Avermectin B1; CASRN 65195-55-3

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 Avermectin B1

File First On-Line 07/01/1989

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	07/01/1989
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 — Avermectin B1
CASRN — 65195-55-3
Primary Synonym — Abamectin
Last Revised — 07/01/1989

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 retinal folds in weanlings, decrease viability and lactation indices, decreased pup body weight, increase of dead pups at birth **2-Generation Rat Reproduction Study** **Merck and Co., 1984**	NOEL: 0.12 mg/kg/day LEL: 0.40 mg/kg/day	300	1	4E-4 mg/kg/day

*Conversion Factors: Actual dose tested

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

Merck and Company. 1984. MRID No. 00164151. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Avermectin was given orally by gavage to randomized groups of 30 male and 30 female Sprague-Dawley rats at dosages of 0 (vehicle), 0.05 mg/kg/day, 0.12, and 0.40 mg/kg/day for two generations with two litters/generation. Intubation with either the vehicle or the test material was initiated daily when these rats were 39 days old and had individual body weights ranging from 142 to 194 g (male rats) and from 113 to 151 g (female rats). Daily dosing was continued until death.

At 0.40 mg/kg/day several effects were observed including increased retinal folds in weanlings, increase of dead pups at birth, decrease viability and lactation indices, and decreased pup body

weight. Therefore, the NOEL for this study is 0.12 mg/kg/day based on the effects observed at 0.40 mg/kg/day.

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

UF — An uncertainty factor of 100 was used to account for the inter- and intraspecies differences. An additional UF of 3 was used to account for the following: 1) the severity of the effects at the LEL dose observed in the critical study, and 2) maternal toxicity (mortality) and developmental toxicity (cleft palate) observed in the mouse teratology studies (Delta-8,9-Isomer).

MF — None

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

Avermectin B1 (technical) is composed of 80% Avermectin B1a and 20% Avermectin B1b. The difference structurally between B1a and B1b is that B1a has a C2H5- group and the B1b has a CH3-group attached to one of the ring structures. Therefore, the only chemical difference between B1a and B1b is a methylene (-CH2) group.

When Avermectin B1 is applied to plants, a plant photoproduct forms which is not present in animals. This plant photoproduct is the delta-8,9-isomer. which possesses Avermectin B1-like toxicological activity. Further photodegradation of Avermectin B1 results in polar degradates in plants but not in animals. The polar degradates do not possess Avermectin B1-like toxicological properties.

The parent compound, Avermectin B1, and the delta-8,9-isomer are regulated toxicologically (tolerance expression in food has both). Although the polar degradates are also present in food, they are not regulated toxicologically since they are toxicologically insignificant.

Data Considered for Establishing the RfD

1) 2-Generation Reproduction - rat: Principal study - see previous description; core grade minimum

2) 2-Year Feeding (oncogenic) - rat: Systemic NOEL=1.5 mg/kg/day; Systemic LEL=2.0 mg/kg/day (HDT; treatment-induced tremors in both sexes); core grade minimum (Merck and Co., 1985a)

3) 52-Week Feeding - dog: NOEL=0.25 mg/kg/day; LEL=0.5 mg/kg/day (mydriasis); core grade guideline (Merck and Co., 1987)

4) Teratology - rat: Maternal, Teratogenic, and Fetotoxic NOEL=1.6 mg/kg/day (HDT); Maternal, Teratogenic, and Fetotoxic LEL=none; core grade minimum (Merck and Co., 1982a)

5) Teratology - rabbit: Maternal NOEL=1 mg/kg/day; Maternal LEL=2 mg/kg/day (decreases in body weight, food consumption and water consumption); core grade minimum (Merck and Co., 1982b)

6) Teratology - mouse: (Avermectin B1a) Teratogenic NOEL=0.2 mg/kg/day; Teratogenic LEL=0.4 mg/kg/day (cleft palate); Maternal toxicity NOEL=none (mortality); core grade minimum (Merck and Co., 1982c)

7) Teratology - mouse: (Avermectin B1b) Maternal NOEL=0.05 mg/kg/day; Maternal LEL=0.075 mg/kg/day (HDT; mortality in 2 mice after 6 doses); Developmental NOEL=0.075 mg/kg/day); Developmental LEL=none; core grade minimum (Merck and Co., 1985b)

Other Data Reviewed:

1) 94-Week Feeding (oncogenic) - mouse: Systemic NOEL=4 mg/kg/day; Systemic LEL=8 mg/kg/day (increased incidence of skin dermatitis in males, increase incidence of extramedullary hematopoiesis in the spleen of males, increased mortality in males and tremors and body weight decrease in females); core grade minimum (Merck and Co., 1985c)

2) 14-Week Feeding - rat: NOEL=0.4 mg/kg/day (HDT; rats used in this study had previously been exposed in utero to the test material); LEL=none; core grade minimum [Merck and Co., n.d.(a)]

3) 18-Week Feeding - dog: NOEL=0.25 mg/kg/day; LEL=0.5 mg/kg/day (tremors, one death, pathology of the liver, decreased body weight); core grade minimum [Merck and Co., n.d.(b)]

4) Teratology - rat: (Delta-8,9-Isomer) Maternal and Developmental NOEL=1.0 mg/kg/day (HDT); core grade minimum (Merck and Co., 1988a)

5) Teratology - mouse: Three mouse teratology studies conducted with the Delta-8,9-Isomer of Avermectin yielded the following results: Study No. 84- 722-1: Maternal NOEL=0.1 mg/kg/day; Maternal LEL=0.5 mg/kg/day (mortality); Teratogenic NOEL=0.05 mg/kg/day; Teratogenic LEL=0.1 mg/kg/day (cleft palate); core grade minimum (Merck and Co., 1985d); Study No. 85-710-0: Maternal NOEL=0.6 mg/kg/day; Maternal LEL=none; Teratogenic NOEL=0.06

mg/kg/day; core grade minimum (Merck and Co., 1985d) Study No. 85-710-1: Maternal NOEL=0.1 mg/kg/day; Maternal LEL=0.5 mg/kg/day (mortality); Teratogenic NOEL=0.03 mg/kg/day; Teratogenic LEL=0.1 mg/kg/day (cleft palate); core grade minimum (Merck and Co., 1985d) Based on the above studies, the NOEL for maternal toxicity in mice is 0.1 mg/kg/day, and the LEL is 0.5 mg/kg/day. The NOEL for teratogenic toxicity is 0.06 mg/kg/day (based on the highest NOEL observed), and the LEL is 0.1 mg/kg/day. This latter NOEL of 0.06 mg/kg/day, if divided by a 100-fold uncertainty factor, would essentially yield the same RfD as verified.

6) Teratology - mouse: (Citrus-Derived Polar Degradates) Maternal, Developmental, and Teratogenic NOEL=1.0 mg/kg/day (HDT); core grade minimum (Merck and Co., Inc. 1988b)

Data Gap(s): None

I.A.5. Confidence in the Oral RfD

Study — Medium
Database — High
RfD — High

The critical study is of adequate quality and is given a medium confidence rating. Additional data are supportive and of good quality and therefore the database is given a high confidence rating. High confidence in the RfD follows.

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

Source Document — This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation — Pesticide Registration Files

Agency Work Group Review — 04/20/1989

Verification Date — 04/20/1989

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 Avermectin B1 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 — Avermectin B1
CASRN — 65195-55-3
Primary Synonym — Abamectin

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Avermectin B1
CASRN — 65195-55-3
Primary Synonym — Abamectin

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 — Avermectin B1
CASRN — 65195-55-3
Primary Synonym — Abamectin

VI.A. Oral RfD References

Merck and Company. 1982a. MRID No. 00130819. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Merck and Company. 1982b. EPA Accession No. 249152. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Merck and Company. 1982c. EPA Accession No. 246894. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Merck and Company. 1984. MRID No. 00164151. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Merck and Company. 1985a. MRID No. 40069601, 40375511, 40517801. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Merck and Company. 1985b. EPA Accession No. 265572. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Merck and Company. 1985c. MRID No. 40069602, 40375512, 40517802. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Merck and Company. 1985d. EPA Accession No. 265564. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Merck and Company. 1987. MRID No. 00164022, 40375510. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Merck and Company. 1988a. MRID No. 40713403. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Merck and Company. 1988b. MRID No. 40912701. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Merck and Company. No date, a,b. EPA Accession No. 246895. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References

None

VII. Revision History

Substance Name — Avermectin B1
CASRN — 65195-55-3
Primary Synonym — Abamectin

Date	Section	Description
07/01/1989	I.A.	Oral RfD summary on-line
10/28/2003	I.A.6.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Avermectin B1
CASRN — 65195-55-3
Primary Synonym — Abamectin
Last Revised — 07/01/1989

- 65195-55-3
- ABAMECTIN
- ANTIBIOTIC C 076B1a
- AVERMECTIN A1a, 5-O-DEMETHYL-
- AVERMECTIN B1
- AVERMECTIN B1a
- 5-O-DEMETHYLAVERMECTIN Ala