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

MEMORANDUM SEP 14 1993

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Iprodione- Combined chronic toxicity/carcinogenicity in rats
6(a)(2) data

TO: Barbara Briscoe PM 51
Special Review and Reregistration Division

FROM: K. Clark Swentzel, Section Head K. Clark Swentzel 9/9/93
Toxicology Branch II

THROUGH: Marcia van Gemert, Ph.D. Marcia van Gemert 9/10/93
Branch Chief
Toxicology Branch II

Submission: S435926
Barcode: D188475
MRID NO.: 426378-01
CASWELL NO.: 470A
PC CODE: 109801
REGISTRANT: Rhone-Poulenc

Action Requested

120 day review

Response

This study has been reviewed by Clement; the DER is attached.

Conclusions

Iprodione was fed to male and female Sprague-Dawley rats at dietary levels of 0, 150, 300 or 1600 ppm (6.1, 12.4, 69.0 mg/kg/day in males and 8.4, 16.5, 95.0 mg/kg/day in females) for 2 years.

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At 1600 ppm, an increased incidence of benign interstitial cell tumors of the testes was observed. No increase in the incidence of any tumor type was observed in treated females in this study.

At 300 ppm, generalized enlargement of the cells of the zona glomerulosa in males and females and rarefaction and fine vacuolation of the zona fasciculata in the adrenal cortex were observed in males. Generalized fine vacuolation of the zona reticularis in the adrenal cortex was also seen in males. Also, males showed interstitial cell hyperplasia in the testes, reduced spermatozoa in the epididymides, reduced secretion of the seminal vesicles and an increased liver weight (adjusted for body weight). Increased hemosiderosis in spleen was noted in females. Males showed centrilobular hepatocellular enlargement at the interim sacrifice.

At 1600 ppm, decreases were observed in body weight gain (≈14-74%) and food consumption (≈5-8%) among males and females. At necropsy, males showed increases in testes (with epididymides) weights (after adjustment for body weight), testicular masses, small prostates and small seminal vesicles with minimal contents. Histopathology revealed atrophy of the prostate and seminiferous tubule, prominent abnormal spermatogenic cells and centrilobular hepatocellular enlargement in males. The effects in the adrenal cortex noted at 300 ppm were also observed in males at this dietary level. At the interim sacrifice both sexes showed generalized rarefaction and fine vacuolation of the zona fasiculata, males showed generalized enlargement of the cells of the zona glomerulosa and generalized fine vacuolation of the zona reticularis of the adrenal cortex and females showed increased extramedullary hematopoiesis in the spleen.

NOEL: 150 ppm (6.1 & 8.4 mg/kg/day in males and females, respectively)

LEL: 300 ppm (12.4 & 16.5 mg/kg/day in males and females, respectively)

Core Classification

The contract reviewer classified this study Core Supplementary for a combined chronic toxicity/carcinogenicity study since it was concluded that a NOEL for systemic toxicity was not established. The registrant was subsequently asked by TB II (via telephone) to provide historical control data regarding the spontaneous incidence of fine vacuolation of the zona reticularis of the adrenal cortex in Sprague-Dawley males from the testing facility. Following this request, slides prepared from the adrenals of 350 control males from 7 studies were reexamined for this lesion. These data have been received and show that the incidence of this lesion in low-dose males was comparable to the mean (approximately 23%) from the historical control data (attachment 1) which were generated between February 1988 and June 1989 (attachment 2); the subject study was initiated in 1990. The concurrent control data appeared to be atypical. Based on the assessment of the submitted historical control data, it is TB II's opinion that the classification of chronic toxicity segment of this study should be **Core-minimum**. The Core Classification of the carcinogenicity segment of this study will be determined following review by the HED Cancer Peer Review Committee. This study will be considered concurrently with

a carcinogenicity study in mice (currently under review in TB II) as well as a Discussion Document (Iprodione: Carcinogenicity in Rodents MRID No. 428250-01) submitted by the registrant which includes a discussion of the possible mechanisms of action for the tumors induced in these studies (attachment 3).

Pending regulatory actions

A preliminary report from a mouse carcinogenicity study, dated March 15, 1993, was previously submitted under 6(a)(2) to the Agency. The report indicated that "there appears to be an increased incidence of benign and malignant liver tumors in both sexes along with an increased incidence of benign ovarian tumors at or above the maximum tolerated dose (4000 ppm)." As noted above, the final report for this study is currently under review in TB II.

Due to the many food uses for Iprodione, both of these studies were given high priority for scientific review and probable cancer peer review. Since a consensus on the possible cancer risk for the consuming public can not be attained until these reviews have been completed, pending regulatory actions involving Iprodione can not be toxicologically supported at this time.