2-11-80

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: February 8, 1980

SUBJECT: EPA Reg.#100-ANT; Ridomil 2E
CASWELL#375AA (metalaxyl) 2/11/80 WHD

FROM: William Dykstra
Toxicology Branch (TS-769)

TO: Henry Jacoby
Product Manager#21

M. Adrian Gross, Chief William W. Butler for M. Adrian Gross
Toxicology Branch (TS-769)

Action Requested: Request for conditional registration for use on tobacco.

Recommendations:

(1) Since certain types of studies are currently in progress (see item #2 below), certain toxicological aspects (oncogenicity, reproduction, etc.) of the pesticide have not as yet been evaluated. Consequently, all of the potential risks to humans from the requested action are not known. However, the toxicity data presented in the review may support the requested action provided that exposure to applicators of the formulation and consumers of treated tobacco is minimal (See EFB and RCB reviews).

(2) The following toxicology studies with the technical metalaxyl are in progress:

(a) Reproduction Study - Rat
(b) Chronic/Oncogenic - Rat
(c) Oncogenic - Mouse
(d) 90-Day Subchronic Inhalation - Rat
(e) Final Report of 4-Week Subchronic Inhalation - Rat

(3) The interim report of the 4-week rat subchronic inhalation study is acceptable as supplementary data.

Review:

A. Toxicity Studies previously submitted

1. Toxicity studies on the 2E formulation:

a) Acute oral LD_{50} in rats; 2342 mg/kg for males and 1520 mg/kg for females, 1890 mg/kg combined; Category III.

b) Acute dermal LD_{50} in rabbits; 3571 mg/kg; Category III.

c) Primary eye irritation in rabbits; corneal opacity and conjunctival irritation persisting through 7 days; Category I.

166

e) 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; Toxicity Category III.

2. Toxicity studies on technical grade Ridomil:

a) Acute oral LD_{50} in rats; 669 mg/kg; Toxicity Category III.

b) Acute dermal LD_{50} in rabbits; greater than 6000 mg/kg; Toxicity Category III.

c) Acute dermal LD_{50} in rats; greater than 3170 mg/kg; Toxicity Category III.

d) Skin irritation in rabbits; Draize index = 0.1/8, mild skin irritant; Toxicity Category IV.

e) Primary eye irritation in rabbits; corneal involvement, completely clearing in 3 days; Toxicity Category II.

f) Skin sensitization in guinea pigs; negative.

g) Three-month dietary study in rats; NOEL = 250 ppm.

h) 90-Day dietary study in dogs; NOEL = 250 ppm.

i) Teratology study in rats; not teratogenic at doses up to 120 mg/kg.

j) Salmonella/mammalian microsome mutagenicity study - not mutagenic.

k) Mouse dominant lethal mutagenic study - not mutagenic.

B. Toxicity data submitted with this action

1. Interim report of 4-week toxicity study of the pyrolysis products of CGA-48988 in cigarette tobacco smoke. (Hazelton Labs, Jan. 9, 1980)

The study was initiated on November 21, 1979 and the final exposure was on December 19, 1979. The study consisted of four groups of 10 male and 10 female rats each, with each animal being exposed to the smoke from 16 cigarettes per day, puffed by A.D. Little, Mark II smoking machines at the rate of one 35-ml puff per minute and delivered into 38-liter cylindrical glass and stainless steel static chambers for 20 seconds per puff. Three groups (Groups 2, 3, and 4) received exposures to smoke from cigarettes made from tobacco sprayed with CGA-48988 Technical in weight proportions of 130, 3,900, and 13,000 ppm, respectively. Group I was exposed to smoke from untreated tobacco. The males in each group were exposed in the mornings, five days per week, for four weeks. The females were similarly exposed during the afternoons. The rats were weighed weekly at the same time of day (± 1 hour) each week.

At termination, blood was drawn from the abdominal aorta for serum chemistry analyses of calcium, potassium, BUN, glucose, alkaline phosphatase, GOT, GPT, bilirubin, and total cholesterol. Prior to initiation and at termination, blood from the clipped tail of each rat was analyzed for RBC, WBC, and differential leukocyte counts; hematocrits; and hemoglobin concentration.

At termination, a complete necropsy was performed on each rat (none died during the study) and tissue samples from the following were taken and prepared for histopathological evaluation:

brain	kidney	small intestine
thyroid	larynx	large intestine
trachea	nasal turbinates	gonads
lungs	spleen	peripheral nerve
heart	adrenal gland	skeletal muscle
liver	stomach	

During the course of the study, Cambridge filter (25 cm) samples of smoke were taken fron each 20-second static exposure period during at least four smoking sessions for Groups 2, 3, and 4 and during three sessions for Group 1. The filters were placed in a freezer until analyzed for CGA-48988 content. The particulate matter so collected was analyzed using the G.C. method you supplied. The results of these analyses indicated the following mean concentrations of CGA-48988 were present during the exposure periods: Group 1: 0.0006 ug/L; Group 2: 0.09 ug/L; Group 3: 1.18 ug/L; Group 4: 5.79 ug/L. These values reflect the rank-order of the CGA-48988 spikes, but do not closely follow the ratios of spike values between Groups 2 and 3 - Group 3 appears to be somewhat low while Group 2 may be somewhat high.

Plasma nicotine analyses were made from arterial blood drawn immediately after exposure to the smoke from four successive cigarettes. Four extra rats each were exposed to the smoke from the four types of cigarettes used, i.e., the four "spikes". The mean values obtained were 26.5, 37.3, 32.5, and 41.8 ppb for the 0; 130; 3,900; and 13,000 ppm cigarettes, respectively. The overall mean was 34.5 ppb. These values indicate that the animals were inhaling particulate phase smoke (nicotine is present only in particulate phase) and thus could be expected to have been inhaling CGA-48988 (or its pyrolysis product) to the extent that it left the cigarette in either particulate or vapor phase.

The results available to date indicate little or no toxic impact from these exposures to CGA-48988-spiked cigarette smoke. There were no differences in pharmacotoxic signs observed (all groups had a few animals which salivated, all animals appeared to squint and become inactive during each exposure, and all animals preened actively between cigarettes), and there were no biologically meaningful hematology or serum chemistry differences except possible slightly lowered calcium (dose-related) in the CGA-48988 female groups vs Group 1. There were no meaningful organ or organ/body weight differences nor remarkable gross pathology to distinguish groups.

Thus, despite evidence of about 40 minutes of inhalation exposure to a 64-fold range of non-pyrolyzed CGA-48988 from 0.09 ug up 5.8 ug/liter (and an undetermined amount and range of its pyrolysis product), no important toxicological effects have been seen to result. Microscopic examination of the listed tissues is scheduled for later this month.

Classification: Supplementary Data

C. Preliminary Toxicological Analyses of Hazards to Cigarette Smokers. Exposure data on cigarette smoke was obtained per oral communication with RCB.

90-Day Rat Study
NOEL = 250 ppm
or 2.5 mg/kg/day
÷ 2000 safety factor
equals
0.0125 mg/kg/day
or 12.5 ug/kg/day

Exposure

6 ug/cigarette
X 40 cigarettes = 240ug
÷ 60 kg = 4 ug/kg/day

margin of safety ≅ 6000

90-Day Dog Study
NOEL = 250 ppm
or 6.25 mg/kg/day ?
÷ 2000 SAFETY FACTOR
equals
.003125 mg/kg/day
or 3.125 ug/kg/day

Exposure

6 ug/cigarette X
40 cigarettes = 240 ug
÷ 60 kg = 4 ug/kg/day

margin of safety ≅ 1600

It should be noted that the LEL in the 90-day dog study was 1250 ppm and the "effect" consisted of increased alkaline phosphatase in some dogs. Logically the true NOEL is between 250 and 1250 ppm.

TOX/HED:th:RD Initial CFRICK:2-8-80

C. Frick 2/11/80

4

169