



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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

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

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

SUBJECT: Vinclozolin (RONILAN), PP#3F2934. EPA Reg. No. 7969-53.
Petition for tolerances and registration of vinclozolin
in leaf lettuce, onions, and raspberries.
Accession 071761. CASWELL 323C.

Dir. Jacoby 12-12-83
W/B 12/14/83
File petition

Petitioner: BASF Wyandotte Corporation
100 Cherry Hill Road
Parsippany, New Jersey 07054

Action Requested:

The applicant requests establishment of tolerances of 10 ppm for residues of vinclozolin in leaf lettuce, onions, and raspberries. Additional residue data are submitted to support the petition.

Published tolerances at 10 ppm currently exist for kiwi fruit, strawberries, and lettuce under 40 CFR 180.380. The tolerance in lettuce is for both head lettuce and leaf lettuce since these are not separated in the Toxicology Branch consumption data files. However, since previous residue data were provided for head lettuce only, Residue Chemistry Branch had recommended against labeling for use on leaf lettuce. Leaf lettuce residue data are provided in the current submission and support a 10 ppm tolerance in leaf lettuce also. From the standpoint of Toxicology Branch the label restriction against leaf lettuce may therefore be removed.

Previously Reviewed Toxicity Data:

Memo of 4/17/78 from R. Gessert; PP#8G2068.

1. Studies Conducted with Formulation, RONILAN:

- a) Rat Acute Oral LD₅₀ > 16,000 mg/kg (both sexes)
- b) Rabbit Acute Dermal LD₅₀ > 2,000 mg/kg (both sexes)
- c) Rat Acute Inhalation LC₅₀ > 1.7 mg/L for 4 hours

2. Studies Conducted with Technical Chemical:

- a) Rat Acute Oral LD₅₀ > 10,000 mg/kg (both sexes)
- b) Acute Dermal LD₅₀ > 2,500 mg/kg (both sexes)
- c) 90-Day Rat Feeding: NOEL = 450 ppm (22.5 mg/kg/day)
- d) 90-Day Dog Feeding: NOEL = 300 ppm (7.5 mg/kg/day)
- e) Mouse Teratology: Negative at 600 ppm (90 mg/kg/day)
- f) 3-Generation Rat Reproduction: NOEL = 1458 ppm
(72.9 mg/kg/day)
- g) Dominant Lethal Assay in Mice: Negative at 2000 mg/kg
- h) Chronic Feeding/Oncogenicity in Rats for 103 Weeks:
NOEL = 486 ppm (24.3 mg/kg); Oncogenic potential:
Negative
- i) Chronic Feeding/Oncogenicity in NMRI Mice for 26 Months:
Possibly weakly positive for benign lung tumors.
(Lung tumors in females: 1 at 162 ppm; 1 at 486 ppm;
4 at 1458 ppm; 5 at 4374 ppm)
- j) Metabolism: Repeated oral dosing in rats. 93% excreted
within 24 hours in urine and feces. After final
dose, levels declined with half-life of about 20
hours.

3. Further assessment of mouse oncogenicity data raised possible questions relating to leukemia/lymphoma, lung adenomas, and liver adenomas/hepatomas. Detailed appraisal of data of mice at all dosage levels together with data from control mice in 5 other studies conducted concurrently in the same laboratory under the same conditions and in the same mouse strain and in other studies reported in the literature, revealed an incidence of leukemia/lymphoma in the historical controls which equaled or exceeded the incidence seen in the vinclozolin study. These data indicate that vinclozolin presents no oncogenic risk for leukemia/lymphoma. (See "Assessment of Complete Mouse Oncogenicity Data. Accession #248,264." Review dated May 5, 1983).

Mutagenicity:

A dominant lethal study originally submitted for vinclozolin was found negative. Other studies recently submitted in response to our request include:

In Vivo Sister Chromatid Exchange in Chinese Hamster - Negative. (See Mutagenicity and Cytogenetic Data Review. Accessions 250,113 and 250,114; 8/23/83.)

Rec-Assay (DNA Repair) - Negative. However, registrant was requested to repeat study because it was not conducted in a satisfactory manner. (See Mutagenicity and Cytogenetic Data Review. Accessions 250,113 and 250,114; 8/23/83).

Reverse mutation, with and without metabolic activation. (Ames Salmonella Plate Test and Host Mediated Assay) - Negative. (See Mutagenicity and Cytogenetic Data Review. Accessions 250,113 and 250,114; 8/23/83).

The literature (Georgopoulos, et al.) also summarizes a study in which vinclozolin increases the frequency of mitotic recombination in diploid colonies of Aspergillus nidulans. This study is noted but cannot be evaluated in the absence of the complete protocol and data.

As indicated above, 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 # 248,264, review dated May 5, 1983. To obtain estimates of virtually safe dose levels relative to this action, a risk assessment was performed considering the mouse oncogenicity study as positive for lung adenomas.

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

Subjecting the TMRC for onions to this value:

$$\frac{0.12417}{60} \times 1.1 \times 10^{-2} \text{ (mg/kg/day)} = 2.3 \times 10^{-5}$$

additional increment of lifetime dietary risk from onions

Subjecting the TMRC for raspberries to the Q^* value:

$$\frac{0.00450}{60} \times 1.1 \times 10^{-2} \text{ (mg/kg/day)}^{-1} = 8.3 \times 10^{-7}$$

additional increment of lifetime dietary risk from raspberries

Combining the TMRCs of onions and raspberries, 0.12417 mg/day + 0.00450 mg/day = 0.12867 mg/day.

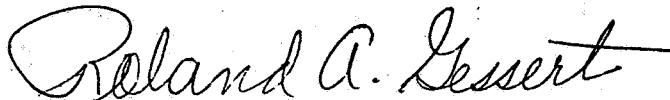
Subjecting the combined TMRCs of onions and raspberries to the Q* value,

$$\frac{0.12867}{60} \times 1.1 \times 10^{-2} \text{ (mg/kg/day)} = 2.4 \times 10^{-5}$$

The animal bioassay data indicate that EPA can be 95% certain that the average lifetime increment of cancer risk attributable to Vincolzin, from eating onions and raspberries will not exceed 2.4×10^{-5} per person.

The total TMRC for these new uses plus previously approved uses is 0.3570 mg/day. The new uses will result in an increased increment of 0.1287 mg/day, an increase of 56% over the previous daily intake. However, the new total TMRC will constitute only 2.45% of the acceptable daily intake.

Computer printout is attached.



Roland A. Gessert, D.V.M.
Review Section #1
Toxicology Branch/HED (TS-769)

TS-769:GESSERT:s11:X73710:11/16/83 card 5

File last updated 4/19/83

ACCEPTABLE DAILY INTAKE DATA

RAT, Older	NOEL	S.F.	ADI	MPI
mg/kg	ppm		mg/kg/day	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
Lettuce (84)	10.000	1.31	0.19622

MPI	TMRC	% ADI
14.5800 mg/day (60kg)	0.2283 mg/day (1.5kg)	1.57

Current Action 3F2934

CROP	Tolerance	Food Factor	mg/day (1.5kg)
Lettuce (84)	0.000	1.31	0.00000
Onions (105)	10.000	0.83	0.12417
Raspberries (135)	10.000	0.03	0.00450

MPI	TMRC	% ADI
14.5800 mg/day (60kg)	0.3570 mg/day (1.5kg)	2.45

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