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

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

**MEMORANDUM:**

**SUBJECT:** Review of Supplemental information to MRID # 42085201, a repeated 21 day dermal toxicity study in New Zealand White Rabbits and the Supplemental information to MRID# 42012003, the General Metabolism Study of Imazalil in the rat.

Bar code D 197280
S 454461
Case 816389
(PC code) ID # 111901-043813
MRID # 43016802,
MRID # 43016803

**TO:** Kathleen DePukat
PM # 52
Reregistration Branch
SRRD (H7508W)

**FROM:** Henry Spencer, Ph.D.
Pharmacologist
Review Section 3
Toxicology Branch 1
Health Effects Division (H7509C)

Henry Spencer 10/12/94

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

K Hamernik 10/12/94 KB 10/14/94

**ACTION:** 1. Review the supplemental information contained in MRID #43016802 on a 21 day dermal toxicity study in rabbits submitted to support the upgrading of the study.

2. Review the supplemental information contained in MRID # 43016803 on a general metabolism study in the rat submitted to support the upgrading of the study.

**RESULTS AND CONCLUSIONS:**

1. The 21 day dermal toxicity study in rabbits is up graded to core: minimum. The issues raised in the review and justification of dosing levels have been adequately addressed. The study fulfills GL 82-2.

2. The general metabolism study is up graded to core: minimum. The characterization of the 2 major metabolite fractions (3 and 4) has been adequately carried out and submitted. The study fulfills GL 85-1.

**EVALUATION:**

1. 21- Day Dermal toxicity study in New Zealand Rabbits.

Q-1. An issue of the justification for the use of sesame oil as a vehicle was raised.

A-1. The use of an oil rather than the use of water to suspend Imazalil was necessary because the chemical is insoluble in water. There was not considered to be a difference in the use of sesame oil or corn oil.
The issue has been adequately addressed.

Q-2. An issue concerning the number of measurements at each concentration level not being specified was raised.

A-2. The registrant noted that both a direct analysis and a second derivative analysis was conducted but only one time each for each concentration level.
The issue has been adequately addressed.

Q-3 An issue concerning the dose volume not being indicated was raised.

A-3. The dose was expressed in mg/kg/day. However, there was sufficient information in the DER to know that the dose volume was 2.0 ml/kg, ie. approx. 2 grams/kg, with the concentrations being 0%, 0.5%, 2.0% or 8% w/w. These values calculate out to be 0, 10, 40, and 160 mg/kg/day.
The issue has been adequately addressed.

Q-4. Information on the temperature and humidity was not provided in the study report.

A-4. An addendum to the study report was provided which shows the missing data.
The issue has been adequately addressed.

Q-5. An issue concerning how much of the area of the skin surface was exposed in the study was raised.

A-5. The registrant has indicated that not less than 10% of the body surface was used for exposure to the test material.
This issue has been adequately addressed.

Q-6. An issue of the time before and during the study at which the animals may have been shaved.

A-6. The registrant has indicated that the test animals were shaved approximately 24 hours prior to testing. Further shavings were made as needed (1-2 times) in a week during the study.
This issue has been adequately addressed.

Q-7. A question was raised whether the animals were fasted over night prior to blood samples being taken.

A-7. The registrant indicated that the animals were not fasted over night prior to blood sampling.
This question has been adequately addressed. The lack of a fasted blood sample does not alter the out come of the study.

Q-8. The normal range of WBC values for this species of rabbit were not provided.

A-8. The normal range of the WBC values for this strain of rabbit were provided by the registrant.
However, additional data from Hazleton Labs, USA, indicate that the range of values for the rabbits in the study are within the values which would normally be seen in such a study.
This issue has been adequately addressed.

Q-9. The normal range of serum sodium values was not reported in the study.

A-9. The registrant submitted a table of normal values for the white rabbit used in the study. The values reported in the study are normal for both male and female sexes of that specie.
This issue has been adequately addressed.

Q-10. The reviewers questioned how the urine samples were collected.

A-10. The registrant provided information that the urine samples were obtained at the time of sacrifice.
This question has been adequately addressed.

Q-11. A question was raised on the justification of the dose selection used in the study.

dose selection used in the study.

A-11. The registrant submitted a report: Dermal Irritation Study in New Zealand White Rabbits- Dose Range Finding Study (R23979), Experiment No. 2418 Janssen Pharmaceutica.

Two rabbits were used in each dose: 0, 63, 250, and 1000 mg/kg. Results indicated that clinical observations, skin irritation, fissuring, necrosis, scaling were essentially non existent in the controls and 63 mg/kg group. Significant fissuring, and scaling at the top two dose levels was reported. In addition, swollen livers were also reported in the highest two dosed groups.

This study was only 6 days long and the study reported was to 21 days. The Toxicology Branch 1 considers the highest test dose of 160 mg/kg to be appropriate.
The question of dose selection justification is adequately addressed.

The individual issues enumerated above have been adequately addressed to the extent that the 21 day dermal toxicity study in rabbits is up graded to core: minimum.

Study : General Metabolism of Imazalil in the Rat Report No. R 23979/FK1116, MRID No. 42012003.

This study was reviewed and found to be lacking the identification of 2 major urinary metabolites. The study was graded as core: supplementary. The registrant has submitted further identification data on these two metabolites. These data are listed in MRID No. 43016803.

1. Metabolite 3 consists of 2 metabolite subgroups, 3A and 3B.
   a. metabolite 3A, MS 5 fraction was determined to be carboxylic acid form as 3-[1-(2,4-dichlorophenyl) -2-(1H-imidazol-1-yl)ethoxy]-2-hydroxypropanoic acid.

   b. metabolite 3B, composed of 2 HPLC fractions MS 6 and MS 7, is an alanine conjugate of a carboxylic acid metabolite of metabolite 3A or metabolite 4;

2. Metabolite 4 is composed of 2 HPLC fractions: MS 8 and MS 9, both carboxylic acid forms and equivalent to MS 5 above.

MS 5 fraction is identified as 3-[1-(2,4-

dichlorophenyl)-2-(1H-imidazol-1-yl)ethoxy]-2-hydroxypropanoic acid and is probably a diastereomer of metabolite 3A.

The proposed metabolic pathway which was omitted in the original study report has been submitted and is attached for reference.

The question of characterization of the 2 major Metabolites 3 and 4 has been adequately addressed. The study is therefore up graded to Core: Minimum.

RIN 1067-98

Imazalil Tox Review

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Pages _____ through _____ are not included.

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