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

11/17/85

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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Response to Comments on Review of Curacron Rabbit
Teratology Study. Acc.No. 254648. Caswell #266AA

TO: William H. Miller (PM-16)
Registration Division (TS-767C)

FROM: Gary J. Burin, Toxicologist *Gary J. Burin*
Toxicology Branch/Science Integration Staff

THRU: Laurence D. Chitlik, D.A.B.T. *W. Teeters for L. Chitlik*
Head, Section V *11-0-85*
Toxicology Branch
and
Theodore M. Farber, Chief
Toxicology Branch *H. for W. H. B. 11/17/85*

Background: A review of this study was transmitted in my memorandum of October 25, 1983 to William Burnam. I recommended that this study tentatively be classified as Supplementary Data pending resolution of the following three issues: determination of appropriate statistical methods for determination of maternal toxicity, submission of historical data for "runting" and for variations and malformations.

Discussion/Conclusions

I submitted the study itself (EPA Acc. No. 250451), my October 25 review, and the comments of the registrants on my review to Bert Litt, Leader of the Toxicology Branch Statistical Staff for resolution of the statistical issue. On September 19, 1985, I received a handwritten response stating that regression analysis to establish a trend and related t-tests were used to evaluate specific differences. The dose levels of 60, 90 and 175 mg/kg were found to be significantly different than the control i.e., the NOEL for maternal toxicity is 30 mg/kg based on body weight change.

With respect to the incidence of runting, the submitted historical control data indicate a range of 0.0 to 20.0 average % runts/litter with a mean of 7.6. The incidence within this study is clearly within the historical range and is similar to the historical mean. Furthermore

182

the two dose levels with apparent slight increase in runting are levels which are now considered to be maternally toxic. It is therefore concluded that no compound related effect on the incidence of runts is observed in this study.

With respect to other variations, an apparent increase in ossification delays of the phalanges and metacarpals was observed in the high dose group (4/7 (57%) litters and 6/49 (12%) fetuses affected vs. 4/15 (27%) litters and 8/122 (7%) fetuses in the control group). I compared the number of fetuses affected in the high dose group with the controls and found that the difference was not significant at the $p < .05$ using the chi square statistic. Again, this high dose level was a dose level which induced maternal toxicity. It is therefore concluded that additional data regarding the historical incidence of these ossification delays are not needed.

It is recommended that this study be upgraded to "Core-Minimum" status. The NOEL for maternal toxicity is 30 mg/kg. The NOEL for developmental toxicity (embryo/fetotoxicity) is 175 mg/kg. A teratogenic potential was not observed at the highest dose level tested (175 mg/kg).

7