RCB 1-4-85

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

JAN 4 1985

004182

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Ronilan Fungicide (Vinclozolin) - Amendment of PP#4E2998. CASWELL No. 323C

TO: Henry Jacoby, PM #21
Fungicide-Herbicide Branch
Registration Division (TS-767C)

FROM: Carlos A. Rodriguez C.A. Rodriguez 1/4/85
Review Section #6
Toxicology Branch/HED (TS-769)

THRU: Jane E. Harris, Ph.D., Section Head J.E. Harris 1/4/85
Review Section #6
Toxicology Branch/HED (TS-769)

Applicant: BASF Wyandotte Corporation
100 Cherry Hill Road
P.O. Box 181
Parsippany, N.J. 07054

Action Requested:

Established tolerance for residues of the fungicide Ronilan (vinclozolin), 3-(3-5-dichlorophenyl)-5-ethenyl-5-methyl-2, 4-oxazolidinedione and its metabolites 3,5-dichloroaniline moiety in/on peppers at 3.0 ppm.

Evaluation:

The 6-Month Dog Feeding Study with Ronilan (vinclozolin) showed an increased absolute and relative adrenal weight in both male and female dogs and decreased absolute kidney weight in male dogs at the dose level of 300 ppm (7.5 mg/kg/day). Based on these findings it appears that the dog is the more sensitive animal species to this compound. Therefore, Toxicology Branch recommends that the acceptable daily intake (ADI) should be based on the NOEL of 100 ppm (2.5 mg/kg/day) of the 6-month dog study rather than the two year rat NOEL of 486 ppm (24.3 mg/kg/day).

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It should be noted that the effects reported for the rat at the LEL of 1458 ppm, namely body weight reduction and reduced serum bilirubin, represent a less serious toxicological profile than the effects reported at the LEL of the 6-month dog study. (300 ppm)

Conclusions:

A review of the existing toxicity data base indicates that following risks from both the existing and proposed uses:

1. The onocogenic lifetime dietary risk for both published and unpublished Toxicology Branch approved uses is 4.5×10^{-5}.

2. The incremental oncogenic lifetime dietary risk for peppers at 3.0 ppm is 10.1×10^{-7}.

3. The oncogenic dietary risk for previously approved and currently considered tolerances is 4.6×10^{-5}.

4. The current pepper tolerance will produce an absolute increase of 0.00552 mg/day in the TMRC which will result in a 2.25% increase of the total TMRC of all previously approved tolerances.

5. The toxicity data (exclusive of oncogenicity) used to calculate the ADI of 0.025 mg/kg/day is based on the 6-month dog study with a NOEL of 100 ppm (2.5 mg/kg). An increased adrenal weights in both sexes and increased kidney weights in male dogs at 300 ppm (7.5 mg/kg) were observed.

6. All previously approved and currently considered tolerances occupy 16.72% of the ADI.

Summary of Selected Toxicology Data Considered in Setting the requested Tolerance.

a. Acute Oral LD_{50} (rat) = > 10,000 mg/kg (both sexes) Core-Classification: Minimum.

b. Acute Dermal LD_{50} (rat) = > 2,500 mg/kg (both sexes) Core-Classification: Minimum.

c. 90-Day Feeding Study (rat): NOEL = 450 ppm (22.2 mg/kg) highest dose level tested. Levels tested: 0, 150 and 450 ppm. Core- Classification: Minimum.

d. 90-Day Feeding Study (Dog): NOEL = 300 ppm (7.5 mg/kg/day). LEL = 1,000 ppm (25 mg/kg/day) increased platelet count, Howell-Jolly bodies in differential blood counts, cholestasia of liver, fatty deposits in renal tubules, cholestasia of kidneys. Levels tested: 0, 100, 300, 1000 and 2000 ppm. Core-Classification: Supplementary Study.

e. 6-Month Feeding Study (Dog): NOEL = 100 ppm (2.5 mg/kg/day). LEL = 300 ppm (7.5 mg/kg/day) increased absolute and relative adrenal weight (M/F); decreased absolute kidney weight (M). Levels tested: 0, 100, 300, 600 and 2000 ppm. Core-Classification: Minimum.

f. Mouse Teratology - Teratology NOEL = 6000 ppm (900 mg/kg/day) highest dose level tested. Maternal NOEL = 6000 ppm (900 mg/kg/day) highest dose level tested. Fetotoxic LEL 6000 ppm (900 mg/kg/day) - resorptions (highest dose level tested).

Levels tested: 0, 600 and 6000 ppm. Core-Classification: Minimum.

g. Rabbit Teratology - Teratogenic potential is not indicated in this study.

Maternal NOEL = > 300 mg/kg/day (900 ppm)
Fetotoxic NOEL = 80 mg/kg/day (2640 ppm)
Fetotoxic LEL = 300 mg/kg/day (9,900 ppm) - weight loss, post inplantation loss.
Levels tested: 0, 20, 80 and 300 mg/kg/day.
Core Classification: Minimum.

h. Mutagenic-host-mediated assay - In-vivo reverse mutation using T. typhimirium G46 was negative. There was no increase in mutation frequency in vinclozolin treated groups. Core-Classification: Acceptable.

i. Dominant Lethal Assay in Mice: Negative at 2000 mg/kg, only level tested.

j. 3-Generation Rat Reproduction: NOEL = 1458 ppm (72.9 mg/kg/day) - highest dose level tested.

k. Chronic Feeding/Oncogenicity Study in rats for 103 weeks: NOEL = 486 ppm (24.3 mg/kg)
LEL = 1458 ppm (72.9 mg/kg) body weight reduction, reduced serum bilirubin.
Oncogenic NOEL = > 4374 ppm (219 mg/kg) highest dose level tested.
Levels tested: 162, 486, 1458 and 4374 ppm.

l. 26-Month feeding/onco study (NMRI strain mice).
Systemic NOEL = 486 ppm (72.9 mg/kg)
Systemic LEL = 1458 ppm (218.7 mg/kg) decreased body weight in males.

Oncogenicity

1. An increase in leukemia/lymphoma was observed in males. However historical control data on this type of tumor equalled or exceeded the level observed in this study, indicating that the increase may not be real. (Accession No. 248264; Review dated May 5, 1983).

2. An apparent dose related increase in lung adenoma was noted in females. Historical data from 5 studies using the same strain (NMRI) indicated that in 4 of 5 studies the historical control incidence was significantly lower than that observed in the treated groups of this study. Along with considerations of the benign nature of the tumor and because latency did not decrease, it is concluded that the chemical is weakly positive in the production of lung tumors.

3. A low incidence of production of liver adenoma was observed in 3/50 male mice receiving vinclozolin at the high dose tested (4374 ppm) when compared with the control group 0/50 (0%). Based upon the findings that: the tumors were benign and occurred only at the highest dose in males, and the historical control data from this laboratory showed incidences of liver adenoma in males of 2 to 3% which are not significantly different from that observed in the vinclozolin-treated animals, and that a decrease in the latency of tumor appearance did not occur as a result of the treatment, we conclude that vinclozolin may be at most a weak and questionable oncogen for liver tumors in the NMRI strain of mice.

As indicated above (Summary of Tox. Data) the oncogenic potential of vinclozolin for lung adenomas is negative in the rat and weakly positive in the mouse. See "Assessment of Complete Oncogenicity Data", Accession #248267, review dated May 5, 1983. To obtain estimates of virtually safe dose relative to this action, a risk assessment was performed considering the mouse oncogenicity study for lung adenomas.

Toxicology Branch statistician Bert Litt performed a mutistage risk analysis for lung adenomas; and Q* value (lifetime dietary risk factor) of 0.0108 (or 1.1×10^{-2}) was obtained.

The lifetime dietary risk for previously approved uses (published and unpublished Toxicology Branch approved) is calculated using the total TMRC for the previously approved uses:

$$\frac{0.2452}{60} \times 1.1 \times 10^{-2} \text{ (mg/kg/day)} = 4.5 \times 10^{-5}$$

Using the TMRC for peppers, the lifetime dietary risk is:

$$\frac{0.00552}{60} \times 1.1 \times 10^{-2} \text{ (mg/kg/day)} = 10.1 \times 10^{-7}$$

The lifetime dietary risk for previously approved uses (published and unpublished Toxicology Branch approved) plus current action on peppers is calculated as follows:

$$\frac{0.2507}{60} \times 1.1 \times 10^{-2} \text{ (mg/kg/day)} = 4.6 \times 10^{-5}$$

m) Metabolism study (rat): Dosing at 40 mg/kg for 7 days. Six days after final dose - 47% eliminated in the urine; 52.8% eliminated in the feces; 0.7% retained in the gastrointestinal tract, 0.4% retained in liver. Core-Classification: Minimum.

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Evaluation of the ADI:

The acceptable daily intake (ADI) based on the 6-month dog feeding study (NOEL 100 ppm or 2.5 mg/kg) and using a 100-fold safety factor, is calculated to be 0.0250 mg/kg/day. The maximum permitted intake (MPI) for a 60 kg human is calculated to be 1.5 mg/day. The theoretical maximum residue contribution (TMRC) from existing tolerances for a 1.5 kg diet is calculated to be 0.2452 mg/day. The current action will increase the TMRC by 0.0055 mg/day (2.24%) and utilize an additional 0.37% of the ADI. Please, refer to the attached printout.

Attachment

TS-769:RODRIGUEZ:sll:x73710:12/6/84 Card Mis. 1

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CFR 180.380 Ronilan 11/28/84

File last updated 4/24/84

C.A. not needed

ACCEPTABLE DAILY INTAKE DATA

Dog mg/kg	NOEL ppm	S.F.	ADI mg/kg/day	MPI mg/day(60kg)
2.500	100.00	100	0.0250	1.5000

Noel change not rec.

DRAFT

Published Tolerances

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Kiwi Fruit(204)	10.000	0.03	0.00450
Strawberries(152)	10.000	0.18	0.02759
Lettuce(84)	10.000	1.31	0.19622

MPI	TMRC	% ADI
1.5000 mg/day(60kg)	0.2283 mg/day(1.5kg)	15.22

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Unpublished, Tox Approved 3F2934

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Lettuce(84)	0.000	1.31	0.00000
Onions(105)	1.000	0.83	0.01242
Raspberries(135)	10.000	0.03	0.00450

MPI	TMRC	% ADI
1.5000 mg/day(60kg)	0.2452 mg/day(1.5kg)	16.35

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Current Action 4E2998

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Peppers(120)	3.000	0.12	0.00552

MPI	TMRC	% ADI
1.5000 mg/day(60kg)	0.2507 mg/day(1.5kg)	16.72

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