



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

003769

APR 20 1984

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: PP#4G3017 - Imazalil Temporary Tolerance Petition
CASWELL No. 497AB.

TO: Mr. Henry Jacoby, PM #21
Fungicide-Herbicides Branch/RD (TS-767)

THRU: R. Bruce Jaeger, Section Head
Review Section #1
Toxicology Branch/HED (TS-769)

FROM: Carlos A. Rodriguez
Review Section #1
Toxicology Branch/HED (TS-769)

car 4/12/84
for CC-763 4/20/84

Registrant:

Janssen Pharmaceutica
40 Kingsbridge Road
Piscataway, New Jersey 08854

Action:

Janssen Pharmaceutica proposes the following temporary tolerances be established for the combined residues of imazalil 1-[2-(2,4-dichlorophenyl)-2-(2-propenyloxy)ethyl]-1H-imidazole and its metabolite 1-[2,4-dichlorophenyl]-2-(1H-imidazole-1-yl)-1-ethanol in/on fruiting vegetables as follows:

<u>Crop Group</u>	<u>Proposed Tolerance</u>	<u>Application</u>
Fruiting Vegetables (Cucurbits)	10 ppm	Pre and Post-Harvest
Fruiting Vegetables (Except Cucurbits)	10 ppm	Postharvest

Conclusion:

The theoretical maximum residue contribution (TMRC) from published and unpublished, TOX approved tolerances for a 1.5 kg diet is calculated to be 0.5966 mg/day. The current action will increase the TMRC by 0.8753 mg/day (146.7%). The current action will utilize an additional 116.71 per cent of the ADI. The amount of Imazalil added to the human diet from the proposed uses will, in theory, significantly increase the dietary exposure.

For the following reasons, however, TOX Branch concludes that the temporary tolerances will not result in an unreasonable adverse effects:

- ° The EUP is limited in scope (time and amount).
- ° The toxicological effects of this chemical demonstrated in the 2 year dog and rat feeding studies are of a minor nature; decreased body weight in the dog, and increased liver weight in the rat at the LEL.
- ° The oncogenic studies in mice and rats are negative.
- ° There are no adverse reproductive or teratogenic effects.

Toxicology Branch recommends the Registrant consider means of reducing the tolerances levels if they intend to pursue permanent tolerances at some future time. They should reconsider the Good Agriculture Practices, such as application rate, pds. a.i. per acre, frequency of applications, etc.).

Review of Data submitted with this request:

1. Dermal Sensitization Study on Guinea Pigs with Imazalil Antifungal R23979, (Janssen Pharmaceutica N.V., Protocol No. 965, 4-3-80).

10 healthy male guinea pigs outbred Pirbright strain with initial age of 16 weeks and body weight ranges between 350-400g received the test substance intradermally as 68% w/w (1000 ppm dilution) to the closely clipped backs. The procedure consisted of an initial intradermal injection of 0.05 ml followed after 2 days by an injection of 0.01 ml of the test substance (induction period) three times weekly on alternate days (Monday, Wed. and Friday) for three consecutive weeks, so that a total of 10 treatments is administered. The injections were given in a different location for back treatment. A control group of 10 male guinea pigs (same strain, age and weight as above) received intradermally arachid oil (1000 ppm dilution) in the same manner as the

treated group. Two weeks after the last sensitizing injection the control group and the treated groups were challenged with 0.1 ml of the test substance. (Method use: Maurer et al., 1975 Technique).*

Results: (Laboratory Report)

The mean reaction representing the skin irritation "threshold" for each individual animal was calculated after 4 injections. Any challenge reaction greater than the threshold value during the induction period was considered an allergic reaction.

No challenge reaction in either the control group or in the treated group was greater than the threshold value in the induction period.

Conclusion:

Imazalil failed to produce any sensitizing or allergic reaction to the guinea pigs in this type of test.

*Maurer T., et al., "The Optimization Test in the Guinea - Pig: A Method for the Predictive Evaluation of the Contact Allergenicity of Chemicals". Proc. Eur. Soc. Tox. 1976, 17, P. 203-208.

Classification: Core Minimum Study.

2. Toxicity data considered in setting the requested temporary tolerances:
 - ° Rat oral LD₅₀ - 320 mg/kg
 - ° 2 year chronic feeding (rat)
 - NOEL = 3 mg/kg (male)
 - LEL = 12.1 mg/kg (male)
 - NOEL = 3.8 mg/kg (female)
 - LEL = 14.7 mg/kg (female)
 - (liver weight increase)
 - ° 2 year feeding (dog)
 - NOEL = 1.25 mg/kg
 - LEL = 5 mg/kg
 - (decreased body weight gain)
 - ° Oncogenicity (rat)
 - NOEL = 40 mg/kg (HDT)

- Oncogenic (mouse)
NOEL = 40 mg/kg (HDT)
 - 3-generation reproduction (rat)
NOEL = 40 mg/kg (HDT)
 - Teratology (rat)
NOEL = 40 mg/kg (HDT)
 - Mutagenicity (dominant lethal) - (mouse) Negative
at 160 mg/kg (HDT)
 - Metabolism (rat) - little tissue retention (80% excreted
within 48 hrs.)
3. No RPAR criteria have been exceeded and no regulatory
actions are pending against the pesticide. . . -
4. Data gaps: Teratology, 2nd species.

Evaluation of the ADI:

The acceptable daily intake (ADI), based on the dog feeding study (NOEL 1.250 mg/kg/day) and using a 100-fold safety factor, is calculated to be 0.0125 mg/kg/day. The maximum permitted intake (MPI) for a 60 kg human is calculated to be 0.7500 mg/day. The theoretical maximum residue contribution (TMRC) from existing tolerances for a 1.5 kg diet is calculated to be 0.5966 mg/day. The current action will increase the TMRC by 0.8753 mg/day (146.7%) and utilize an additional 116.71 per cent of the ADI. Please, refer to the enclosed printout.

Attachment

TS-769:RODRIGUEZ:sll:X73710:4/12/84 card 4

File last updated 2/15/84

ACCEPTABLE DAILY INTAKE DATA

Dog	NOEL	S.F.	ADI	MPI
mg/kg	ppm		mg/kg/day	mg/day(60kg)
1.250	50.00	100	0.0125	0.7500

Published Tolerances

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Bananas(7)	0.200	1.42	0.00426
Citrus Fruits(33)	10.000	3.81	0.57179
<u>Citrus</u> (214)	25.000	0.03	0.01125
Meat, red(90)	0.010	10.81	0.00162
Liver(211)	0.500	0.03	0.00023
Milk&Dairy Products(93)	0.010	28.62	0.00429

MPI	TMRC	% ADI
0.7500 mg/day(60kg)	0.5934 mg/day(1.5kg)	79.13

Unpublished,Tox Approved 2F2651

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Cottonseed (oil)(41)	0.020	0.15	0.00004
Barley(8)	0.020	0.03	0.00001
Wheat(170)	0.020	10.36	0.00311

MPI	TMRC	% ADI
0.7500 mg/day(60kg)	0.5966 mg/day(1.5kg)	79.55

Current Action 4G3017

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Cucurbits(49)	10.000	2.84	0.42616
Fruiting Vegetables(60)	10.000	2.99	0.44916

MPI	TMRC	% ADI
0.7500 mg/day(60kg)	1.4719 mg/day(1.5kg)	196.26

DRAFT