4-27-82

CASWELL FILE

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

APR 27 1982 23 APR 1982

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

TO: Henry Jacoby (21)
Registration Division (TS-767)
and
Residue Chemistry Branch
Hazard Evaluation Division (TS-769)

SUBJECT: Metalaxyl; Ridomil 2E; EPA Reg.#100-607;
PP#1F2500/1H5299; Metalaxyl in/on various crops
Accession#070767-769 CASWELL#375AA

Recommendations:

1) The permanent tolerances can be toxicologically supported.

2) The 2-year rat feeding study is acceptable as Core-Minimum Data. The oncogenic potential is negative. The NOEL is 50 ppm.

3) The following studies are required to be submitted within a reasonable period of time:

a) mouse oncogenicity
b) mutagenicity - multi-test evidence

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Review:

1. Revised Section F

SECTION F

PROPOSED PESTICIDE TOLERANCES

PP#1F2500

The registrant hereby requests tolerances for combined residues of the fungicide, metalaxyl [N-(2,6-dimethylphenyl)-N-(methoxyacetyl) alanine methyl ester] and its metabolites containing the 2,6-dimethylaniline moiety, each expressed as metalaxyl, in or on the following raw agricultural commodities:

Green onions at 10.0 ppm
Tomatoes at 1.0 ppm
Dry bulb onions at 1.0 ppm
Kidney of cattle, goats, hogs, horses, poultry and sheep at 1.0 ppm
Cucumbers at 1.0 ppm
Potatoes at 0.5 ppm
Melons at 1.0 ppm
Liver of cattle, goats, hogs, horses, poultry and sheep at 0.3 ppm
Cottonseed at 0.1 ppm
Eggs and meat of poultry excluding liver and kidney at 0.05 ppm
Meat, fat, and meat by-products excluding liver and kidney at 0.05 ppm
Milk at 0.02 ppm

PROPOSED FOOD ADDITIVE TOLERANCES

PP#1H5299

The registrant hereby requests feed additive tolerances for combined residues of the fungicide, metalaxyl [N-(2,6-dimethylphenyl)-N-(methoxyacetyl) alanine methyl ester] and its metabolites containing the 2,6-dimethylaniline moiety, each as expressed as metalaxyl, in or on the following processed foods:

Dry tomato pomace at 16.0 ppm
Wet tomato pomace at 5.0 ppm
Processed tomato products at 3.0 ppm
Potato chips at 4.0 ppm
Potato granules at 4.0 ppm
Dried potato meal at 4.0 ppm

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2. Formulation to be used is Ridomil 2E (EPA Reg.#100-607). Inerts are cleared under 180.1001.

3. No permanent tolerances for metalaxyl have been established.

4. No RPAR criteria have been exceeded and no regulatory actions are pending against the pesticide.

5. Toxicity Studies on Ridomil 2E Previously Submitted

- Acute Oral LD_{50} in Rats: 2342 mg/kg for males and 1520 mg/kg for female, 1980 mg/kg combined; Category III.
- Acute Dermal LD_{50} in Rabbits: 3571 mg/kg; Category III.
- Primary Eye Irritation in Rabbits: Corneal opacity and conjunctival irritation persisting through 7 days; Category I.
- Primary Skin Irritation: Draize score 0.5; Category IV.,
- An Acute Inhalation Study in Rats: Was not acceptable because the LD_{50} was not determined. However, no deaths at 3.38 mg/L for 6M & 6F rats; Category III.

6. Toxicity Studies on Technical Metalaxyl Previously Submitted

- Acute Oral LD_{50} in Rats: 669 mg/kg; Category III.
- Acute Dermal LD_{50} in Rabbits: Greater than 6000 mg/kg; Category III.
- Acute Dermal LD_{50} in Rats: 3170 mg/kg; Category III.
- Skin Irritation in Rabbits: Draize Index = 0.1/8, mild skin irritants; Category IV.
- Primary Eye Irritation in Rabbits: Corneal involvement, completely clearly in 3 days; Category II.
- Skin Sensitization in Guinea Pigs: Negative
- 3-Month Dietary Study In Rats: NOEL = 250 ppm
- 90-Day Dietary Study in Dogs: NOEL = 250 ppm

°Teratology Study in Rats: Not teratogenic at doses up to 120 mg/kg..

°Salmonella/Mammalian Microsome Mutagenicity Study: Not mutagenic.

°Mouse Dominant Lethal Mutagenic Study: Not mutagenic.

°21-Day Subacute Dermal in Rabbits: NOEL = 1000 mg/kg/day

°Rabbit Teratology: Negative at 20 mg/kg

°3-Generation Rat Reproduction: NOEL = 1250 ppm

°6-Month Oral Dog: NOEL = 250 ppm

7. Toxicity Studies Submitted with this Petition

a) CGA 48 988: Toxicity and oncogenicity in dietary administration to rats for two years (Final Report, Life Science Research Report No. 80/CIA009/315, 7/10/81)

Test Material: CGA 48 988; a white/beige crystalline material; Batch No. P14, purity 93%; Batch No. EN 32212, purity 94.6%; Batch No. P14 was used from week 1 to week 70 and Batch No. EN 32212 from week 71 to week 105.

Groups of 80 male and 80 female Sprague-Dawley rats were fed diets containing 0 (controls), 50, 250 or 1250 ppm of test material. After 55 weeks of study, 10 male and 10 female rats from each group were sacrificed. Terminal sacrifice occurred after 105 weeks of treatment. Criteria evaluated were toxic signs, mortality, body weight, food consumption, ophthalmoscopic examination, hematology, clinical chemistry, urinalysis, palpable masses, organ weights and gross and microscopic examination of tissues and organs. Statistical analyses of the data were performed.

Results: No effects considered to be treatment-related were noted with respect to toxic signs, mortality (Survival was greater than 50% for both sexes of all groups at 18 months), body weight, food consumption, ophthalmologic examination and hematology.

With respect to clinical chemistry, female rats at after 13, 25 and 51 weeks of treatment had lowered SGPT and SGOT values. Male rats after 25 weeks of treatment also displayed lower SGPT and SGOT values. After 78 weeks of treatment there was an increase in SGPT and SGOT values in females receiving 250 or 1250 ppm of test material. After 104 weeks of study SGOT were comparable between control and treated rats of both sexes. These clinical chemistry changes may be treatment-related.

No compound-related effects were noted in urinalysis or palpable masses. Relative liver weight was increased in females fed 1250 ppm at 55 weeks. Males fed 250 and 1250 ppm had increased relative liver weights at 105 weeks. Females fed 1250 ppm also had increased relative liver weights at 105 weeks. These effects are considered to be treatment-related. There were no treatment-related gross or microscopic findings. The incidence, type and distribution of tumors was comparable between control and treated groups.

However, the occurrence of parafollicular cell adenomas of the thyroid in female rats was as follows:

Group (ppm in diet)	Incidence
control (0)	2/80
Group 2 (50)	7/80
Group 3 (250)	10/80
Group 4 (1250)	5/80

Statistical analysis, using Fisher's Exact test, indicated that the incidence of this tumor type in Group 3 female rats was statistically significant ($P = 0.015$).

This finding is not considered an oncogenic effect, since the test for a linear trend was not significant, i.e., no dose-response relationship, and in other studies of a similar duration at the laboratory, a historical control incidence of 21/280 was found. When the historical control data are compared to the incidence in group 3 female rats, no statistical significance is acheived.

Conclusion: The NOEL for chronic toxicity is 50 ppm. The LEL is 250 ppm and the effect is increased relative liver weight in males. The oncogenic potential is negative.

Classification: Core-Minimum Data

8. Calculation of the ADI

The ADI is based on the NOEL of 250 ppm (6.25 mg/kg/day). A 1000 fold safety factor is used to calculated the ADI.

$$\text{ADI} = 6.25 \text{ mg/kg/day} \times \frac{1}{1000}$$

$$\text{ADI} = 0.00625 \text{ mg/kg/day}$$

The MPI for a 60 kg person is 0.375 mg/day.

9. Unpublished, Tox approved tolerances utilize 33.80% of the ADI. The current action utilizes 44.88% of the ADI. All tolerances utilize 78.68% of the ADI.

Conclusions and Recommendations:

The permanent tolerances can be toxicologically supported.

WDO 4/23/82

William Dykstra, Ph.D
Toxicology Branch
Hazard Evaluation Division (TS-769)

Attachment

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