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

MEMORANDUM AUG - 3 1982

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

TO: Henry Jacoby (21)
Registration Division (TS-767)

THRU: Orville E. Paynter, Chief
Toxicology Branch
Hazard Evaluation Division (TS-769)

SUBJECT: Vinclozolin (RONILAN), Revision of Section F to provide a tolerance of 10 ppm in head lettuce with a 28-day PHI. EPA Reg. No. 7969-53; PP#2F2595

Recommendations:

1) The ADI would be increased by only 0.68% by doubling the residue tolerance for lettuce. We believe the added increase in the ADI would be toxicologically insignificant and acceptable. Therefore, Toxicology Branch believes the increased tolerance in lettuce can be toxicologically supported.

2) A one-year dog feeding study is required.

The registrant proposes revising PP#2F2595 to provide a tolerance of 10 ppm for residues of vinclozolin in head lettuce. A Tox approved, unpublished temporary tolerance of 5 ppm currently exists.

Published tolerances exist for kiwi fruit and strawberries at 10 ppm under 40 CFR 180.380.

Unpublished Toxicology Branch approved tolerances also exist for the following:

Grapes, not raisins ---------- 6 ppm

Peaches ---------- 4 ppm

Cherries ---------- 4 ppm

Plums, not prunes ---------- 1 ppm

Toxicology Branch Considerations:

1. No new toxicity data were submitted.

2. Studies Conducted with Formulation: Ronilan (Review of PP#8G2068 by Roland A. Gessert, 4/17/78).

a) Rat Acute Oral $LD_{50}$ > 16,000 mg/kg (both sexes)

b) Rabbit Acute Dermal $LD_{50}$ > 2000 mg/kg (both sexes)

c) Rat Acute Inhalation $LD_{50}$ > 1.7 mg/L for 4 hours

3. Studies Conducted with Technical Chemical.

a) Rat Acute Oral $LD_{50}$ > 10,000 mg/kg (both sexes)

b) Acute Dermal $LD_{50}$ > 2500 mg/kg (both sexes)

c) 90-Day Rat Feeding: NOEL = 450 ppm

d) 90-Day Dog Feeding: NOEL = 300 ppm

e) Mouse Teratology: Negative at 600 ppm

f) 3-Generation Rat Reproduction: NOEL = 1458 ppm

g) Dominant Lethal Assay in Mice: Negative at 2000 mg/kg for five days.

h) Chronic Feeding/Oncogenicity in Rats for 103 Weeks: Oncogenic potential: negative; NOEL = 486 ppm

i) Chronic Feeding/Oncogenicity in Mice for 26 Months: NOEL = 1458 ppm. Oncogenic potential: Possibly positive for leukemia in males at 4374 ppm. Histological data requested at low and mid dose levels.

j) Metabolism: Repeated oral dosing in rats.

4. Evaluation of the provisional ADI (PADI).

The dog is the most sensitive species for which feeding toxicity data are available. Chronic or subchronic feeding studies are as follows:

| | |
|---|---|
| 90-day dog | NOEL = 300 ppm, or 7.5 mg/kg/day |
| 90-day rat | NOEL = 450 ppm, or 45.0 mg/kg/day |
| Chronic rat | NOEL = 486 ppm, or 24.3 mg/kg/day |
| Chronic mouse | NOEL = 1458 ppm, or 218.7 mg/kg/day |

Previous tolerances were based on the 90-day dog feeding study. Since we have chronic rat and mouse studies completed, the tolerances should be based on one of these studies. In these studies the rat is the more sensitive species (NOEL 486 ppm, or 24.3 mg/kg).

Based on the NOEL of 24.3 mg/day from the rat data and a safety factor of 100, the ADI is 0.2430 mg/kg/day and the maximum permissable intake is 14.58 mg/day for a 60 kg person.

Currently published and Toxicology Branch approved tolerances provide a theoretical maximum residue contribution of 0.2321 mg/day, or 1.59% of the acceptable daily intake (ADI).

Increasing the tolerance on lettuce from 5 ppm to 10 ppm would provide an additional theoretical residue contribution of 0.0981 mg/day to the diet, for a total TMRC of 0.3303 mg/day, or 2.27% of the ADI. This represents an additional 0.68% of the ADI.

Two months ago the registrant was informed that re-evaluation of data from the mouse oncogenicity study of vinclozolin raised suspicions that vinclozolin at 4374 ppm may cause leukemia type tumors in male mice, and we requested that tissues from the mid and low dose mice also be subjected to histopathological evaluation and that a report of the evaluation be submitted. We also recognized that this type tumor is not rare in the mouse and purportedly the registrant has agreed to submit historical data on the test mice.

Roland A. Gessert 7/30/82

Roland A. Gessert, D.V.M.
Toxicology Branch
Hazard Evaluation Division (TS-769) 8/2/82

TS-769:th:TOX/HED:RAGessert:7-28-82:card 3

CFR 180.350 Acmilan 7/28/82

NOEL change not recorded per

File last updated 7/8/82

ACCEPTABLE DAILY INTAKE DATA

| RAT,Older mg/kg | NOEL ppm | S.F. | ADI mg/kg/day | MPI mg/day(60kg) |
|---|---|---|---|---|
| 24.300 | 486.00 | 100 | 0.2430 | 14.5800 |

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 |

| MPI | TMRC | % ADI |
|---|---|---|
| 14.5800 mg/day(60kg) | 0.0321 mg/day(1.5kg) | 0.22 |

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Unpublished,Tox Approved 1E2457,2F2595,9G2204,2F2650

| CROP | Tolerance | Food Factor | mg/day(1.5kg) |
|---|---|---|---|
| Lettuce( 84) | 5.000 | 1.31 | 0.09811 |
| Grapes, not raisins( 67) | 6.000 | 0.45 | 0.04047 |
| Peaches(114) | 0.000 | 0.90 | 0.00000 |
| Lettuce( 84) | 0.000 | 1.31 | 0.00000 |
| Cherries( 30) | 0.000 | 0.10 | 0.00000 |
| Plums,not prunes(124) | 0.000 | 0.09 | 0.00000 |
| Peaches(114) | 4.000 | 0.90 | 0.05396 |
| Cherries( 30) | 4.000 | 0.10 | 0.00613 |
| Plums,not prunes(124) | 1.000 | 0.09 | 0.00138 |

| MPI | TMRC | % ADI |
|---|---|---|
| 14.5800 mg/day(60kg) | 0.1321 mg/day(1.5kg) | 1.59 |

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Current Action 2F2595

| CROP | Tolerance | Food Factor | mg/day(1.5kg) |
|---|---|---|---|
| Lettuce( 84) | 5.000 | 1.31 | 0.09811 |

| MPI | TMRC | % ADI |
|---|---|---|
| 14.5800 mg/day(60kg) | 0.3303 mg/day(1.5kg) | 2.27 |

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