (attached).

5. Registrant's Conclusion

" This document has addressed comments from the EPA review of a rat teratology study with Benefin. Additional information has been provided as requested by the EPA. Corrective action has been taken to rectify minor data errors. However, study 6180-101 still represents a valid assessment of the teratogenic potentital of Benefin. Data generated in study 6180-101 support a maternal toxicity NOEL of 225 mg/kg/day and a developmental toxicity NOEL of 1000 mg/kg/day (the highest dose level tested). "

6. Toxicology Branch Recommendation

Registrant's responses to the deficiencies cited in the previous Toxicology B anch Review of this study (TB Memo 9/8/86 J. Chen) appear to be justified. Therefore, the study is upgraded to Core Guideline.

Maternal Toxicity NOEL = 225 mg/kg/day
Maternal Toxicity LEL = 475 mg/kg/day (decreased maternal body weight)
Developmental Toxicity NOEL = 1000 mg/kg/day (HDT)

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Pages 5 through 11 are not included.

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