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

OFFICE OF
PREVENTION PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

DATE: January 6, 2000

SUBJECT: Imazalil: Evaluation of Supplementary Data to Combined Chronic/Carcinogenicity Study in Rats and Evaluation of Teratogenicity Studies in Mice

FROM: Abdallah Khasawinah, Toxicologist
Reregistration Branch 4
Health Effects Division (7509C)

TO: Dean Monos/ Betty Shackleford, PM #53
Reregistration Section
Special Review and Reregistration Division (7508W)

THRU: Sanjivani Diwan, Senior Toxicologist
and
Susan V. Hummel, Branch Senior Scientist
Reregistration Branch 4
Health Effects Division (7509C)

TASK ID: DP Code: D260347 Submission: S569931, P.C. Code: 111901
Case: 816389 Chemical: Imazalil

Registrant: Janssen Pharmaceutica

Action Requested: Evaluate the data submission to determine their acceptability in meeting the guideline requirements

Agency's Response:

The registrant of Imazalil, Janssen Pharmaceutica, has provided additional information related to the carcinogenicity study in rats (MRID # 44858001) and its teratogenicity in mice. The additional information is identified as follows:

1) Imazalil 83-2: Interim Report: Combined Chronic Toxicity/Carcinogenicity Study in the Wistar Rat (18 month data), MRID # 44567801

2) Imazalil Sulfate: Embrytoxicity and Teratogenicity Study in Albino Mice, MRID 44567803

3) Imazalil Sulfate: Embrytoxicity and Teratogenicity Study in COBS CD1 Mice, MRID 44567802

1) The 18-month interim report. The 18-month interim report of a 24-month Combined Chronic Toxicity/Carcinogenicity Study in the Wistar Rat, (MRID # 44858001) does not provide any new information not covered in the final report. However, this requirement has been met by MRID # 44858001 and the study has been reviewed by HED and was found acceptable.

2) Range finding teratogenicity study in mice. In a range finding study (MRID 44567803) pregnant Cobs CD1 mice were orally dosed with imazalil sulphate at 40, 80, or 120 mg/kg from day 6 to 16 of gestation. Maternal toxicity was characterized by reduced body weight gains and food consumption at 80 and 120 mg/kg. Increased resorptions were observed at 40 and 80 mg/kg, but these findings were not statistically significant and were within normal ranges. At 120 mg/kg, increased numbers of resorptions correlated with a reduction in litter size. No effects on the offspring were noted at any dose level. Based on these findings the dose levels of 10, 40, 80 and 120 mg/kg/day were selected for the main study (MRID 44567802).

3) Teratogenicity study in mice. In a developmental toxicity study with(MRID 44567802) imazalil sulphate (98.2% a.i.) was administered by gavage at 0, 10, 40, 80, or 120 mg/kg/day to pregnant mice (30 females/dose) on gestation days (GD) 6-16. Dams were sacrificed on GD 19. **Maternal LOAEL** = 40 mg/kg/day, based on reduced body weight gains, corrected body weight gains, and food consumption. **Maternal NOAEL** = 10 mg/kg/day. **Developmental LOAEL** = 80 mg/kg/day, based on a significant increase of fetuses and litters with extra 14th pair of ribs at $\geq$ 80 mg/kg. **Developmental NOAEL** = 40 mg/kg/day.

This developmental toxicity study is classified **acceptable [GLN 8700.3700 (§83-3a)]** and satisfies the guideline requirement for a developmental toxicity study in the mouse (DER is attached).

SignOff Date:	1/6/00
DP Barcode:	D260347
HED DOC Number:	013962
Toxicology Branch:	RRB4