Chlorothalonil FILE

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

May 4, 1990

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Review of a Teratology Study in Rats with T-117-11 (Wil Research Laboratories # WIL-11003

FROM: Laurence D. Chitlik, D.A.B.T.
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As part of the review of the developmental toxicity data for Chlorothalonil, it was noted that the existent review of the rat developmental toxicity study, Wil Research Laboratories, # 11003, was extremely brief and apparently did not present a full assessment of the data. The purpose of this memo is to provide an additional level of assessment which should be considered in addition to the original 5/3/84 review of D. L. Ritter and R. B. Jaeger.

An obvious question exists relative to the test materials used in the rat versus the new rabbit study. The test material utilized in the most recent rabbit study (conducted at Bio/dynamics and reviewed in my memo of 4/12/90) was identified as T-117-12, while the material used in the Wil rat study is identified as T-117-11. This difference apparently has nothing to do with a difference in batches, and clarification should be requested. Possibly, the difference has to do with a change in the impurities of the technical material produced since 1983. Regardless, this difference needs to be resolved as the actual identification of the test material in the two studies is not as clear as it should be (e.g.-batch numbers not provided and purity only assumed).

A copy of the Materials and Methods section of the test report is appended. Twenty-five females in each of four test groups received dosages of 0, 25, 100, and 400 mg/kg/day of test material in a dose volume of 10 ml/kg (0.5 % aqueous methylcellulose). Based

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upon initial analytical results, it was determined that methods of preparation were inadequate and preparation procedures were revised.

Maternal Toxicity:

Four animals died during the test period. One animal died due to technician error at the 100 mg/kg/day level. Three additional animals died at the high dose level during gestation days 12 to 18. Animal number 3738 was noted to have congested lungs at necropsy which at times has been associated with dosing error. However, the cause of death for the three high dose animals was not determined at necropsy. There were no clinical signs of toxicity noted in the 100 mg/kg/day dose group. At the 400 mg/kg/day level, increased incidences of observations included mucoid, loose or white discoloration of the feces and brown material around the nose and mouth, matting of the urogenital fur and a slight increase in the incidence of animals with alopecia.

Body weights, body weight gain and food consumption all demonstrated statistically significant effects at the 400 mg/kg/day dose level. At the intermediate dose level (100 mg/kg/day), decreases in body weight gain were also apparent and consistent but did not attain statistical significance. Only during gestation days 6-9 was food consumption also affected at the mid and low dose levels ($p<0.01$). However, these differences did not persist during the rest of the dosing period or to the post-dosing period. In consideration of the body weight effects also observed at the mid-dose level, only the low dose appears to be without consistent body weight and/or food consumption effects.

Developmental Toxicity

At the mid and low dose levels there were no effects upon any cesarean derived data. At the high dose level there was an increase in the incidence of early resorptions and a slight decrease in the number of viable fetuses per litter. A copy of Table 7 from the test report is attached which reflects these findings.

A review of the malformation and variation tables numbers 8-11, (copies of these tables are attached) suggests that examination of the fetuses for delays or reductions in ossification are incomplete. For example, the authors present incidences of unossified hyoid in all dose groups outside the range of historical control data, but claim that due the lack of a clear dose response relationship, the the finding is not of concern. Contrary to this, it is this reviewers opinion that the fetuses should be re-examined for reductions in ossification as well as absence of ossification for this and other findings, to ascertain the

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presence or absence of a dose response relationship. In addition, historical data need to be presented in a more detailed and complete manner rather than just presenting ranges for various findings. Historical data need to be available for individual studies and cover a period of at least 2 years prior to and at least 2 years after the the study in question.

Recommendation

At this time, this study should be classified as supplementary data as there may be no NOAEL for developmental toxicity. If questions can be resolved relative to the increased incidences of variations (e.g.-hyoid unossified) and whether this finding is associated with administration of the test material, this study may potentially be upgraded. However, this will likely require a re-reading of skeletons if they are still available. In addition, questions relative to the identity of the test material will also need to be resolved.

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