

Isoxaben; CASRN 82558-50-7

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 Isoxaben

File First On-Line 09/26/1988

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	09/26/1988
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	yes	09/01/1991

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Substance Name — Isoxaben
CASRN — 82558-50-7
Primary Synonym — EL-107
Last Revised — 09/26/1988

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 BUN; decreased serum AP and AST; decreased food consumption efficiency; increased heart/body weight	NOEL: 125 ppm (5 mg/kg/day, males; 6.2 mg/kg/day, females)	100	1	5E-2 mg/kg/day
	LEL: 1250 ppm (50.7 mg/kg/day, males; 61.8 mg/kg/day, females)			
2-Year Rat Feeding Study				
Elanco Products, 1985a				

*Conversion Factors: Actual doses tested

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

Elanco Products Company. 1985a. MRID No. 00164553. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Fisher 344 rats, 60/sex/group (2 replicates of 30/sex/group), were fed isoxaben in the diet for 2 years at levels of 0, 125, 1250, or 12,500 ppm (actual doses 0, 5, 50.7, and 526.5 mg/kg/day in males; 0, 6.2, 61.8, and 646.6 mg/kg/day in females). Observed effects included the following:

1) Mid dose (1250 ppm): Increased BUN, decreased serum levels of alkaline phosphatase (AP) and aspartate aminotransferase (AST), decreased food consumption efficiency (males and females); increased heart-to-body weight (males)

2) High dose (12,500 ppm): Decreased body weight and body weight gains; increase in alkaline phosphatase; increased liver-to-body weight ratios, kidney-to-body weight, and brain-to-body

weight (males and females); increased creatinine, decreased prostate weights, increased liver weights, and increased heart-to-body weight (males)

No effects were observed at the lowest dose tested (125 ppm) and is considered the NOEL for systemic toxicity.

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

UF — An uncertainty factor of 100 was used, 10 each to account for the inter- and intraspecies differences.

MF — None

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

Data Considered for Establishing the RfD:

- 1) 2-Year Feeding (oncogenic) - rat: Principal study - see previous description; core grade minimum
- 2) 1-Year Feeding - dog: NOEL=10 mg/kg/day; LEL=100 mg/kg/day (increased alkaline phosphatase; liver-to-brain weight ratio elevated in males and females, liver-to-body weight ratio elevated in females, some liver microsomal enzyme induction in high dose males); core grade minimum (Elanco Products Company, 1985b)
- 3) 3-Generation Reproduction - rat: Maternal NOEL=500 ppm (25 mg/kg/day); Maternal LEL=2500 ppm (125 mg/kg/day) (lowered body weight, body weight gains, increased liver/body weight in males and females); Reproductive NOEL=2500 ppm (125 mg/kg/day); Reproductive LEL=12500 ppm (625 mg/kg/day) (decreased number viable pups F2a, F2b; lowered body weight of progeny on postpartum day 21); Developmental NOEL=2500 ppm (125 mg/kg/day); Developmental LEL=12500 ppm (625 mg/kg/day) (decreases in viable fetuses/litter, increased hydroureter, microphthalmia); core grade minimum (Elanco Products Company, 1984a)
- 4) Teratology - rat: Maternal NOEL=320 mg/kg/day; Maternal LEL=1000 mg/kg/day (decreased body weight gain); Developmental NOEL=320 mg/kg/day; Developmental LEL=1000 mg/kg/day (increased preimplantation loss, increased resorptions, smaller litter size, increased number of runt fetuses); core grade minimum (Elanco Products Company, 1984b)
- 5) Teratology - rabbit: Maternal and Developmental NOEL=1000 mg/kg/day (HDT); Maternal and Developmental LEL=none; core grade minimum (Elanco Products Company, 1984c)

Other Data Reviewed:

- 1) 2-Year Feeding (oncogenic) - mice: Systemic NOEL=100 ppm (14 mg/kg/day); Systemic LEL=143 mg/kg/day) (lowered body weight, body weight gain in males; hepatocellular hyperplasia, hepatocellular cytomegaly); core grade minimum (Elanco Products Company, 1985c)
- 2) 1-Year Feeding - rat: NOEL=125 ppm (6.25 mg/kg/day); LEL=1250 ppm (62.5 mg/kg/day) (decreased body weight, body weight gain, food efficiency in high dose females; liver microsomal enzyme induction in high-dose males and females, mid-dose females [6, 12 months], and mid-dose males [3, 6 months]; serum glucose increase in males and females at 6 months); core grade minimum (Elanco Products Company, 1984d)
- 3) 90-Day Feeding - dog: Systemic NOEL=110 mg/kg/day; Systemic LEL=500 mg/kg/day (increased liver weight, liver-to-body weight ratio); core grade minimum (Elanco Products Company, 1984e)
- 1) 2-Year Feeding (oncogenic) - mice: Systemic NOEL=100 ppm (14 mg/kg/day); Systemic LEL=143 mg/kg/day) (lowered body weight, body weight gain in males; hepatocellular hyperplasia, hepatocellular cytomegaly); core grade minimum (Elanco Products Company, 1985c)
- 2) 1-Year Feeding - rat: NOEL=125 ppm (6.25 mg/kg/day); LEL=1250 ppm (62.5 mg/kg/day) [decreased body weight, body weight gain, food efficiency in high dose females; liver microsomal enzyme induction - high dose males and females, mid-dose females (6, 12 months), mid-dose males (3, 6 months); serum glucose increase in males and females at 6 months]; core grade minimum (Elanco Products Company, 1984d)
- 3) 90-Day Feeding - dog: Systemic NOEL=110 mg/kg/day; Systemic LEL=500 mg/kg/day (increased liver weight, liver/body weight ratio); core grade minimum (Elanco Products Company, 1984e)

Data Gap(s): None

I.A.5. Confidence in the Oral RfD

Study — High
Database — High
RfD — High

The critical study is of good quality and is given a high confidence rating. Additional studies are supportive and of good quality and therefore, the data base 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 — 10/14/1987

Verification Date — 10/14/1987

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 Isoxaben conducted in November 2001 identified one or more significant new studies. IRIS users may request the references for those studies from 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 — Isoxaben

CASRN — 82558-50-7

Last Revised — EL-107

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Isoxaben

CASRN — 82558-50-7

Primary Synonym — EL-107

Last Revised — 09/01/1991

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

Classification — C; possible human carcinogen

Basis — Based on a statistically significant increased incidence of benign liver tumors in one species.

II.A.2. Human Carcinogenicity Data

None.

II.A.3. Animal Carcinogenicity Data

Limited. There was a statistically significant increased incidence of a single tumor type in both sexes of one species. Isoxaben was fed to 60 B6C3F1 mice/sex/group at 0, 100, 1000, and 12,500 ppm for 2 years (Elanco, 1985). Decreased survival observed in the low-dose males and the mid-dose females did not contribute to any significant dose-related survival disparities for either sex. The OPP Peer Review committee agreed that, based on hepatic toxicity, the MTD was reached or slightly exceeded at the high dose (Rinde, 1987). There was also a statistically significant positive trend in hepatocellular adenoma incidence with dose for both sexes. In the

high-dose group there was a statistically significant increase in this tumor type in both male and female mice when compared to their respective controls. The incidences of hepatocellular adenomas in male mice were 3/44, 1/41, 3/47 and 12/48 in the control, low-, mid- and high-dose groups, respectively, and in female mice were 0/52, 3/52, 2/46 and 7/52 in the control, low-, mid- and high-dose groups, respectively (Swentzel, 1989). There was no statistically significant increase in hepatocellular carcinoma incidence nor a dose-related trend in either sex for this tumor type. The incidence of hepatocellular carcinomas in the control, low-, mid- and high-dose males was 9/56, 5/49, 5/55 and 5/55, respectively; the incidence of hepatocellular carcinomas in females receiving the same doses was 0/52, 1/52, 0/46 and 2/52, respectively (Swentzel, 1989). There was, however, a significant dose-related trend for combined hepatocellular adenomas/carcinomas in both sexes. There was an increase in these combined tumors in the high-dose females only (9/52) when compared to the female control group (0/52).

Isoxaben was fed to Fischer 344 rats (60/sex/group) at 0, 125, 1250 or 12,500 ppm for 2 years (Elanco, 1985). The OPP Peer Review Committee concluded that, although the MTD was slightly exceeded in the rat study (as indicated by observation of glomerulonephrosis and >10% decrease in body weight) these toxic effects did not compromise the relevance of the tumor data (Rinde, 1987). The Scientific Advisory Panel (SAP) also considered the doses in the rat study to have exceeded the MTD (U.S. EPA, 1988). A significant increasing trend in mortality with dose was found for male rats. There was an apparent increase in benign adrenal pheochromocytomas in males at the high dose when compared to controls; a statistically significant positive trend was found. The incidences of benign adrenal medulla pheochromocytomas in male rats were 10/59, 9/59, 9/59 and 18/59 in the control, low-, medium- and high- dose groups, respectively (Rinde, 1987). There were no significant findings in females.

II.A.4. Supporting Data for Carcinogenicity

Isoxaben was negative in a Salmonella assay for reverse mutation both with and without activation (Elanco, 1983a). It was also negative in a forward mutation assay in mouse lymphoma both with and without activation (Elanco, 1983c) and in an unscheduled DNA repair assay using rat hepatocytes (Elanco, 1983b).

Isoxaben was weakly positive in a male mouse micronucleus study (Elanco, 1984); however, this study was later evaluated as inconclusive by OPP because only a single dose level, not shown to be the MTD, was used and females were not tested (Rinde, 1987). A repeat study in male mice using 0, 800, 2000 or 5000 mg/kg confirmed the earlier presumptive positive result in males (Dearfield, 1988). Micronuclei were increased at all dose levels in the repeat study.

A search of several databases showed no structurally-related compounds of toxicological interest.

The OPP Peer Review committee designated isoxaben a Group C compound on the basis of a statistically significant increase in benign liver tumors in male and female mice. In contrast, the SAP classified isoxaben a Group D compound because significant hepatocarcinogenesis was observed only at the highest dose, a level at which hepatotoxicity (elevated serum enzymes, nodular hyperplasia, fatty degeneration) occurred. In a follow-up meeting, the Peer Review committee reiterated its original opinion that the weight-of-evidence is adequate for a Group C classification based on the following: 1) although chronic compound-induced hepatotoxicity can cause histopathological alterations, the mechanism involved in the compound-induced histopathological alterations is not the primary issue of consideration, 2) an MTD was not exceeded solely because there was target organ toxicity, and 3) the noted liver tumors are most likely compound-induced (Swentzel, 1989).

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

Not available.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

Not available.

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation

Source Document — Rinde, 1987; Swentzel, 1989

The Office of Pesticide Programs (Health Effects Division, U.S. EPA) peer reviewed data pertaining to the potential carcinogenicity of Isoxaben (Memorandum from K.C. Swentzel to R. Mountfort, Peer Review of Isoxaben- Reevaluation Following the September 7, 1988 Science Advisory Panel Review. 01/04/1989).

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Work Group Review — 05/03/1989

Verification Date — 05/03/1989

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the cancer assessment for Isoxaben conducted in November 2001 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.

II.D.3. EPA Contacts (Carcinogenicity Assessment)

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).

III. [reserved]

IV. [reserved]

V. [reserved]

VI. Bibliography

Substance Name — Isoxaben
CASRN — 82558-50-7
Primary Synonym — EL-107

VI.A. Oral RfD References

Elanco Products Company. 1984a. Accession No. 073297, 073298. Available from EPA. Write to FOI, EPA, Washington DC 20460.

Elanco Products Company. 1984b. Accession No. 073229. Available from EPA. Write to FOI, EPA, Washington DC 20460.

Elanco Products Company. 1984c. Accession No. 073299. Available from EPA. Write to FOI, EPA, Washington DC 20460.

Elanco Products Company. 1984d. Accession No. 073295. Available from EPA. Write to FOI, EPA, Washington DC 20460.

Elanco Products Company. 1984e. Accession No. 073293. Available from EPA. Write to FOI, EPA, Washington DC 20460.

Elanco Products Company. 1985a. MRID No. 00164553. Available from EPA. Write to FOI, EPA, Washington DC 20460.

Elanco Products Company. 1985b. Accession No. 265733. Available from EPA. Write to FOI, EPA, Washington DC 20460.

Elanco Products Company. 1985c. Accession No. 265737, 265738. Available from EPA. Write to FOI, EPA, Washington DC 20460.

VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References

Dearfield, K. 1988. U.S. EPA, Washington, DC. Memorandum to M. Jones, Office of Pesticide Programs, U.S. EPA, Washington, DC. Overview of submitted mutagenicity studies on Isoxaben. June 17.

Elanco Products Company. 1983a. MRID No. 00132136. Available from EPA. Write to FOI, EPA, Washington DC 20460.

Elanco Products Company. 1983b. MRID No. 00132137. Available from EPA. Write to FOI, EPA, Washington DC 20460.

Elanco Products Company. 1983c. MRID No. 00132138. Available from EPA. Write to FOI, EPA, Washington DC 20460.

Elanco Products Company. 1984. MRID No. 164555. Available from EPA. Write to FOI, EPA, Washington DC 20460.

Elanco Products Company. 1985. MRID No. 164553. Available from EPA. Write to FOI, EPA, Washington DC 20460.

Rinde, E. 1987. U.S. EPA, Washington, DC. Memorandum to R. Mountfort, Office of Pesticide Programs, U.S. EPA, Washington, DC. Peer Review of Isoxaben. October 5.

Swentzel, K.C. 1989. U.S. EPA, Washington, DC. Memorandum to R. Mountfort, Office of Pesticide Programs, U.S. EPA, Washington, DC. Peer Review of Isoxaben-Reevaluation Following the September 7, 1988 Science Advisory Panel Review. January 4.

U.S. EPA. 1988. FIFRA Science Advisory Panel Executive Summary: A set of Scientific Issues Being Considered by the Agency in Connection with the Peer Review Classification of Isoxaben as a Class C Oncogen. Stephen L. Johnson, Executive Secretary.

VII. Revision History

Substance Name — Isoxaben
CASRN — 82558-50-7
Primary Synonym — EL-107

Date	Section	Description
09/26/1988	I.A.	Oral RfD summary on-line
09/01/1991	II.	Carcinogenicity assessment on-line
12/03/2002	I.A.6., II.D.2.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Isoxaben
CASRN — 82558-50-7
Primary Synonym — EL-107
Last Revised — 09/26/1988

- 82558-50-7
- Benzamide, N-(3-(1-ethyl-1-methylpropyl)-5-isoxazolyl)-2,6-dimethoxy-
- Caswell No. 419F
- Compound 121607
- EL-107
- EPA Pesticide Chemical Code 125851
- Isoxaben
- N-(3-(1-Ethyl-1-methylpropyl)isoxazol-5-yl)-2,6-dimethoxybenzamide
- N-(3-(1-Ethyl-methylpropyl)-5-isoxazolyl)-2,6-dimethoxybenzamide
- N-(3-(1-Ethyl-1-methylpropyl)-5-isoxazolyl)-2,6-dimethoxybenzamide (9CI)