

Trifluralin; CASRN 1582-09-8

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 Trifluralin

File First On-Line 09/30/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	07/01/1989
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	yes	08/22/1988

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Substance Name — Trifluralin

CASRN — 1582-09-8

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 liver weights; increase in methemoglobin 12-Month Dog Feeding Study Hoechst Aktiengesellschaft, 1984a	NOEL: 30 ppm (0.75 mg/kg/day) LEL: 150 ppm (3.75 mg/kg/day)	100	1	7.5E-3 mg/kg/day

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

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

Hoechst Aktiengesellschaft. 1984a. MRID No. 00151908. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Beagle dogs (6/sex/dose) were fed diets containing 0, 30, 150, or 750 ppm (0, 0.75, 3.75, and 18.75 mg/kg/day) of trifluralin for 12 months. At 750 ppm (HDT; 18.75 mg/kg/day) there was a decreased weight gain in males and females. There were some significant decreases in red blood cell parameters in high-dose males and females. There was an increase in methemoglobin in mid- and high-dose males and females. Total serum lipids, triglycerides, and cholesterol were increased in high-dose males and females when compared with controls. There were increases in liver weight in males receiving 150 and 750 ppm (3.75 and 18.75 mg/kg/day) and females receiving 750 ppm trifluralin and increases in mean spleen weight in females receiving 750 ppm. There were no histologic findings that correlated with organ weight changes. Based on the increases in liver weights and methemoglobin, the LEL is 150 ppm (3.75 mg/kg/day) and the NOEL is 30 ppm (0.75 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.

MF — None

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

The previous RfD for trifluralin was established using a 3-month rat feeding study (Eli Lilly & Co., 1985) with a Systemic LEL of 2.5 mg/kg/day (lowest dose tested) based on increased alpha 1, alpha 2 and beta globulins in the urine. The original data from this study was re-examined with regard to total protein, alpha 1, alpha 2, and beta and gamma globulin. This reexamination concluded that an NOEL was established at 50 ppm (2.5 mg/kg/day) and an LEL at 200 ppm (10 mg/kg/day) based on evidence of protein excretion (TP, alpha 1, alpha 2, and beta globulins). Therefore, when the complete database for trifluralin is considered, the chronic dog study is the appropriate study to establish the RfD.

Data Considered for Establishing the RfD

- 1) 1-Year Feeding - dog: Principal study - see previous description; core grade guideline
- 2) 2-Year Feeding (oncogenic) - rat: Systemic NOEL=200 ppm (10 mg/kg/day); Systemic LEL=800 ppm (40 mg/kg/day) (body weight changes); core grade guideline (Hoechst Aktiengesellschaft, 1986a)
- 3) 2-Generation Reproduction - rat: Systemic NOEL=200 ppm (10 mg/kg/day); Systemic LEL=630 ppm (31.5 mg/kg/day) (decreased body weight); Reproductive NOEL=2000 ppm (100 mg/kg/day) (HDT); Reproductive LEL=none; core grade minimum (Elanco Product Co., 1986)
- 4) 2-Generation Reproduction - rat: Reproductive NOEL=650 ppm (32.5 mg/kg/day); Reproductive LEL=2000 ppm (100 mg/kg/day) (HDT; reduced litter size); Developmental NOEL=200 ppm (10 mg/kg/day); Developmental LEL=650 ppm (32.5 mg/kg/day) (increased weanling body weight); Parental NOEL=none; Parental LEL=200 ppm (10 mg/kg/day) (LDT; increased kidney weights); At 650 ppm renal lesions of the proximal tubules and increased relative kidney weights; core grade minimum (Hoechst Aktiengesellschaft, 1984b)
- 5) Teratology - rat: Maternal NOEL=225 mg/kg/day; Maternal LEL=475 mg/kg/day (decreased body weight and food consumption); Fetotoxic NOEL=475 mg/kg/day; Fetotoxic LEL=1000 mg/kg/day (decreased mean fetal body weight); Teratogenic NOEL=1000 mg/kg/day (HDT); Teratogenic LEL=none; core grade minimum (Elanco Product Co., 1984a)

6) Teratology - rabbit: Maternal NOEL=100 mg/kg/day; Maternal LEL=225 mg/kg/day (body weight loss); Fetotoxic NOEL=225 mg/kg/day; Fetotoxic LEL=500 mg/kg/day (HDT; decreased fetal weight and increased number of fetal runts); Teratogenic NOEL=500 mg/kg/day (HDT); Teratogenic LEL=none; core grade minimum (Elanco Product Co., 1984b)

Other Data Reviewed:

1) Oncogenicity - mouse: Systemic NOEL=50 ppm (7.5 mg/kg/day); Systemic LEL=200 ppm (30 mg/kg/day) (increased liver weight in males); At 800 ppm (120 mg/kg/day) (HDT) an increase in liver weight in males and females was observed; core grade supplementary (pending submission of historical control data) (Hoechst Aktiengesellschaft, 1986b)

2) 6-Month Feeding - dog: NOEL=none; LEL=400 ppm (10 mg/kg/day) (LDT; enlarged livers, discolored kidneys, corneal vascularization, hemolytic anemia and increase alkaline phosphatase); core grade supplementary (Hoechst Aktiengesellschaft, 1981)

3) 3-Month Feeding - rat: NOEL=none; LEL=800 ppm (40 mg/kg/day) (LDT; liver/body weight increases and pituitary/body weight decreases in all doses); core grade minimum (Hoechst Aktiengesellschaft, 1980)

4) 3-Month Special Urinalysis Study - rat: NOEL=50 ppm (2.5 mg/kg/day); LEL=200 ppm (10 mg/kg/day) [evidence of protein excretion (TP, alpha 1, alpha 2, and beta globulins)]; core grade minimum (Eli Lilly & Co., 1985)

5) Teratology - rat: Maternal NOEL=100 mg/kg/day; Maternal LEL=500 mg/kg/day (decreased food consumption and increased liver and spleen weights); Developmental NOEL=none; LEL=20 mg/kg/day (reduced skeletal maturity and increased vascular fragility); core grade supplementary (Hoechst Aktiengesellschaft, 1983)

6) Teratology - rabbit: Maternal and Developmental NOEL=60 mg/kg/day (HDT); Maternal and Developmental LEL=none; core grade supplementary (Hoechst Aktiengesellschaft, 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; 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 Standard, June 1985; Position Document 1/2/3, August 1979; Position Document 4, July 1982; Pesticide Registration Files

Agency Work Group Review — 05/30/1986, 02/18/1987. 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 Trifluralin conducted in September 2002 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 — Trifluralin
CASRN — 1582-09-8

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Trifluralin

CASRN — 1582-09-8

Last Revised — 08/22/1988

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 — Classification is based on the induction of urinary tract tumors (renal pelvis carcinomas and urinary bladder papillomas) and thyroid tumors (adenomas/carcinomas combined) in one animal species (F344 rats) in one study. Trifluralin is structurally similar to ethalfluralin, a carcinogen in the rat.

II.A.2. Human Carcinogenicity Data

None.

II.A.3. Animal Carcinogenicity Data

Limited. A chronic bioassay of trifluralin was performed in F344 rats in which 60 animals/sex received dietary doses of 0, 813, 3250 and 6500 ppm for 2 years (Emmerson et al., 1980).

Statistically significant ($p < 0.05$) increases in the incidences of bladder papillomas and renal pelvis carcinomas were found at the highest dose level tested in female and male rats, respectively. In addition, a significant ($p < 0.05$) increase in the incidence of follicular cell tumors of the thyroid gland (adenomas plus carcinomas combined) occurred at the highest dose tested in male rats. All of the previous increased tumor incidences exceeded historical incidences for similar tumors in other studies performed at the test laboratory.

Four other rodent chronic bioassays of trifluralin in the diet have been performed. These included a 2-year study in Sprague-Dawley rats (0, 200, 1000 and 2000 ppm) (Eli Lilly, 1966), a 78-week study in Osborne-Mendel rats (0, 3250 and 6500 ppm) (NCI, 1978a), a 78-week study in B6C3F1 mice (0, 2375 and 5000 ppm) (NCI, 1978b) and a 2-year study in B6C3F1 mice (0, 563, 2250 and 4500 ppm) (Eli Lilly, 1980). Trifluralin did not produce statistically significant increases in tumors in any of these studies.

II.A.4. Supporting Data for Carcinogenicity

Trifluralin is structurally related to ethalfuralin, which is oncogenic, producing mammary gland fibroadenomas in female F344 rats. In addition, both trifluralin and ethalfuralin produce a common urinary metabolite in rats that produces nonneoplastic renal pathology, including bladder calculi.

There was no evidence of mutagenicity for trifluralin in rat dominant lethal, L5178Y mouse lymphoma, Salmonella typhimurium, Saccharomyces cerevisiae, and DNA repair assays, nor did it induce sister chromatid exchange in Chinese hamster ovary cells.

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

II.B.1. Summary of Risk Estimates

Oral Slope Factor: $7.7E-3/\text{mg}/\text{kg}/\text{day}$

Drinking Water Unit Risk: $2.2E-7/\text{ug}/\text{L}$

Extrapolation Method — linearized multistage procedure, extra risk

Drinking Water Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	5E+2 ug/L
E-5 (1 in 100,000)	5E+1 ug/L
E-6 (1 in 1,000,000)	5 ug/L

II.B.2. Dose-Response Data (Carcinogenicity, Oral Exposure)

Tumor Type: combined renal pelvis carcinomas, urinary bladder papillomas and/or thyroid adenomas and carcinomas

Test animals: rat/F344, male

Route: diet

Reference: Emmerson et al., 1980

Administered Dose (ppm)	Human Equivalent Dose (mg/kg)/day	Tumor Incidence
0	0	5/60
813	5.1	5/60
3250	21.9	9/60
6500	46.5	17/60

II.B.3. Additional Comments (Carcinogenicity, Oral Exposure)

Incidence data were based on observation of at least one tumor at any of the indicated sites.

The unit risk should not be used if the water concentration exceeds 5E+4 ug/L, since above this concentration the slope factor may differ from that stated.

II.B.4. Discussion of Confidence (Carcinogenicity, Oral Exposure)

Tumors were induced at different sites in F344 rats of one or both sexes. An adequate number of animals was observed in a lifetime study.

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 — U.S. EPA, 1982, 1986

The Toxicology Branch Peer Review Committee reviewed data on trifluralin.

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

Agency Work Group Review — 05/13/1987, 06/03/1987, 06/24/1987

Verification Date — 06/24/1987

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 Trifluralin conducted in September 2002 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 — Trifluralin
CASRN — 1582-09-8

VI.A. Oral RfD References

Elanco Product Company. 1984a. MRID No. 00152419. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Elanco Product Company. 1984b. MRID No. 00152421. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Elanco Product Company. 1986. MRID No. 00162543. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Eli Lilly and Company. 1985. MRID No. 00157156, 40138301. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Hoechst Aktiengesellschaft. 1980. MRID No. 00151906. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Hoechst Aktiengesellschaft. 1981. MRID No. 00151907. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Hoechst Aktiengesellschaft. 1983. MRID No. 00151899. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Hoechst Aktiengesellschaft. 1984a. MRID No. 00151908. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Hoechst Aktiengesellschaft. 1984b. MRID No. 00151901, 00151903. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Hoechst Aktiengesellschaft. 1984c. MRID No. 00151900. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Hoechst Aktiengesellschaft. 1986a. MRID No. 00153496, 00162456, 00162458. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Hoechst Aktiengesellschaft. 1986b. MRID No. 00158935. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

VI.B. Inhalation RfD References

None

VI.C. Carcinogenicity Assessment References

Eli Lilly Company. 1966. Rat oncogenicity study of trifluralin. (Cited in U.S. EPA, 1986)

Eli Lilly Company. 1980. Mouse oncogenicity study of trifluralin. (Cited in U.S. EPA, 1986)

Emmerson, J.L., E.C. Pierce, J.P. McGrath, et al. 1980. The chronic toxicity of compound 36352 (trifluralin) given as a compound of the diet to the Fischer 344 rats for two years. Studies R-87 and R-97 (unpublished study received September 18, 1980 under 1471-35; submitted by Elanco Products Co., Division of Eli Lilly and Co., Indianapolis, IN).

NCI (National Cancer Institute). 1978a. Rat oncogenicity study of trifluralin. (Cited in U.S. EPA, 1986)

NCI (National Cancer Institute). 1978b. Mouse oncogenicity study of trifluralin. (Cited in U.S. EPA, 1986)

U.S. EPA. 1982. Trifluralin (TREFLAN) Position Document 4. Office of Pesticides and Toxic Substances, Washington, DC, July.

U.S. EPA. 1986. Toxicology Branch Peer Review Committee Memorandum on Trifluralin, April 11.

VII. Revision History

Substance Name — Trifluralin
CASRN — 1582-09-8

Date	Section	Description
08/22/1988	II.	Carcinogen summary on-line
05/01/1989	I.A.	Withdrawn; new RfD verified (in preparation)
07/01/1989	I.A.	Oral RfD summary replaced; RfD changed
12/03/2002	I.A.6., II.D.2.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Trifluralin
CASRN — 1582-09-8
Last Revised — 09/30/1987

- 1582-09-8
- AGREFLAN
- AGRIFLAN 24
- BENZENAMINE, 2,6-DINITRO-N,N-DIPROPYL-4-(TRIFLUOROMETHYL)-
- CRISALIN
- DIGERMIN
- 2,6-DINITRO-N,N-DIPROPYL-4-(TRIFLUOROMETHYL)BENZENAMINE
- 2,6-DINITRO-N,N-DI-n-PROPYL-alpha,alpha,alpha-TRIFLUORO-p-TOLUIDINE
- 2,6-DINITRO-4-TRIFLUORMETHYL-N,N-DIPROPYLANILIN
- 4-(DI-n-PROPYLAMINO)-3,5-DINITRO-1-TRIFLUOROMETHYLBENZENE

- ELANCOLAN
- L-36352
- LILLY 36,352
- NCI-C00442
- NITRAN
- N,N-DIPROPYL-2,6-DINITRO-4-TRIFLUORMETHYLANILIN
- N,N-DI-n-PROPYL-2,6-DINITRO-4-TRIFLUOROMETHYLANILINE
- N,N-DIPROPYL-4-TRIFLUOROMETHYL-2,6-DINITROANILINE
- OLITREF
- SU SEGURO CARPIDOR
- TREFANOCIDE
- TREFICON
- TREFLAM
- TREFLAN
- TREFLANOCIDE ELANCOLAN
- s-TRIAZINE, 2-CHLORO-4,6-BIS(ETHYLAMINO)-
- TRIFLUORALIN
- alpha,alpha,alpha-TRIFLUORO-2,6-DINITRO-N,N-DIPROPYL-p-TOLUIDINE
- Trifluralin
- TRIFLURALINE
- TRIFUREX
- TRIKEPIN
- TRIM