CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
HUMAN HEALTH ASSESSMENT BRANCH

SUMMARY OF TOXICOLOGY DATA

Metalaxyl

Chemical Code # 2132 **, Document Processing Number (DPN)** 408
SB 950 # 198
2/15/96, 2/4/16

DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effect
Chronic toxicity, dog:	No data gap, no adverse effect
Oncogenicity, rat:	No data gap, possible adverse effect
Oncogenicity, mouse:	No data gap, no adverse effect
Reproduction, rat:	No data gap, no adverse effect
Developmental toxicity, rat:	No data gap, no adverse effect
Developmental toxicity, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, possible adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	Data gap

Toxicology one-liners are attached.

All record numbers for the above study types through 283730 (Document No. 408-0401) were examined. This includes all relevant studies indexed by DPR as of 2/4/16

In the 1-liners below:
indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.

File name: T160204
Revised by T. Moore, 2/4/16

NOTE: The following symbols may be used in the Table of Contents which follows:
* = data adequately address FIFRA requirement
† = study(ies) flagged as "possible adverse effect"
N/A = study type not currently required

This record contains summaries of studies. Individual worksheets may be useful for detailed assessment.

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METABOLISM AND PHARMACOKINETICS

408-0237; 89285; "Rat Metabolism Studies: Tissues and Excreta"; (C.E. Jameson; ABC Laboratories, Inc., Columbia, MO; Project ID No. 37613; 8/20/90); Five Sprague-Dawley rats/sex/group were dosed iv (Group I) or orally by gavage (Group II) with 1.00 mg/kg of ^{14}C-Metalaxyl (lot no. GAN-XV-13, radiochemical purity: 97.2%, specific activity: 88.6 µCi/mg). In Group III, 5 animals/sex were dosed orally for 14 days with 1.00 mg/kg/day of unlabeled metalaxyl (lot no. 585-0831, purity: 96.5%), followed by a dose of 1.00 mg/kg of the radiolabeled test material. In the fourth group, five animals/sex were dosed orally by gavage with 200 mg/kg of ^{14}C-Metalaxyl (lot no. CL-XVIII-83, radiochemical purity: 97.3%, specific activity: 5.1 µCi/mg). Urine and fecal samples were collected from each group for up to 7 days post-dose. For the males, the predominate pathway of excretion was via the feces, ranging from 54.2 to 63.6% of the administered dose, regardless of the dosing procedure over a dose range of 1 to 200 mg/kg. For the females, the radiolabel was largely excreted via the urine, ranging from 65.1 to 73.9% of the administered dose. The manner of treatment did not greatly affect the excretion profile. Seventy to 82.5% of the radiolabel was excreted in the 1st 24 hours. Based on the similarity of the excretion profile for the animals dosed either by iv injection or orally by gavage, the test material was well absorbed. For the iv-injected animals, fecal excretion of the radiolabel was 59.4% for the males and 35.7% for the females. Biliary excretion was a significant pathway of elimination. At 7 days post-dose, the liver, intestine and red blood cells were the sites where the radiolabel was predominately isolated. For the 200 mg/kg treatment group, the radiolabel was also sequestered in the fat. **Study supplemental** (there was no characterization of the metabolites, a time course of tissue distribution or pharmacokinetic evaluation of the test material). (Moore, 6/26/15)

408-0237; 89285; "Characterization and Identification of Phenyl-[^{14}C]-Metalaxyl Metabolites in Rats"; (W. Itterly; Ciba-Geigy Corporation, Metabolism Department, Greensboro, NC and Analytical Bio-Chemistry Laboratories, Inc., Columbia, MO; Project ID No. ABR-90079; 10/19/90); Urine and fecal samples were previously recovered from Sprague Dawley rats of both sexes which had been treated with Phenyl-[^{14}C]-Metalaxyl by iv injection with 1.0 mg/kg (Group I), by oral gavage with 1.0 mg/kg (Group II), by oral gavage with multiple doses of 1.0 mg/kg/day (15x) (Group III), and by oral gavage with 200 mg/kg (Group IV) (see C.E. Jameson, ABC Laboratories, Inc., Columbia, MO; Project ID No. 37613; 8/20/90, vol. no. 408-0237). Urine samples collected between 0 and 36 hours post-dose from each of the treatment groups were combined and subjected to two-dimensional thin layer chromatography analysis. Extracts of combined fecal samples from the same treatment groups spanning 0 to 72 hours post-dose were analyzed in the same manner. These combined urine samples and fecal extracts were further analyzed by treatment with glucuronidase and arylsulfatase in order to identify those moieties which had undergone secondary conjugation. The aqueous soluble conjugates were treated first with glucuronidase and the ethyl acetate-soluble radiolabeled fraction was isolated. The remaining fraction which was still water soluble was then treated with arylsulfatase and the resulting ethyl acetate-soluble fraction was determined. Of the 33 metabolites isolated in both

the urine and fecal samples, the total percentage of radiolabel for which a metabolite was identified ranged from 19.6 to 51.4% for the urine samples and from 46.4 to 75.9% for the fecal extracts. The conjugated moieties of these metabolites constituted another pool of radiolabel. The conjugated moieties comprised from 49.9 to 96.8% of the radiolabel in the urine and 28.7 to 50.9% of the radiolabel in the feces. Three major pathways and one minor one were proposed. Hydrolytic demethylation of the acetyl moiety (CGA-67869), followed by the demethylation of the methyl acetyl alanine moiety (CGA-107955). Ultimately oxidation of the alcohol moiety of CGA-67869 resulted in the formation of the acid (CGA-79353) and the dealkylation of the alanine moiety formed the hydroxyacetamide (CGA-37734). The second pathway entailed the oxidation of the methyl moiety on the benzyl ring, resulting in the formation of CGA-94689 isomers A and B. These moieties were further metabolized to Metabolite M9 through demethylation of the methyl acetyl alanine moiety (A isomer) or further oxidation of the benzyl alcohol moiety to the acid CGA-108905 (B isomer). In the third pathway, direct hydrolytic demethylation of the methyl acetyl alanine moiety resulted in the formation of CGA-62826 and ultimately to the formation of Metabolite M9. A minor metabolite was also isolated which entailed the hydroxylation of the benzyl ring (CGA-100255). The report author identified all of these metabolites as being available for secondary glucuronidation or sulfation. However, only a certain number of them possessed hydroxyl groups which permitted the secondary bonding to occur. **Study supplemental.** (Moore, 7/2/15)

GUIDELINE ACUTE STUDIES ON ACTIVE INGREDIENT

Acute oral toxicity, rat

408-359; 183267; Acute Oral Toxicity; 811; rat; Product Safety Labs, East Brunswick, NJ; Project #: 9853; 12/14/00; Metalaxyl Technical (purity: ~97% metalaxyl); Lot #: 61K; 0.25 (females only), 0.50 (females only), and 1.00 g/kg (M/F) in a 30% w/w suspension in a 1% w/w solution of carboxymethylcellulose in distilled water; single, oral-gavage dose, with a 14-day observation period; 5 females/dose for 0.25 and 0.50 g/kg dose level, 5 test subjects/sex/1.00 g/kg dose level; mortality: 0.250, 0/5 F; 0.500, 2/5 F; 1.00 (M/F), 1/5, 4/5; clinical signs: 0.250, piloerection, hypoactivity, prone posture, and ataxia; 0.500, (decedents) - hypoactivity, hunched and prone posture, and/or tremors; (survivors) - hypoactivity, hunched posture, ataxia, and/or tremors; 1.00, (decedents) - hypoactivity and hunched and prone posture; (survivors) - hypoactivity, hunched posture, and piloerection up to Day 2; body-weight gain was positive in survivors; necropsy: 0.250, no gross abnormalities reported; 0.500, (decedents) - red/yellow intestines and rigor mortis in 2/5 F; (survivors) - no gross abnormalities reported; 1.00, (decedents) - moderately red lungs, discolored liver, and/or red intestines; (survivors) - no gross abnormalities reported; LD_{50} (M) > 1.00 g/kg; LD_{50} (F) = 0.625 (0.344 - 1.45) g/kg; Toxicity Category III; **Acceptable**. (Hansen, 01/09/02)

Acute dermal toxicity

408-359; 183268; Acute Dermal Toxicity; 812; rat; Product Safety Labs, East Brunswick, NJ; Project #: 9854; 12/11/00; Metalaxyl Technical (purity: ~97% metalaxyl); Lot #: 61K; 2.00 g/kg (70% w/w dry paste mixture with distilled water; 2.86 g/kg of test mixture); single, 24-hour dermal exposure, with a semi-occlusive wrap and a 14-day observation period; 5 test subjects/sex/dose; mortality: none; clinical signs: none reported; body-weight gain was positive over the course of the study, except for weight loss in 1 F from Days 7 to 14; necropsy: no gross abnormalities reported; LD_{50} (M/F) > 2.0 g/kg; Toxicity Category III; **Acceptable**. (Hansen, 01/10/02)

Acute inhalation toxicity, rat

408-359; 183269; Acute Inhalation Toxicity; 813; rat; Product Safety Labs, East Brunswick, NJ; Project #: 9855; 12/04/00; Metalaxyl Technical (purity: ~97% metalaxyl); Lot #: 61K; 2.55 mg/L (gravimetric; nominal concentration: 18.35 mg/L; neat); MMAD (GSD): 3.5 (2.11) µm; single, 4-hour whole-body inhalation exposure, with a 14-day observation period; 5 test subjects/sex/dose; mortality: none; clinical signs: (in-chamber), ocular and nasal discharge, hunched posture, and hypoactivity; (post-exposure), clear ocular and nasal discharge, with full recovery within 1 hour; body-weight gain was positive over the course of the study; necropsy: no gross abnormalities reported; LC_{50} (M/F) > 2.55 mg/L; Toxicity Category IV; **Acceptable**. (Hansen, 01/10/02)

Primary eye irritation, rabbit

408-359; 183270; Primary Eye Irritation; 814; rabbit; Product Safety Labs, East Brunswick, NJ; Project #: 9856; 12/14/00; Metalaxyl Technical (purity: ~97% metalaxyl); Lot #: 61K; 0.1 mL/eye (0.07 - 0.09 g; neat); single, ocular instillation, with a 7-day observation period; 3 test subjects/sex/dose; mortality: none; clinical signs: corneal opacity, grade 1 in 6/6 at 24 hours, decreasing to grade 1 in 5/6 at 48 and 72 hours and grade 1 in 1/6 by Day 4, with clearing by Day 7; iritis, grade 1 in 4/6 at 24 hours, decreasing to grade 1 in 1/6 at 48 hours, with clearing by 72 hours; conjunctivae, redness - grade 2 in 3/6 at 24 hours (grade 1 in 3/6), decreasing to grade 1 in 6/6 at 48 hours and 5/6 at 72 hours and 3/6 by Day 4, with clearing by Day 7; chemosis - grade 1 in 5/6 at 24 hours, decreasing to grade 1 in 2/6 at 72 hours and 1/6 by Day 4, with clearing by Day 7; discharge - grade 2 in 3/6 at 24 hours (grade 1 in 3/6), decreasing to grade 1 in 6/6 at 48 hours and 4/6 at 72 hours and 1/6 by Day 4, with clearing by Day 7; Maximum Mean Total Score = 23.5 (reported); Toxicity Category III; **Acceptable**. (Hansen, 01/10/02)

Primary dermal irritation

408-359; 183271; Primary Dermal Irritation; 815; rabbit; Product Safety Labs, East Brunswick, NJ; Project #: 9857; 08/08/01; Metalaxyl Technical (purity: ~97% metalaxyl); Lot #: 61K; 0.5 g/site of a 60% w/w dry paste mixture in distilled water (0.83 g of test mixture); single, 4-hour dermal exposure, with a semi-occlusive wrap and a 72-hour observation period; 3 test subjects/sex/dose level; mortality: none; clinical signs: erythema, none reported; edema, none reported; Primary Dermal Irritation Index (reported) = 0.0; Toxicity Category IV; **Acceptable**. (Hansen, 01/10/02)

Dermal sensitization

408-359; 183272; Skin Sensitization; 816; guinea pig; Product Safety Labs, East Brunswick, NJ; Project #: 9858; 12/14/00; Metalaxyl Technical (purity: ~97% metalaxyl); Lot #: 61K; all treatments were 0.4 mL for 6-hour topically, with occlusive wraps; induction: 80% test article concentration (w/w in distilled water; 1 treatment/week/3 weeks/20 female test subjects); challenge: 80% test-article concentration (w/w in distilled water), 27 days after the first induction treatment; naïve-challenge: 80% test article concentration with 10 female test subjects; positive control (10 females): 0.08% DNCB for the induction and 0.04% DNCB for the challenge and naïve-challenge (5 females) treatments; mortality: none; clinical signs: induction treatments 1 to 3, no erythema reported; challenge, no erythema reported; naïve challenge, no erythema reported; the positive control, 1-chloro-2, 4-dinitrobenzene (DNCB), was positive for dermal sensitization indicating that the test system was effective; body-weight gain was positive over the course of the study for all subjects; not a dermal sensitizer; **Acceptable**. (Hansen, 01/10/02)

408-0401; 283730; “Dermal Sensitization Test in Guinea Pigs – Magnusson and Kligman (M & K) Method”; (J. Durando; Product Safety Labs, Dayton, NJ; Study No. 39784; 2/20/15); Ten Hartley albino male guinea pigs received a total of 6 intradermal injections of 0.1 ml each, 2 each of Freund’s Complete Adjuvant: distilled water (1:1), 3% (w/w) dilution of Metalaxyl TC (batch no. F-81; purity: 98.9%) in propylene glycol, and 3% (w/w) dilution of the test material in Freund’s Complete Adjuvant: water (1:1)/propylene glycol (1:1) on day 0 of induction. On day 7, the skin of the treated animals was exposed to 0.5 g of a 70% (w/w) preparation of the test material in propylene glycol for 48 hours under an occlusive wrap as the second induction treatment. Five control animals were treated in the same manner for both induction treatments except that the test material was not included in the treatment regimen. Twenty days after the initial induction treatment, the skin of each of the study animals was exposed for 24 hours under Hill Top chamber to 0.4 ml of a 53% (w/w) preparation of the test material in propylene glycol. In the challenge, four of 9 animals demonstrated a score of 1 at 24 hours post-exposure, diminishing to three of nine with that score at 48 hours. For the control group, none of the 5 animals demonstrated a positive score at 24 or 48 hours post-exposure. The positive control was functional. The test material is a dermal sensitizer in accordance with the Guinea Pig Maximization Test. **Study acceptable.** (Moore, 6/17/15)

SUBCHRONIC STUDIES

Rat Subchronic Dietary Toxicity Study

408-003 990419 "3 months dietary study in rats with compound CGA 48 988: (J. C. Drake, Geigy Pharmaceuticals, 2/25/77) CGA 48 988 technical, 99%, batch P.3, was fed in the diet to Sprague Dawley rats for 3 months. There were 25/sex fed 0 or 1250 ppm and 20/sex fed at 50 or 250 ppm. Five per sex in the control and 1250 ppm groups were held for 1 month recovery period following treatment. Observations included hematology, limited clinical chemistry, urinalysis and clinical observations with no treatment-related affects identified. There was a slight increase in liver weights in the treated groups. The only affect of note was minimal hypertrophy in some female rats at 1250 ppm, considered by the author to be "physiological 'work' hypertrophy". Supplemental for dose setting for the 2-year study. (Gee, 2/9/96).

Rabbit 21-Day Repeated Dosing Dermal Toxicity Study

408-0004; 990397; “A 21-Day Subacute Dermal Toxicity Study in Albino Rabbits”; (J.E. Calkins; Toxigenics, Inc., Decatur, IL; Study No. 410-0226; 11/14/80); The skin of 10 New Zealand albino rabbits/sex/group was exposed to 0, 10, 100 or 1000 mg/kg/day of CGA-48988 Technical (no lot no.; purity: 92%) for 6 hours/day, 5 days/week for 3 weeks. For the first 3 days of the study, the test material was not moistened. At the behest of the sponsor, the site of application was sprayed with 0.5 ml of deionized water, covered with an occlusive wrap under which the test material was applied. This procedure was not adequate to ensure that the test material was adequately moistened. One male in the 100 mg/kg treatment group died on day 20. Lesions on the skin of animals across the treatment groups were populated with *Staphyloccocus aureus* colonies. Hepatic lesions were noted in a large percentage of the rabbits as a consequence of a parasitic infestation with *Eimeria stiedae*. The protozoan parasite, *Encephalitozoon cumiculi* was isolated in the kidneys of the study animals. The presence of these infestations compromised the study results. There were no treatment-related effects on the mean body weights or food consumption. No clinical signs were attributed to the treatment. The hematological evaluation did not indicate any treatment-related effects. No clinical chemical parameters were affected by the treatment. The mean absolute and relative organ weights were not affected by the treatment. The histological evaluation did not reveal any apparent treatment-related lesions. **No adverse effects were evident. Reported Rabbit**

21-Day Repeated Dosing Dermal NOEL: (M/F) 1000 mg/kg/day (based upon the lack of treatment-related effects on the 1000 mg/kg treatment group); **Study unacceptable**, not upgradeable. (Moore, 6/25/15)

CHRONIC STUDIES

Chronic, rat

** 006, 007, 008, 064, 065, 066 990425, 990426, 990427, 990429, 990430, 990422 "CGA 48 988: Toxicity and Oncogenicity in Dietary Administration to Rats for Two Years", (R. Ashby, Life Science Research, England, Report # 80/CIA009/315, 23 September 1980). The test article is identified as CGA 48 988 (metalaxyl) with 93% purity. 80 CD (Sprague-Dawley derived) rats per sex per group received 0, 50, 250, and 1250 ppm in the diet for 105 weeks. 10 per sex per group were necropsied after 55 weeks of treatment. Group mean liver weights relative to bodyweights were increased for high dose females at 55 week sacrifice and for mid and high dose males and high dose females at the 105 week sacrifice. Also in females at 105 weeks an increase in the incidence of follicular cell adenomas of the thyroid were noted at 50, 250 and 1250 ppm. Chronic NOEL = 50 ppm. Oncogenicity NOEL = 1250 ppm. Originally reviewed as acceptable (J. Remsen, 5/29/85). Re-reviewed as **acceptable** (H. Green and Gee, 2/14/96).

Chronic, dog

** 010, 255 990417, 115268, "Six Month Chronic Oral Toxicity Study with CGA-48988 Technical in Beagle Dogs", (L. Steven Beck, D.V.M., M.S., Elars Bioresearch Laboratories, Inc., Fort Collins, CO., Project # 1545, 20 January 1981). The test article is identified as CGA-48988 (metalaxyl) technical with 92% purity. 6 or 8 (control and high dose) Beagle dogs per sex per group received 0, 50, 250, and 1000 ppm in the diet for 180 days. 2 per sex from the control and high dose groups served as recovery animals and were fed untreated diet for an additional 4 weeks. Variations in hematology and serum chemistry parameters (increase in alkaline phosphatase levels) fall within historical control ranges. Chronic NOEL = 50 ppm (Group mean liver weights relative to brain weight were increased at the mid and high dose levels). Histopathology revealed no remarkable changes. NOAEL = 1000 ppm. **Study design does not meet with current guidelines.** However, since no adverse changes other than hepatomegaly were noted at a nominal 1000 ppm the study previously reviewed as unacceptable, upgradeable upon submission of dietary concentration is now acceptable. (H. Green, and P. Iyer, 1/31/96).

Oncogenicity, rat

See Chronic, rat above.

103 024214, "Carcinogenicity of the Fungicide Ridomil* 25WP in Albino Rats", (R. Fytizas and G. Vassiliou, Institution of Phytopathology Benaki, Athens, Greece). The test article is identified as Ridomil* WP 25. 15 (treated) or 20 (control) Wistar-derived rats per sex per group received 0, 200, 400, and 800 mg/kg in the diet for 23 months. **Lymphoma is indicated**. Insufficient information for NOEL determination. **Unacceptable** and not upgradeable (dosing level rationale, incomplete results presentation, etc.). (J. Remsen, 5/28/85; updated to electronic format, H. Green, 10/18/95).

Oncogenicity, mouse

** 045, 112, 254, 256, 257 036174, 115267, 115269, 115270, "CGA 48988: Oncogenicity in Dietary Administration to Mice for Two Years, Final Report", (T.W. McSheehy, Life Science Research, England, Report # 80/CIA008/442, 31 October 1980). The test article is identified as CGA 48988 (metalaxyl, 93.8% - 95.2% purity). 60 ICI Alderley Park (Swiss strain origin) mice per sex per group received 0, 50, 250, and 1250 ppm of test article in the diet for 104 weeks.

Large hepatocytic fatty vacuolation was increased for high dose males and females killed and dying during weeks 0 to 104 and for high dose males at terminal sacrifice compared to controls. Bodyweights for high dose males were reduced 5% to 10% during treatment weeks 22 through 90. Chronic NOEL = 250 ppm (liver changes and reduced bodyweights in high dose males). Oncogenicity NOEL = 1250 ppm. NOAEL = 1250 ppm. Unacceptable but upgradeable upon submission of rationale for dosing and test article characterization (J. Remsen, 5/30/85 (Record # 036174 only); reviewed after submission of rationale for dosing and purity of test material. **Acceptable** (H. Green and Gee, 2/23/96).

GENOTOXICITY

Gene mutation

003 990438, "Salmonella/Mammalian-Microsome Mutagenicity Test with CGA 48988 (Test for Mutagenic Properties in Bacteria)", (Dr. P. Arni and Prof. Dr. D. Muller, Ciba-Geigy Limited, Pharmaceuticals Division, Toxicology/Pathology, Basle, Switzerland, Report # 78-2514, 14 March 1978). The test article is identified as CGA 48988 (metalaxyl, batch P2). Salmonella typhimurium strains TA98, TA100, TA1535, and TA1537 were exposed (in the presence and absence of activation) for 48 hours in triplicate to concentrations of 0 (DMSO), 25, 75, 225, 675, and 2025 mg/0.1 ml/plate. **Mutagenicity is not indicated**. **Unacceptable** and not upgradeable (dosing rationale with no evidence of cytotoxicity or precipitation reported, missing results). (J. Remsen, 5/28/85; upgraded to electronic format, H. Green, 11/2/95)

254 115258, "Salmonella/Mammalian-Microsome Mutagenicity Test", (E. Deparade, Ciba-Geigy Limited, Basle, Switzerland, Experimental Pathology Laboratories: R-1066.210-222, Report # 851007, 18 November 1985). The test article is identified as CGA 48 988 (metalaxyl) technical with 95.7% purity. Salmonella typhimurium strains TA98, TA100, TA102, TA1535, and TA1537 were exposed in triplicate to concentrations of 0, 20, 78, 313, 1250, and 5000 mg/0.1 ml for 48 hours in the presence and absence of activation. **No increase in reversion frequency. Acceptable. (H. Green and Gee, 2/9/96)

046, 254 990437, 115259, "L5178Y/TK$^{+/-}$Mouse Lymphoma Mutagenicity Test", (F.F. Strasser, Ciba-Geigy Limited, Basle, Switzerland, Report # 811258, 1 February 1982 and supplement dated 14 November 1985). The test article is identified as CGA 48 988 (metalaxyl) technical with 94.1% purity. L5178Y/TK$^{+/-}$ mouse lymphoma cells were exposed for 4 hours with eight replicates to concentrations of untreated, 0, 0.125, 0.25, 0.50, and 1.0 mg/ml without activation and to untreated, 0, 0.0625, 0.125, 0.25, and 0.50 mg/ml with activation. **No increase in mutation frequency.**. **Unacceptable** and not upgradeable (no dosing rationale, no repeat assay). (J. Remsen (Gee), 5/31/85; H. Green and Gee, 2/9/96)

Chromosome damage

254 115258, "Salmonella/Mammalian-Microsome Mutagenicity Test", (E. Deparade, Ciba-Geigy Limited, Basle, Switzerland, Experimental Pathology Laboratories: R-1066.210-222, Report # 851007, 18 November 1985). The test article is identified as CGA 48 988 (metalaxyl) technical with 95.7% purity. Salmonella typhimurium strains TA98, TA100, TA102, TA1535, and TA1537 were exposed in triplicate to concentrations of 0, 20, 78, 313, 1250, and 5000 mg/0.1 ml for 48 hours in the presence and absence of activation. **No increase in reversion frequency. Acceptable. (H. Green and Gee, 2/9/96)

046, 254 990437, 115259, "L5178Y/TK$^{+/-}$Mouse Lymphoma Mutagenicity Test", (F.F. Strasser, Ciba-Geigy Limited, Basle, Switzerland, Report # 811258, 1 February 1982 and supplement dated 14 November 1985). The test article is identified as CGA 48 988 (metalaxyl) technical with 94.1% purity. L5178Y/TK$^{+/-}$ mouse lymphoma cells were exposed for 4 hours with eight

replicates to concentrations of untreated, 0, 0.125, 0.25, 0.50, and 1.0 mg/ml without activation and to untreated, 0, 0.0625, 0.125, 0.25, and 0.50 mg/ml with activation. **No increase in mutation frequency.**. **Unacceptable** and not upgradeable (no dosing rationale, no repeat assay). (J. Remsen (Gee), 5/31/85; H. Green and Gee, 2/9/96)

**** 254 115265**, "Clastogenic Evaluation of Metalaxyl Technical, CGA-48988 Tech., in an In Vitro Cytogenetic Assay Measuring Chromosomal Aberration Frequencies in Chinese Hamster Ovary (CHO) Cells", (James L. Ivett, Hazleton Biotechnologies, Kensington, MD., Report # 8584, March 1986). The test article is identified as metalaxyl technical (CGA-48988 technical, 95.7%) Chinese hamster ovary cells (CHO-WBL) were exposed in duplicate (except controls), in the presence and absence of activation (Aroclor 1254 induced male rat liver S9 fraction), to concentrations of untreated medium, solvent control (DMSO), 150, 300, 900, and 1200 mg/ml for 2 hours (activated) and 17.6 hours (non-activated). **An increased frequency of chromosomal aberrations is indicated under non-activated conditions at the highest concentration only**. **Acceptable** (H. Green and Gee, 2/9/96)

003, 254 990440, 115266 "Dominant Lethal Study - CGA 48988 Technical, Mouse (Test for Cytotoxic or Mutagenic Effects on Male Germinal Cells) and Supplement", (Dr. H. Fritz, Ciba-Geigy Limited, Basle, Switzerland, Pharmaceuticals Division, Toxicology/Pathology, Report # 327761, 23 February 1978 and Supplement dated 7 November 1985). The test article is identified as CGA 48988 (metalaxyl, batch P3) technical. 20 NMRI-derived male mice per group received a single oral dose of 0 (CMC), 65, and 195 mg/kg. Beginning immediately after treatment, each male was placed with 2 untreated females per week for 8 weeks. No conclusive evidence of a dominant lethal affect up to 195 mg/kg (1/3 the oral LD50) **Unacceptable** and not upgradeable (inadequate dosing level, no positive control). (J. Remsen, 5/28/85; H. Green and Gee, 2/9/96)

DNA damage or miscellaneous effects

046 990434, "Saccharomyces cerevisiae D7/Mammalian-Microsome Mutagenicity Test In Vitro with CGA 48988 (Test for Mutagenic Properties in Yeast Cells)", (Dr. P. Arni, Ciba-Geigy Limited, Protection of Health and Environment, Toxicology, Basle, Switzerland, Report # 811561, 18 January 1982). The test article is identified as CGA 48988 (metalaxyl). Saccharomyces cerevisiae D7 cells were exposed (10 plates per group) in the presence (6 hours) and absence (2 hours) of activation to 0 (DMSO), 2000, 4000, and 8000 mg/ml. **Mutagenicity is not indicated**. **Unacceptable** and not upgradeable (dosing level justification, individual plate counts, test material characterization, borderline activity with the positive control). (J. Remsen, 5/30/85; updated to electronic format, H. Green, 11/8/95).

046 990435, "Mutagenicity Test on Saccharomyces Cerevisiae MP-1 in Vitro with CGA 48988 (Test for Mutagenic Properties in Yeast Cells)", (Dr. P. Arni, Ciba-Geigy Limited, Protection of Health and Environment, Toxicology, Basle, Switzerland, Report # 79/1346, 10 April 1980). The test article is identified as CGA 48988 (metalaxyl). Saccharomyces cerevisiae MP-1 cells were exposed (10 plates/dose level) to 0 (DMSO), 40, 200, and 1000 mg/ml for 3.5 hours in the absence of activation. **Mutagenicity is not indicated**. **Unacceptable** and not upgradeable (no activation, no dosing level rationale). (J. Remsen, 5/30/85; updated to electronic format, H. Green, 11/7/95).

**046, 254 990439, 115260, "Autoradiographic DNA Repair Test on Rat Hepatocytes, CGA 48988, (In Vitro test for DNA-Damaging Properties) and Supplement", (Dr. E. Puri, Ciba-Geigy Limited, Basle, Switzerland, Report # 811259, 19 January 1982 and Supplement dated 18 November 1985). The test material is identified as CGA 48988 (metalaxyl) technical with 94.1%

purity. Hepatocytes from male Tif: RAI f (SPF) rats were exposed in quadruplicate to untreated medium, 0 (DMSO), 16, 80, 400, and 2000 mg/ml for 5 hours. **No increase in unscheduled DNA synthesis. Acceptable**. (J. Remsen, 5/31/85; H. Green and Gee, 2/9/96).

254 115261, "Autoradiographic DNA Repair Test on Rat Hepatocytes", (Dr. E. Puri, Ciba-Geigy Limited, Basle, Switzerland, Experimental Pathology, Report # 851004, 25 November 1985). The test article is identified as CGA 48 988 (metalaxyl) technical with 95.7% purity. Hepatocytes from male Tif: RAIf(SPF) rats were exposed in quadruplicate to 0 (DMSO), untreated medium, 16, 80, 400, 2000 mg/ml for 5 hours. **No increase in unscheduled DNA synthesis. Acceptable. (H. Green and Gee, 2/9/96)

REPRODUCTIVE TOXICITY, RAT

009 990432, "Effect of CGA 48-988 on Reproductive Function of Multiple Generations in the Rat", (David D. Cozens, et. al., Huntingdon Research Centre, Huntingdon, Cambridgeshire, England, Report # CBG 181/80254, 23 May 1980). The test article is identified as CGA 48-988 (metalaxyl) technical with 93.5% purity. 12 to 25 Crl:COBS CD (SD) BR strain rats per sex per group received 0, 50, 250, and 1250 ppm in the diet through 3 generations with 2 litters per generation. Decreased bodyweights were noted for F1 parental males and females and for F2 males at the mid and high dose levels. Parental NOEL = 50 ppm. Reproductive NOEL = 1250 ppm. NOAEL = 1250 ppm. **Acceptable. (J. Remsen, 5/30/85; updated to electronic format, H. Green, 10/2/95).

DEVELOPMENTAL TOXICITY

Rat

003 990431, "Reproduction Study, CGA 48988 tech., Rat Seg. II (Test for Teratogenic or Embryotoxic Effects)", (Dr. H. Fritz, Ciba-Geigy Limited, Pharmaceuticals Division, Toxicology/Pathology, Basle, Switzerland, Report # 227716, 7 February 1978). The test article is identified as CGA 48988 (metalaxyl) technical. 25 mated Sprague-Dawley derived (Tif/RAI) female rats per group received 0, 20, 60, and 120 mg/kg/day on gestation days 6 through 15. **Teratogenicity is not indicated**. Previously reviewed as Unacceptable and not upgradeable (dosing level rationale, incomplete results, dosing characterization). (J. Remsen, 5/28/85; updated to electronic format, H. Green, 10/26/95).

** 115 036187, 254 115257 "Teratology Study in Rats", (James L. Schardein, M.S., International Research and Development Corporation, Report # 382-100, 3 January 1985). The test article is identified as metalaxyl technical. 27 or 38 (high dose group) mated Charles River COBS* CD* female rats received 0, 50, 250, and 400 mg/kg/day by gavage on gestation days 6 through 15. At 400 mg/kg/day, all dams had convulsions after dosing and 12 of 38 died. At 250 mg/kg/day, 1 of 27 died and 10 had convulsions after dosing. Maternal NOEL = 50 mg/kg/day. Developmental NOEL = 400 mg/kg/day. **Unacceptable** and upgradeable (dosing suspension analyses, dosing rationale). (J.Parker, 11/18/85). Upgraded to Acceptable upon submission of analysis of dosing suspension in 254 115257 (P. Iyer, 1/31/96).

254 115257, "Teratology Study in Rats", Supplemental Information submitted in response to data call-in. (Ciba-Geigy Corporation, Ag. Division, N.C. 6/2/92).
Analyses of dosing suspensions used in previously submitted teratology studies 115 036186 and 036187. Analysis of dosing suspensions prepared prior to initiation and administration in the first week of the study (036186) demonstrated levels of Metalaxyl between 91 and 104% of target concentrations. Test material was determined to be stable in suspension for 6 hours in pilot study. The rationale for dosage selection in 036187 from the results of the range-finding

study (036186) remains unclear. The analysis of dosing suspension and along with submission of methods used for the analyses upgrades the study to Acceptable (P. Iyer 1/31/96).

115 036186 "Range-finding teratology study in rats." (James L. Schardein, International Research and Development Corporation, Report # 382-099, 1/3/85) Five mated Charles River COBS CD female rats per group received metalaxyl technical at 0 (1% methylcellulose), 75, 125, 250 or 500 mg/kg/day by gavage on gestation days 6 through 15. All dams survived. Clinical signs at 500 mg/kg/day included decreased activity, unsteadiness, stained abdominal haircoat, lacrimation. A slight inhibition in food consumption and bodyweight gain were seen at 250 and 500 mg/kg/day. No changes in Cesarean section parameters were reported. No separate worksheet. (Green and Iyer, 1/31/96)

Rabbit

** 114 036184, 036185, 254 115256 "Teratology Study in Rabbits", (Michael F. Kenel, Ph.D., International Research and Development Corporation, Report # 382-098, 4 December 1984). The test article is identified as metalaxyl technical. 18 inseminated Dutch Belted female rabbits per group received 0 (1% methylcellulose), 30, 150, and 300 mg/kg/day by gavage on gestation days 7 through 19. Bodyweight gain and food consumption were reduced for high dose dams during the treatment period. Maternal NOEL = 150 mg/kg/day. Developmental NOEL = 300 mg/kg/day. Previously reviewed to be Unacceptable, upgradeable upon submission of analysis of test material (V. de Vlaming and J. Parker, 11/20/85). 254 115256 provided analysis of dosing material suspensions, upgraded to Acceptable (P. Iyer, 1/29/96).

NEUROTOXICITY

Acute neurotoxicity, rat

Study not submitted.

90-day neurotoxicity, rat

Study not submitted.

Developmental neurotoxicity, rat

Study not submitted.

Delayed neurotoxicity, hen

Study not submitted nor required at this time.

IMMUNOTOXICITY

Study not submitted.

ENDOCRINE DISRUPTOR STUDIES

Study not submitted nor required at this time.

SUPPLEMENTAL STUDIES

Studies not submitted nor required at this time.