

Metalaxyl; CASRN 57837-19-1

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the [IRIS assessment development process](#). Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the [guidance documents located on the IRIS website](#).

STATUS OF DATA FOR Metalaxyl

File First On-Line 01/31/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	01/31/1987
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	not evaluated	

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Metalaxyl

CASRN — 57837-19-1

Last Revised — 01/31/1987

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of

information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Increased serum alkaline phosphatase levels and increased liver-to-brain weight ratio	NOEL: 250 ppm (6.25 mg/kg/day) LEL: 1000 ppm (25 mg/kg/day)	100	1	6E-2 mg/kg/day
6-Month Feeding Dog Study				
Ciba-Geigy, 1981a				

*Conversion Factors -- 1 ppm = 0.025 mg/kg/day (assumed dog food consumption)

I.A.2. Principal and Supporting Studies (Oral RfD)

Ciba-Geigy Corporation. 1981a. MRID No. 00071598. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Four groups of 6 male and 6 female dogs were given diets containing 0, 50, 250, or 1000 ppm metalaxyl for 6 months. Two dogs of each sex were also added to the control and high-dose groups to be continued on control diets after termination of the feeding period. Alkaline phosphatase levels in the dogs given the 1000 ppm diet were significantly higher than those for control group dogs at the 4-, 5-, and 6-month observations. Liver-to-brain weight ratios for the high dose group females were significantly increased in comparison with control group values, and absolute liver weights and liver-to-body weight ratios showed a dose-related trend toward increasing liver weight. However, these trends were not statistically significant. These results suggested a NOEL of 250 ppm (6.3 mg/kg/day) and an LEL of 1000 ppm (25 mg/kg/day).

I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF — Based on a chronic exposure study, an uncertainty factor of 100 was used to account for the inter- and intraspecies differences. An additional UF of 10 to account for the subchronic (6-month) nature of the dog study was not considered necessary since the 3-month rat study and the 2-year rat study have the same NOEL, thus indicating that the effects seen in subchronic exposure studies are not likely to be exacerbated in chronic exposure studies.

MF — None

I.A.4. Additional Studies/Comments (Oral RfD)

Data Considered for Establishing the RfD

1. 6-Month Feeding - dog: Principal study - see discussion above; core grade minimum
2. 3-Month Feeding - rat: NOEL=250 ppm (12.5 mg/kg/day); LEL=1250 ppm (62.5 mg/kg/day) (decreased food consumption and minimal cellular hypertrophy in parenchymal cells); core grade guideline (Ciba-Geigy, 1977)
3. Teratology - rat: Teratogenic NOEL=400 mg/kg/day (HDT); Fetotoxicity NOEL=50 mg/kg/day; LEL=250 mg/kg/day (unossified sternebrae); Maternal toxicity NOEL=50 mg/kg/day; LEL=250 mg/kg/day (convulsions, ataxia); core grade minimum (Ciba-Geigy, 1985)
4. Teratology - rabbit: Maternal toxicity NOEL=150 mg/kg/day; LEL=300 mg/kg/day (HDT) (2.3% body weight loss supported by preliminary range-finding study results, weight loss more pronounced at 500 mg/kg/day in preliminary study and mortality at 1000 mg/kg/day dose level in range-finding study); Embryotoxicity, Fetotoxicity and Teratogenicity NOEL=300 mg/kg/day (HDT); core grade minimum (Ciba-Geigy, 1984)
5. 3-Generation Reproduction - rat: Reproductive Effects NOEL=1250 ppm (62.5 mg/kg/day) (HDT); core grade minimum (Ciba-Geigy, 1980a)
6. 2-Year Chronic Feeding (oncogenic) - rat: Systemic NOEL=250 ppm (12.5 mg/kg/day); LEL=1250 ppm (62.5 mg/kg/day) (HDT) (Increased liver weight and periacinar vacuolization of hepatocytes); core grade minimum (Ciba-Geigy, 1980b)

Data Gap(s): None

Other Data Reviewed

1. 2-Year Oncogenic - mice: Systemic NOEL=250 ppm (37.5 mg/kg/day); LEL=1250 ppm (87.5 mg/kg/day) (fatty infiltration of liver); core grade minimum (Ciba-Geigy, 1981b)

I.A.5. Confidence in the Oral RfD

Study — Medium

Database — High

RfD — High

The principal study appears to be of good quality and is given a medium confidence rating. Additional studies are of good quality and there are no data gaps; therefore, confidence in the database is high. High confidence in the RfD follows.

I.A.6. EPA Documentation and Review of the Oral RfD

Pesticide Registration Files

Agency Work Group Review — 07/08/1986, 12/08/1994

Verification Date — 07/08/1986

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for Metalaxyl conducted in August 2003 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Metalaxyl

CASRN — 57837-19-1

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Metalaxyl
CASRN — 57837-19-1

This substance/agent has not undergone a complete evaluation and determination under US EPA's IRIS program for evidence of human carcinogenic potential.

III. [reserved]

IV. [reserved]

V. [reserved]

VI. Bibliography

Substance Name — Metalaxyl
CASRN — 57837-19-1

VI.A. Oral RfD References

Ciba-Geigy Corporation. 1977. MRID No. 00084110. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Ciba-Geigy Corporation. 1980a. MRID No. 00071600, 00130952. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Ciba-Geigy Corporation. 1980b. MRID No. 00071565, 00080302, 00098481, 00130950. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Ciba-Geigy Corporation. 1981a. MRID No. 00071598. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Ciba-Geigy Corporation. 1981b. MRID No. 00103354, 00127880, 00130951. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Ciba-Geigy Corporation. 1984. MRID No. 00144371. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Ciba-Geigy Corporation. 1985. MRID No. 00144422, 00144423. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References

None

VII. Revision History

Substance Name — Metalaxyl
CASRN — 57837-19-1

Date	Section	Description
10/28/2003	I.A.6.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Metalaxyl
CASRN — 57837-19-1
Last Revised — 01/31/1987

- 57837-19-1
- ALANINE, N-(METHOXYACETYL)-N-(2,6-XYLYL)-, METHYL ESTER, DL-
- APRON 2E
- CG 117
- CGA 48988

- DL-ALANINE, N-(2,6-DIMETHYLPHENYL)-N-(METHOXYACETYL)-, METHYL ESTER
- METALAXIL
- Metalaxyl
- N-(2,6-DIMETHYLPHENYL)-N-(METHOXYACETYL)-ALANINE METHYL ESTER
- N-(2,6-DIMETHYLPHENYL)-N-(METHOXYACETYL)-DL-ALANINE METHYL ESTER
- RIDOMIL
- RIDOMIL 2E
- SUBDUE
- SUBDUE 2E
- SUBDUE 5SP