CASWELL FILE

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

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Chlorothalonil - Evaluation of Supplementary Data Provided for Rat and Rabbit Teratology Studies

Caswell No.: 215B
HED Project No.: 1-0346
DP Barcode: D159512

FROM: Elizabeth A. Doyle, Ph.D., Section Head
Review Section IV, Tox Branch II (H7509C)

E.A. Doyle 4/14/92

TO: Jane Mitchell, PM-74
Special Review and Reregistration Division (H7507C)

THRU: Marcia van Gemert, Ph.D., Branch Chief
Toxicology Branch II
Health Effects Division (H7509C)

Marcia van Gemert 4/15/92

Action Requested: Review of supplementary data provided in support of rat and rabbit developmental toxicity studies for chlorothalonil.

Background: In 1990, a rabbit developmental toxicity study for chlorothalonil was reviewed by L. Chitlik and found to be unacceptable due to missing information. During the same time period, he re-reviewed a rat teratology study and changed the classification from "Guideline" to "Supplementary" pending receipt of additional data. The requested data have been provided and are presented below.

Rabbit Study (MRID 412505-03) - Supplementary data in support of this study were provided in MRID 416793-01 and 416793-02.

1) The lungs of maternal rabbits were reported to be discolored. However, this was not dose related and occurred in controls as well as treated animals. An explanation was requested.

The study pathologist (Dr. Henry F. Bolte) indicated that this observation is common in rabbits at necropsy and is related to the manner of sacrifice rather than an indication of disease.

2) Historical control data for variations was requested.

The data was provided. No evidence of treatment related increases in variations was evident from the original study, and the incidence of variations was within the historical control range.

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3) Historical control data were requested for maternal body weights to evaluate whether the treated groups (30 and 20 mg/kg/day) were within the normal range.

Maternal body weights demonstrated no treatment related effects.

4) The reviewer requested that metabolism and pharmacokinetics data be provided to demonstrate that the treatment levels were appropriate.

The registrant notes that these data are available and have been reviewed as part of the registration process. Further, no evidence of interference with absorption of the test material by the vehicle methyl cellulose has been apparent in any of the other studies submitted in support of chlorothalonil. These arguments are accepted.

5) The reviewer requested external evaluation of fetuses from the range finding study or an explanation as to why this was not done.

The registrant correctly points out that no guidance is given by the Agency for the conduct of a pilot study. This argument is accepted.

6) The reviewer requested a re-examination of the skeletons from the main study to provide some level of grading of reductions in ossification.

The registrant states that with the current report describes structures as normal, incomplete or not ossified, and that no grading system has been validated to further grade this effect. Further, the registrant argues that no additional description is warranted. These arguments are accepted.

7) Incidence of reduced or soft feces from the pilot study were not included in the initial report.

These data have been provided as requested.

Rat Study (Acc. 130733) - Supplementary data were provided in support of a rat developmental toxicity study in MRID 416793-01.

1) As requested, the registrant has clarified the numbering of the test materials in the study. The designation T-117 refers to technical grade chlorothalonil. T-117-11 and T-117-12 refer to two batches of the technical and were used solely to maintain confidentiality during the studies.

2) The reviewer expressed concerns about the incidence of unossified hyoid in all dose groups, but especially in the high dose group. This observation calls into question the establishment of a developmental NOEL.

The registrant notes that the control and two lowest dose groups were within the historical control range and that no dose response is observed. These arguments are accepted.

3) The reviewer noted an increased incidence of resorptions in the high dose group relative to the control and other treated groups.

The registrant clarified this observation by pointing out that this increase is largely due to the occurrence of one female with 16 early resorptions and one live fetus. If this litter is excluded, the mean postimplantation loss is comparable to the control.

Recommendation: Based upon acceptable responses to questions posed and submission of additional data requested in the reevaluation of the subject studies, the rabbit Developmental Toxicity study (MRID 412505-03) and rat Developmental Toxicity study (Acc. 130733) should be classified as "core - Guideline" and satisfy the guideline requirements (83-3a and 83-3b).