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

MAY 19 1988

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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Additional Data Submitted to Complete the Review of the Rat Developmental Toxicity Study on Iprodione®

TO: Lois Rossi, PM 21
Registration Division (TS-767)

FROM: Margaret L. Jones M. L. Jones 12 May 1988
Review Section III
Toxicology Branch (TS-769)

THROUGH: Marcia van Gemert, Ph.D., Head M. van Gemert 5/13/88
Review Section III
Toxicology Branch (TS-769)

and Theodore M. Farber, Ph.D., Chief
Toxicology Branch
Hazard Evaluation Division (TS-769)

Chemical: Iprodione® Record No.: 214942 Accession No: 405149-01, 405149-09

Tox. Chem.: 470A Registrant: Rhone Poulenc

Action Requested: Review additional data submitted to respond to questions or deficiencies in LSR Report No. 85/RHA064/765; "Teratology study in the rat", by Life Science Research, Suffolk, England for Rhone-Poulenc Agrochimie, Lyon, France.

In order to address the questions and comments in the Data Evaluation Record, the registrant submitted a complete description of individual fetal observations which greatly facilitated evaluation of the report. Three points were raised in the original review, including questions why certain clinical signs noted in the range finding study (at 120 mg/kg/day and 240 mg/kg/day) were not observed in the full study (at 200 mg/kg/day), questions about laboratory personnel making the above observations, and a request to present tables with word descriptions rather than using a coding system with letters.

Conclusion: The registrant response to the questions appears in appended pages 1 and 2. These responses adequately address the questions raised in the original review. The study is now fully acceptable and is accordingly upgraded to CORE MINIMUM.

Ref: Memorandum from Jones to Rossi, dated 7/23/87 with review attached (35 pages); copy in Tox. Chem. File No. 470A.
See also, EPA Accession no: 264519

Appended page 1

LIFE SCIENCE RESEARCH

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4 December 1987

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Iprodione : Rat teratology study (LSR Schedule No. RHA/064)

We have considered the comments made by the US Environmental Protection Agency on the subject of the above report, and our responses are as follows.

Our response to the second point first:

2. There were different personnel involved in recording clinical signs in the two studies. However, study direction and supervisory staff did not change, and in all cases staff were well-trained and experienced.

1. The clinical signs recorded in the dose range-finding study suggested a very steep dose response curve. Consequently, there were major differences between groups in the extent of signs seen. At 40 mg/kg/day no signs were recorded, at 120 mg/kg/day there were occasional instances of flaccidity, and at 240 mg/kg/day, flaccidity and other signs were more noticeable. The recording of signs of this nature is subjective, and in this case the marked signs seen at 400 and 800 mg/kg/day would most likely have heightened perception of minor changes at the lower dosages.

cont.....

In the main study this dramatic range of signs was not present, and consequently the observer would not be so perceptive of minor differences in muscle tone. It is probably significant that recordings were made in the afternoon when rats are by nature somewhat torpid and relaxed.

In assessing the results of this study we think it most important to be assured that the compound is absorbed. Reference to page 79 of the dose range-finding study reveals high plasma concentrations of Iprodione following treatment at both 40 and 800 mg/kg/day.

3. We consider our presentation of fetal data facilitates rather than obscures interpretation. The data is summarised in text form in the tables, and the use of the coding system in appendices allows rapid comparison between litters and between types of examination.

However, to be of assistance we have prepared an addendum to the report including the data in text form.

Yours faithfully

P.A. McAnulty

Dr Peter A McAnulty
Deputy Head of Reproductive Studies

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Appended page 2