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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Metalaxyl. Toxicology Chapter for the RED

PC Code 113501
Tox. Chem. No. 375AA
Project No. D197038

TO: Linda Kutney, Chemical Manager
Reregistration Section
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Health Effects Division (H7509C)

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THRU: Karl Baetcke, Ph.D., Branch Chief
Toxicology Branch I
Health Effects Division (H7509C) Karl Baetcke 5/2/95

Background and Request:

Metalaxyl has been scheduled for a Reregistration Eligibility Document (RED) in June, 1994. The Toxicology Branch (TB-I) has been requested to review the available toxicology studies on this chemical and write the toxicology chapter for the RED package.

Toxicology Branch Response:

Attached to this cover memorandum is the Toxicology Chapter for the RED for metalaxyl.

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B. Human Health Assessment

1. Toxicology Assessment

The toxicology data base in support of the food and non-food uses of metalaxyl is adequate and will support reregistration eligibility.

a. Acute Toxicity

Acute Toxicity

Test	Result	Category
Acute Oral LD_{50} (rat)[1]	669 mg/kg	III
Acute Oral LD_{50} (mouse)[2]	788 mg/kg	III
Acute Oral LD_{50} (hamster)[3]	7120 mg/kg	IV
Acute Dermal LD_{50} (rabbit)[4]	>6000 mg/kg	III
Acute Inhalation LC_{50}	Requirement waived[5]	N/A
Eye Irritation (rabbit)[6]	Moderate Irritant	II
Dermal Irritation (rabbit)[7]	Mild Irritant	IV
Skin Sensitization (guinea pig)[8]	Negative	N/A

[1] MRID 00063990
[2] MRID 00063991
[3] MRID 00154308
[4] MRID 00063993
[5] Because metalaxyl cannot be prepared and tested in a respirable form, the requirement for an acute inhalation study was waived by HED on May 10, 1991.
[6] MRID 00084108
[7] MRID 00084107
[8] MRID 00084109
N/A = not applicable

b. Subchronic Toxicity

A 90-day study was conducted with male and female Sprague-Dawley rats fed diets containing 0, 50, 250, or 1250 ppm of metalaxyl. The diet concentrations were equivalent to chemical intakes of 3.4, 17, and 83 mg/kg/day, respectively. At the high dose, food consumption by males was slightly reduced and minimal liver cell hypertrophy was increased in females. Based on these findings, the LOEL was 83 mg/kg/day and the NOEL was 17 mg/kg/day. (MRID 00084110)

A 21-day dermal study was conducted with male and female New Zealand white rabbits. Metalaxyl was applied to intact or abraded skin at dose levels of 10, 100, or 1000 mg/kg/day for 6 hours/day, 5 days/week. Endpoints evaluated included body weight, food consumption, hematology, clinical chemistry, organ weights, and histopathology. No treatment-related dermal or systemic effects were observed at any dose level. Therefore, the NOEL for dermal and systemic toxicity was the highest dose tested, 1000 mg/kg/day. (MRID 00072394)

c. Chronic Toxicity

A 6-month study was conducted with beagle dogs fed diets containing 0, 50, 250, or 1000 ppm of metalaxyl. The diet concentrations were equivalent to chemical intakes of 1.3, 6.3, and 25 mg/kg/day, respectively. Exposure to the high dose was associated with an elevation in serum alkaline phosphatase and an increase in liver weight (absolute and relative to brain weight). No clinical signs or findings in hematology, urinalysis, or histopathology were related to treatment. The LOEL was 25 mg/kg/day and the NOEL was 6.3 mg/kg/day. (MRID 00071598)

In a chronic toxicity/carcinogenicity study, male and female Sprague-Dawley rats were fed diets containing 0, 50, 250, or 1250 ppm of metalaxyl for 2 years. These levels were equivalent to 2.5, 13, and 63 mg/kg/day, respectively. The high dose produced an increase in liver weight (relative to body weight) and an increased incidence of periacinar vacuolation of hepatocytes. Based on the liver changes, the systemic LOEL was 63 mg/kg/day and the NOEL was 13 mg/kg/day. (MRID 00098481, 00132009, 00150185)

d. Carcinogenicity

A 2-year chronic toxicity/carcinogenicity study was conducted with male and female Sprague-Dawley rats. Metalaxyl was administered in the diet at concentrations of 0, 50, 250, or 1250 ppm, which were equivalent to intakes of 2.5, 13, and 63 mg/kg/day, respectively. (MRID 00098481, 00132009, 00150185)

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A 2-year carcinogenicity study was conducted with male and female Swiss mice. Metalaxyl was administered in the diet at concentrations of 0, 50, 250, or 1250 ppm, which were equivalent to intakes of 7.5, 38, and 190 mg/kg/day, respectively. (MRID 00103354, 00150094)

In 1985 the EPA reviewed four major issues concerning the rat and mouse carcinogenicity studies: (1) parafollicular cell adenomas in the thyroid of female rats, (2) adrenal medullary tumors (pheochromocytomas) in male rats, (3) liver tumors in male mice, and (4) use of a maximum tolerated dose. (50 FR 49690)

Concerns about the incidence of thyroid tumors in female rats was mitigated by the following evidence: (1) no progression of adenomas (benign) to carcinomas (malignant), (2) no increase in hyperplastic changes, (3) no dose-response relationship, and (4) two re-evaluations of microscopic slides showing no treatment-related effect. Similar microscopic reassessments of the adrenal gland of male rats and the liver of male mice indicated no compound-related effect on tumor incidence in these organs.

Although the highest dose tested (1250 ppm) was not a maximum tolerated dose (MTD) in either study, the EPA concluded that the rat and mouse studies were sufficient to demonstrate that metalaxyl did not have carcinogenic potential in laboratory animals and further testing was unwarranted. The conclusion was supported by the following evidence: (1) the doses in both studies were high enough to produce treatment-related changes in liver weight and/or histology (i.e., increased liver weight and hepatocellular vacuolation in rats; fatty infiltration in the liver of mice), (2) no structural relationship to known carcinogens, (3) no genotoxic activity, and (4) no effect on neoplasm incidence in mice or rats of either sex at any dose level tested.

e. Developmental Toxicity

A developmental toxicity study was conducted with pregnant Charles River COBS CD rats administered doses of 0, 50, 250, or 400 mg/kg/day by gavage on days 6 through 15 of gestation. Dams were sacrificed on day 20 of gestation. Doses of 250 mg/kg/day and higher were maternally toxic producing ataxia and convulsions. The 400 mg/kg/day dosage resulted in mortality of one-third of the dams. Doses of 250 mg/kg/day and higher produced fetotoxicity manifest as an increased incidence of unossified sternebrae. The LOEL was 250 mg/kg/day and the NOEL was 50 mg/kg/day for both maternal and developmental toxicity. (MRID 00144423, 00148867)

A developmental toxicity study was conducted with Dutch belted rabbits given doses of 0, 30, 150, or 300 mg/kg/day of

metalaxyl on days 7 through 19 of gestation. Does were sacrificed on day 28 of gestation. The high dose does showed a slight loss in body weight. In a range-finding study, 500 mg/kg/day decreased maternal body weight and 1000 mg/kg/day produced mortality. No treatment-related developmental toxicity was observed at any dose level. The LOEL for maternal toxicity was 300 mg/kg/day and the NOEL was 150 mg/kg/day. The highest dose tested, 300 mg/kg/day, was the NOEL for developmental toxicity. (MRID 00144371, 00144372, 00148866, 00154938)

f. Reproduction

A 3-generation reproduction study was conducted with SPF Crl:COBS CD (SD) rats. Metalaxyl was administered in the diet at concentrations of 0, 50, 250, or 1250 ppm. These levels were equivalent to 2.5, 13, and 63 mg/kg/day, respectively. There were no treatment-related effects on parental body weight, food consumption, mating, fertility, gestation length, or macroscopic observations. Pre/post implantation loss, litter size and weight, and incidence of fetal malformations/variations were also unaffected by treatment. The NOEL for reproductive toxicity was the highest dose tested, 63 mg/kg/day (1250 ppm). (MRID 00071600)

g. Mutagenicity

Metalaxyl was negative in bacterial and mammalian gene mutation, in vivo cytogenetics, and several other genotoxicity assays.

Three studies evaluated metalaxyl in the Salmonella typhimurium reverse mutation assay (Ames assay) using tester strains TA 98, TA 100, TA 1535, and TA 1537. Metalaxyl did not increase the frequency of reverse mutations with or without metabolic activation (S9) at concentrations ranging from 25-2025 µg/plate, 20-5000 µg/plate, and 10-5000 µg/plate in the three experiments. (MRID 00084113, 00154301, 00154302)

A gene mutation assay in mammalian cells was conducted using the L5178Y (TK +/-) mouse lymphoma cell line. Concentrations of metalaxyl ranged from 0.125 to 1 mg/ml without S9 and 0.0625 to 0.5 mg/ml with S9. Metalaxyl did not increase forward mutations at the thymidine kinase (TK) locus. (MRID 00103362, 00154309)

Metalaxyl did not increase the frequency of reverse mutations in yeast cells (Saccharomyces cereviseae) at concentrations of 400 to 10,000 µg/ml with or without metabolic activation. Concentrations of 8000 µg/ml and greater were cytotoxic. Assays for recombination and gene conversion were unreliable. (MRID 00103359)

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In an in vivo cytogenetics study, male and female Chinese hamsters were administered two consecutive daily oral doses of 0, 595, 1190, or 2380 mg/kg of metalaxyl. The highest dose was one-third the oral LD_{50} in hamsters (7120 mg/kg). Bone marrow cells were scored 24 hours later for nuclear changes which included single Jolly bodies, fragments of nuclei in erythrocytes, micronuclei in erythroblasts, micronuclei in leukopoietic cells, and polyploid cells. Metalaxyl had no effect on the incidence of nuclear anomalies. (MRID 00103361, 00154307)

A dominant lethal test was conducted with male NMRI mice given a single oral dose of 0, 65, or 195 mg/kg of metalaxyl. The highest dose was one-fourth the reported LD_{50} in mice (788 mg/kg). Each male was cohabited with two untreated females each week for 8 consecutive weeks. Metalaxyl had no effect on mating, pregnancy, number of implants, or embryo viability. A positive control was not used in the study. (MRID 00084114, 00154310)

Metalaxyl was tested twice in the unscheduled DNA synthesis (UDS) assay using primary cultured rat hepatocytes. Concentrations tested ranged from 16-2000 µg/ml in both experiments. Another UDS assay was conducted using human fibroblasts. Metalaxyl concentrations ranged from 4 to 500 µg/ml. Concentrations up to cytotoxic levels were tested in each assay. Metalaxyl did not increase unscheduled DNA synthesis above control levels in any of the three assays. (MRID 00103363, 00154306, 00160037, 00154663)

h. Metabolism

Four studies with rats evaluated the absorption, distribution, excretion, and/or metabolism of orally administered metalaxyl. A dermal absorption study with rats was also conducted.

In a single dose study, male and female rats were administered 0.5 or 25 mg/kg of metalaxyl by gavage. Over 60% of the low or high dose was excreted within 24 hours in urine or feces. Negligible amounts were eliminated in expired air. Low tissue residues six days after treatment indicated no appreciable bioaccumulation. Female rats eliminated the majority of the dose (55-65%) in urine, and males eliminated most (60-70%) in feces. Although metabolites were not identified, the chromatographic pattern was similar for both sexes and doses. (MRID 00071613)

A metabolism study was conducted with female rats administered a single oral dose of 28 mg/kg. Within 48 hours 96% of the dose had been excreted in urine or feces. Consistent with the previous study, females excreted over 60% of the dose in urine and about 30% in feces. Approximately 20% of the metabolites in urine were identified. Hydrolysis of the ether

and ester bonds was shown to be a significant metabolic pathway. Glucuronidase treatment of urine fractions indicated metabolites were either unconjugated or glucuronide conjugates. Fecal metabolites were not identified. (MRID 000716614)

A similar study (females rats given 28 mg/kg as single oral dose) corroborated that ester and ether bond hydrolysis is a primary metabolic pathway. Secondary pathways included oxidation of methyl groups of the phenyl moiety and oxidation of the phenyl moiety itself. Some metabolites in urine were present as glucuronic acid conjugates. A large portion of the metabolites were unidentified. (MRID 00099084)

A recent comprehensive study evaluated metalaxyl pharmacokinetics with male and female Sprague-Dawley rats following a single intravenous dose (1 mg/kg), single oral low dose (1 mg/kg), single oral high dose (200 mg/kg), or repeated oral low doses (1 mg/kg/day for 14 days). The absorption, distribution, and elimination patterns were consistent with previous findings. No major dose or sex differences were observed except that urine was the predominant elimination route for females whereas feces was the major route for males. Metalaxyl was readily absorbed (similar i.v. and oral elimination profiles), extensively metabolized (<1% parent compound in excreta), and rapidly eliminated (70-80% in 24 hours). Ten metabolites were identified. The majority of urinary metabolites were conjugated (glucuronide or sulfate) whereas fecal metabolites were mostly unconjugated. The major metabolite in urine and feces was N-(2,6-dimethylphenyl)-N-(hydroxyacetyl) alanine. Three major and one minor metabolic pathways were proposed. One pathway involved hydrolysis of the ether, followed by oxidation of the resulting alcohol, ester hydrolysis, or N-dealkylation of the ester chain. A second pathway involved oxidation of an aromatic methyl to the benzylic acid or ester hydrolysis. The third major pathway was ester hydrolysis, sometimes followed by benzylic acid formation. The minor pathway involved hydroxylation at the meta position of the phenyl ring. Two major metabolites in urine were not identified. Additional data on major unidentified metabolites must be provided to upgrade this study to acceptable. (MRID 41664501)

A dermal absorption study was conducted with male and female rats treated with 1 or 10 mg/kg. Thirty percent of the dose was absorbed from the skin within 8 hours. The absorption half-times were 12 and 20 hours for males at the low dose and high dose, respectively, and 13 hours for females at both dose levels. Within 72 hours 70-80% of the applied dose had been excreted. The elimination half-times were 36 and 49 hours for males and 42 and 44 hours for females at the low and high doses, respectively. Females eliminated the majority of the dose in urine whereas males eliminated most in feces. (MRID 00161402)

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i. Neurotoxicity

Neurotoxicity studies are not required.

j. Other Toxicological Considerations

Smoke Inhalation Study- Because metalaxyl is used on tobacco, a 90-day smoke inhalation study was conducted. Male and female Fischer 344 rats were exposed to smoke from cigarettes containing 0, 130, 3900, or 13,000 ppm of metalaxyl for 4 hours/day, 5 days/week. The maximum air concentration of metalaxyl was 5 µg/l. The concentrations in test cigarettes were 100 to 10,000 times average residue levels and 30 to 100 times greater than maximum residue levels expected by the HED Chemistry Branch. Although the study was limited in its ability to simulate human exposure, the results were adequate to demonstrate no toxicological effects from exposures likely to exceed exposures associated with heavy smoking. The profile of residues in inhalable smoke indicated 30% was metalaxyl, 4% was 2,6-dimethylaniline, and 65% was unidentified. (MRID 00103364, 00109471)

k. Reference Dose (RfD)

The RfD was established as 0.08 mg/kg/day based on a NOEL of 7.8 mg/kg/day and an uncertainty factor of 100. The NOEL was obtained from a 6-month dog study. The RfD was first approved by the HED (5/23/86) and Agency (7/8/86) Reference Dose Committees and has been updated without change (4/3/94).

A dermal absorption study (MRID 00161402) indicated an absorption rate of 30% of the applied dose (28 mg/kg) in 8 hours. The acute toxicity categories for oral and dermal toxicity of metalaxyl are both III, and the requirement for an acute inhalation study was waived because metalaxyl was not in a respirable form. There were no endpoints in other toxicology studies of metalaxyl appropriate for risk assessment of acute exposures. The 21-day dermal toxicity study (MRID 00072394) established a NOEL > 1000 mg/kg for systemic toxicity and is appropriate for use in the assessment of short term and intermediate occupational exposures.

l. World Health Organization (WHO) Review

In 1982 the FAO/WHO Joint Meeting on Pesticide Residues allocated an Acceptable Daily Intake (ADI) of 0.03 mg/kg/day for metalaxyl.

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Chemical:	**Metalaxyl; ~~D-Alanine, N-(2,6-dimethylphenyl)-N-(met; L-Alanine, N-(2,6-dimethylphenyl)-N-(met~~**
PC Code:	**113501; ~~113502; 113503~~**
HED File Code	**13000 Tox Reviews**
Memo Date:	**05/05/94**
File ID:	**TX011142**
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