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

NOV 29 1993

Nov 29 1993

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM:

SUBJECT: Submission by the Registrant of 6-a-2 Data (Interim Report) on the Mouse Carcinogenicity Study with Imazalil.
MRID # 42890301 and 42972000.

D 195254
S 448726
Tox Chem No. 497 AB
Chem No. 111901

TO: Kathleen Depukat
PM # 52
ReRegistration Branch
SRRD (H7508W)

FROM: Henry Spencer, Ph.D.
Pharmacologist,
Review Section 3
Toxicology Branch 1
Health Effects Division (7509C)

11/17/93

THRU: Karen Hamernik, Ph.D.
Section Head
Review Section 3
Toxicology Branch 1
Health Effects Division (H7509C)

11/22/93

11/29/93

ACTION: Review the summary of the interim findings of a mouse carcinogenicity study as possible 6-a-2 data. MRID#s 42890301, 42972000.

CONCLUSIONS AND RECOMMENDATIONS:

1. A review of the summary data submitted indicates that a 23 month dietary exposure of Imazalil was associated with increased incidences of liver neoplasms in male and female mice. Additionally, the data suggest that there may well be a progression of neoplastic nodules to liver carcinomas in the males. Neoplastic changes occurred at nominal doses of 200 and 600 ppm (approximately 30 and 90

mg/kg/day respectively). The information did not show neoplasia at the lowest dose tested of 50 ppm (approximately 8 mg/kg/day nominal dose).

2. Before the hazard from this study can be fully analyzed, the completed study will be required to be reviewed. Additionally, the chemical may require review by the HED Carcinogenicity Peer Review Committee.

3. Until the full analysis of the carcinogenicity potential of Imazalil has been completed, Toxicology Branch does not support further granting of additional food uses than now exist.

4. A review of the summary information submitted by the registrant is appended.

5. The current RfD (0.013 mg/kg/day) for Imazalil is based on a 2 year feeding study in the dog with a NOEL of 1.125 mg/kg/day (based on decreased body weight) and an uncertainty factor of 100. A two year chronic/carcinogenicity study in the rat with Imazalil was negative for carcinogenicity at the doses tested.

The impact of this study (if any) on the current RfD will be determined after receipt and review of the final report of the study and completion of any related data analysis.

Reviewer: Henry Spencer, Ph.D. HS 11/17/93
Pharmacologist
Review Section 3
Toxicology Branch 1
Secondary Reviewer: Karen Hamernik, Ph.D. KH 11/22/93
Section Head
Review Section 3
Toxicology Branch 1

REVIEW:

Subject: Oral Carcinogenicity Study with R23979 (Imazalil) in mice. Summary of Interim Report. Possible 6-A-2 data submissions.

MRID: 42890301, 42972000

TEST MATERIAL: R23979, Imazalil (base)

ROUTE OF ADMINISTRATION: Dietary

STUDY NUMBER: R23979

SPONSOR: Janssen Pharmaceutica, Turnhoutseweg 30, B-2340 Beerse, Belgium.

TESTING FACILITY: Janssen Pharmaceutica, Beerse, Belgium

TITLE OF REPORT: Oral Carcinogenicity Study with R23979 (Imazalil) in Mice

AUTHORS: A. Verstraeten

REPORT ISSUED: August 11, 1993

CONCLUSIONS:

1. The information presented in this 6-a-2 submission is a summary of the interim report of the Imazalil carcinogenicity study in mice.

2. Individual animal data were not presented in this submission.

3. Mortality and tumor data are presented as totals over 23 months and do not provide when the animals died or when tumors first appeared.

4. Gross incidence of liver tumors increased at 200 and 600 ppm in males and in females at 600 ppm. The final study report will be necessary in order to more closely evaluate whether a real hazard exists from this chemical.

5. Doses administered in the study were nominally: 0, 50 ppm, 200 ppm, and 600 ppm which approximates 8, 30 and 90 mg/kg/day respectively.

INFORMATION SUBMITTED:

1. A table of histological findings summarized for both male and female mice over the length of the study.(excerpted).

2. A table of historical control data which was derived from studies completed from 3-5 years prior to the start of the present mouse study.

3. A table of cumulative mortality for the 23 months of the study.

4. A table of total food consumption in the study.

5. A table of hematological data for the study animal groups at weeks 51 to 52 of study.

6. A table of liver weight data for the study animal groups at sacrifice.

7. A table of non-neoplastic liver changes for male mice on study.

8. A table of summary information as an overview of mutagenicity study results for the chemical.

COMMENTS ON THE ABOVE DATA TABLES:

1. Total hepatic neoplasms are statistically significantly increased* in male mice at both 200 and 600 ppm of imazalil in the diets for 23 months. Incidences are 2 fold greater than the highest values found in the historical data submitted. Additionally, the hepatocytic carcinoma incidence is elevated above controls (both historical and concurrent) and suggests a progression from neoplastic nodules to carcinomas in the study males. On the other hand, female mice while showing a statistically significant increase in the incidence of total hepatic neoplasms and an increase in hepatic nodules at 600 ppm, do not show a significant increase in hepatic carcinomas.

2. Historical control data only represent older time frames than the actual dates of this study and are somewhat limited in that the data do not encompass the time frame of the study in question.

* Significant by one-tailed Chi-square test.

3. The table of cumulative mortality does not provide sufficient data to indicate that the chemical may or may not have caused an early demise in the test animals. Only a slight increase in total mortality is noted in the females by 23 months (32/50 at 600 ppm vs. 27/50 in the control group).

4. Total food consumption as presented in the table indicates that the test animals consumed from about 10 to 20% more diet than controls. However, the registrant suggests that wastage was the reason for the apparent increased feed consumptions and not real intake of the feed. Data presented here do not allow a further evaluation of this point.

5. Hematological data for weeks 51-52 indicate that at the highest 2 doses (200 and 600 ppm) increases were noted in their hematocrit, hemoglobin and red cell values. However, the registrant indicates that those values, though significantly different from controls at 52 weeks, were comparable to the controls at the end of the study. Data do not allow for a further evaluation of this point.

6. Liver weight data indicate that absolute and relative weights were increased in males at 600 ppm while only relative weight was increased (not significantly) at 200 ppm. Data for the female liver weights indicated that only at 600 ppm was there an effect of liver enlargement.

7. Non-neoplastic liver changes were evident in male mice at 200 and 600 ppm in the form of increased incidences of focal cellular changes, large vacuoles, and swollen sinusoidal cells (200 ppm) with increased pigmentation in sinusoidal cells at the highest dose. Females were reported by the registrant to show these histological liver changes at 600 ppm.

8. The registrant provided a summary of mutagenicity studies which in most cases had been submitted to the agency for review and suggested that the studies with Imazalil did not show any mutagenic potential.

9. The above summary tables are appended to this document.

10. Conclusion: The data in preliminary manner indicates that mice treated with Imazalil by the dietary route for 23 months produce liver neoplasms which appear to progress to carcinomas in males. Neoplastic changes were also reported for female mice at the highest dose.

5

RW 1067-98

Imazalil Tox Review

Page_____ is not included in this copy.

Pages 6 through 17 are not included.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product impurities.

_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

X FIFRA registration data.

_____ The document is a duplicate of page(s) _____.

_____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.
