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RCB
4/15/83

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

Hammond
Anthony
file: PP#9G2204

MEMORANDUM APR 15 1983

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

TO: Henry Jacoby
Registration Division (TS-767)

THRU: William L. Burnam, Acting Chief
Toxicology Branch/HED (TS-769)

WLB

SUBJECT: Vinclozolin for Use on Stonefruit. Experimental Use Permit 7969-EUP-13. Temporary Tolerance PP#9G2204. CASWELL#323C

Action Requested:

The petitioner requests an experimental use permit for 14,616 pounds of RONILAN Fungicide 50-W, equivalent to 7,308 pounds active ingredient vinclozolin, to be used on stonefruit (apricots, cherries, nectarines, peaches, plums, and fresh prunes).

The petitioner also requests temporary tolerances of 25 ppm for residues of vinclozolin 3-(3,5-dichlorophenyl)-5,ethenyl-5-methyl-2,4-oxazolidinedione and its dichloroaniline-containing metabolites in or on the raw agricultural commodities, the aforementioned stonefruit.

Recommendation:

The oncogenic potential of vinclozolin is negative in the rat and may be questionable in the mouse. To obtain estimates of virtually safe dose levels relative to this action, a risk assessment was performed tentatively considering the mouse oncogenicity study as positive for lung tumors.

The NOEL for reproductive effects is negative in the rat at 1458 ppm. The teratogenic NOEL is 600 ppm in the mouse. Vinclozolin is not on the RPAR list.

The lifetime dietary risk is based upon findings of lung adenomas in NMRI mice at a dietary level of 1458 ppm. The multi-stage model provided a Q^* of 0.011 $(mg/kg/day)^{-1}$. The lifetime risk for existing tolerances is 4.2×10^{-5}. The lifetime risk for stonefruits at a tolerance level of 25 ppm is 8.57×10^{-5} or twice that of existing tolerances. This assumes that exposure is for a lifetime and 100% of the crop is treated. Since exposure is only for a couple of years, the risks would be proportionately less ($8.57 \times 10^{-5} \times \frac{2}{70} = 2.45 \times 10^{-6}$). Since the EUP is for 7,308 pounds which would treated approximately 1000 acres, the per cent of crop is considerably less than 100%.

Discussion:

Lung Tumor and Liver Tumor data from the vinclozolin mouse oncogenicity study are shown below:

Group	No. Animals	% Lung Adenomas	% Lung Carcin.	% Lung Tumors	% Liver Tumor
0 ppm	50M	4	4	8	0
	50F	0	0	0	0
162 ppm	50 M	2	2	4	0
	50 F	2	0	2	0
486 ppm	50 M	0	6	6	0
	50 F	2	0	2	0
1458 ppm	50 M	2	4	6	0
	50 F	8	0	8	0
4374 ppm	50 M	8	2	10	6
	50 F	10	0	10	0

Lung and Liver Tumor data from NMRI controls of 5 other studies of the same duration conducted in the same laboratory at about the same time are given below. In addition, control data from NMRI mice in studies published in the literature (Green, Henschler, Haase) are shown following the 5 studies conducted concurrently with the vinclozolin study.

HISTORICAL DATA FROM ONCO STUDIES OF NMRI MICE

Study	No. of Animals and Sex	% Lung Adenomas	% Lung Carcinomas	% Lung Tumors	% Liver Tumors
I	100 M	15	5	20	2
	100 F	9	2	11	0
II	50 M	8	0	8	0
	50 F	4	0	4	0
III	70 M	2.9	1.4	4.3	2.9
	70 F	5.7	0	5.7	1.4
IV	50 M	4	0	4	0
	50 F	0	0	0	0
V	50 M	2	0	2	0
	50 F	6	0	6	0
Green	14 M			50	0
	15 F			27	0
Henschler	30 M	3.3	16.7	20	6.7
	29 F	10.3	3.4	13.7	0
Haase	M & F	10			

Previously Reviewed Toxicity Data: Memo of 4/17/78 from R. Gessert. PP#8G2068.

1. Studies Conducted with Formulation, RONILAN:

   a) Rat Acute Oral LD_{50} > 16,000 mg/kg (both sexes)
   b) Rabbit Acute Dermal LD_{50} > 2,000 mg/kg (both sexes)
   c) Rat Acute Inhalation LD_{50} > 1.7 mg/L for 4 hours

2. Studies Conducted with Technical Chemical:

   a) Rat Acute Oral LD_{50} > 10,000 mg/kg (both sexes)
   b) Acute Dermal LD_{50} > 2,500 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
   h) Chronic Feeding/Oncogenicity in Rats for 103 Weeks:
      Oncogenic Potential: Negative; NOEL = 486 ppm
   i) Chronic Feeding/Oncogenicity in NMRI Mice for 26 Months:
      Questionable oncogenic potential for benign lung and liver tumors
   h) Metabolism: Repeated oral dosing in rats

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.

   Toxicology Branch statistician Bert Litt performed a multi-stage risk analysis for lung adenomas; a Q* value of 0.010762 (or 0.011) was obtained. Subjecting the TMRC of stonefruit (0.4676 mg/day/1.5 kg) to this value:

$$\frac{0.4676}{60} \times 0.011\ (\text{mg/kg/day})^{-1} = 0.0077933 \times 0.011 = 8.57 \times 10^{-5} =$$

lifetime dietary risk from stonefruit

   Applying the Q* value to the total TMRC for vinclozolin residue tolerances:

$$\frac{0.6959}{60} = 0.0115983;\ 0.0115983 \times 0.011 = 1.275 \times 10^{-4} = \text{total}$$

lifetime dietary risk, all commodities

   Risk assessments were not performed for applicators; no exposure data are currently available.

4. Chronic feeding studies have been completed in the rat and mouse. The ADI is based on the rat. (Rat NOEL is 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/kg/day for a 60 kg person.

5. Residue Chemistry Branch concludes that residues will not exceed the 25 ppm level requested in the tolerance petition. (William L. Anthony and Robert Hummel, oral communications 2/24/83; followed by memo). The 25 ppm residue level far exceeds the levels that actually will be expected to exist when additional data are provided. (William Anthony, oral communication, 3/30/83).

RCB Review States:

a) Residue data on cherries following 1-6 applications at rates ranging from 0.75-3 lb. active ingredient (AI) show residues ranging from 0.87 ppm to 14.8 ppm at a 0-day PHI.

b) Peaches, nectarines, and apricots: In 15 studies, following 1-12 applications at rates of 0.25-1 lb. AI/A, residues ranged from < 0.05-27.5 ppm. The highest residue reflects 9 applications (vs the proposed 7) at the 1 pound AI/A rate and a 1-day (vs the proposed 3-day) PHI.

c) Plums, fresh prunes: In 6 studies following 1-4 applications at the rate of 0.25-1 pound AI/A, residues at a PHI of 5 days or longer were all < 0.90 ppm.

6. Published tolerances established under 40 CFR 180.380 utilize 0.22% of the ADI. Unpublished Toxicology Branch approved tolerances utilize the ADI to 1.57%. The current stonefruits action will utilize the ADI to 4.77%. (Computer printout attached).

7. Only one mutagenicity study was submitted by the registrant; a dominant lethal assay in the mouse was negative at a level of 2000 mg/kg.

The published literature also presents data demonstrating the ability of vinclozolin to induce mitotic recombination (positive against Aspergillus nidulans in mitotic recombination test). No other mutagenicity data are known to exist.

A complete battery of mutagenicity data will be required prior to granting any new permanent tolerances.

Published References Cited:

U. Green, et al. Comparative Study of the Carcinogenic Effect of BHP and BAP on NMRI Mice. Cancer Letters, 9 (1980) 257-261.

D. Henschler, et al. Carcinogenicity Study of Trichloroethylene by Longterm Inhalation in Three Animal Species. Arch. Toxicol. 43, 237-248 (1980).

P. Haase, et al. Evaluation of Dimethylhydrazine Induced Tumours in Mice as a Model System for Colorectal Cancer. Br. J. Cancer (1973) 28, 530.

Spyros G. Georgopoulos, et al. Mitotic Instability in Aspergillus nidulans Caused by the Fungicides Iprodione, Procymidone and Vinclozolin. Pestic. Sci. 1979. 10, 389-392.

Roland A. Gessert LDC 4/14/83

Roland A. Gessert, D.V.M.
Veterinary Medical Officer
Toxicology Branch/HED (TS-769)

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ACCEPTABLE DAILY INTAKE DATA

RAT,Older NOEL mg/kg	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 2F2595

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Lettuce(84)	10.000	1.31	0.19622

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

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Current Action 2F2650

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Stone Fruits(151)	25.000	1.25	0.46755

MPI	TMRC	% ADI
14.5800 mg/day(60kg)	0.6959 mg/day(1.5kg)	4.77

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