

US EPA ARCHIVE DOCUMENT

INTEGRATED RISK INFORMATION SYSTEM

Substance Name: Trifluralin
CASRN: 1582-09-8

Last Revised: 01/01/92

Health risk assessment information on a chemical is included in IRIS only after a comprehensive review of chronic toxicity data by work groups composed of U.S. EPA scientists from several Program Offices. The summaries presented in the Oral RfD, Inhalation RfC and Carcinogenicity Assessment Sections represent a consensus reached in the review process. The other sections contain U.S. EPA information which is specific to a particular EPA program and has been subject to review procedures prescribed by that Program Office. The Regulatory Actions Section may not be based on the most current risk assessment, or may be based on a current, but unreviewed, risk assessment, and may take into account factors other than health effects (e.g., treatment technology). When considering the use of regulatory action data for a particular situation, note the date of the regulatory action, the date of the most recent risk assessment relating to that action, and whether technological factors were considered. Background information and explanations of the methods used to derive the values given in IRIS are provided in the five Background Documents, which are available in each section of the chemical files.

| <u>Category (section)</u> | <u>Status</u> | <u>Last Revised</u> |
|----------------------------------|---------------|---------------------|
| Oral RfD Assessment | Available | 07/01/89 |
| Inhalation RfC Assessment | empty | |
| Carcinogenicity Assessment | Available | 08/22/88 |
| Drinking Water Health Advisories | empty | |
| U.S. EPA Regulatory Actions | Available | 01/01/92 |
| Supplementary Data | empty | |

REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name: Trifluralin
CASRN: 1582-09-8

The Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. 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 Oral RfD Background Document for an elaboration of these concepts.

RfDs can also be derived for the noncarcinogenic health effects of compounds which 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 the Carcinogenicity Assessment Section of this file when a review of that evaluation is completed.

RfD ASSESSMENT SUMMARY TABLE

Crit. Dose: 0.75 mg/kg-day [Study 1 NOEL(adj)]
UF: 100 MF: 1 RfD: 7.5E-3 mg/kg-day Confidence: High

Crit Effect: (1) Increased liver weights; increase in methemoglobin

| | NOAEL (Study 1) | LOAEL (Study 1) |
|------------|-----------------------------------|-----------------------------------|
| Reported | 30 ppm | 150 ppm |
| ADJ | 0.75 mg/kg-day | 3.75 mg/kg-day |
| Study Type | 12-Month Dog Feeding Study | 12-Month Dog Feeding Study |
| Reference | Hoechst Aktiengesellschaft, 1984a | Hoechst Aktiengesellschaft, 1984a |

- 1) Hoechst Aktiengesellschaft, 1984a
12-Month Dog Feeding Study

Critical Effect: Increased liver weights; increase in methemoglobin

Defined Dose Levels:

NOAEL= 30 ppm
NOAEL(ADJ)= 0.75 mg/kg-day
LOAEL= 150 ppm
LOAEL(ADJ)= 3.75 mg/kg-day

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

DISCUSSION OF PRINCIPAL AND SUPPORTING STUDIES

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

REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

(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 was 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).

UNCERTAINTY AND MODIFYING FACTORS

UNCERTAINTY FACTORS:

An uncertainty factor of 100 was used to account for the inter- and intraspecies differences.

ADDITIONAL COMMENTS / STUDIES

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

REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

(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

CONFIDENCE IN THE RfD

Study: High

Data Base: 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 data base is given a high confidence rating. High confidence in the RfD follows.

REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)EPA DOCUMENTATION AND REVIEW

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: 05/30/86, 02/18/87, 04/20/89

Verification Date: 04/20/89

EPA CONTACTS

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BIBLIOGRAPHY

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.

===== REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD) =====

Write to FOI, EPA, Washington D.C. 20460.

----- REVISION HISTORY -----

02/89 RfD Data: Oral RfD summary noted as pending change
05/89 RfD Data: Withdrawn; new RfD verified (in preparation)
07/89 RfD Data: Oral RfD summary replaced; RfD changed

Trifluralin

RfC-1

REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Substance Name: Trifluralin
CASRN: 1582-09-8

Status: empty

CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name: Trifluralin
CASRN: 1582-09-8

The Carcinogenicity Assessment Section provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. 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 Carcinogen Assessment Background Document provides details on the rationale and methods used to derive the carcinogenicity values found in IRIS. Users are referred to the Oral RfD and Inhalation RfC Sections for information on long-term toxic effects other than carcinogenicity.

EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

WEIGHT-OF-EVIDENCE CLASSIFICATION

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.

HUMAN CARCINOGENICITY DATA

None.

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

 CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

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.

SUPPORTING DATA FOR CARCINOGENICITY

Trifluralin is structurally related to ethalfluralin, which is oncogenic, producing mammary gland fibroadenomas in female F344 rats. In addition, both trifluralin and ethalfluralin 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.

 QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

Slope Factor: 7.7E-3 per mg/(kg/day)
 Unit Risk: 2.2E-7 per ug/liter
 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/liter |
| E-5 (1 in 100,000) | 5E+1 ug/liter |
| E-6 (1 in 1,000,000) | 5E+0 ug/liter |

 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

| 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 |

 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.

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.

QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

No Data Available

EPA DOCUMENTATION AND REVIEW

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

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

The Toxicology Branch Peer Review Committee reviewed data on trifluralin.

Agency Work Group Review: 05/13/87, 06/03/87, 06/24/87

Verification Date: 06/24/87

EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

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William Burnam / OPP -- (703)305-4791

BIBLIOGRAPHY

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.

REVISION HISTORY

08/88 Ca Data: Carcinogen summary on-line

Trifluralin

DWHA-1

DRINKING WATER HEALTH ADVISORIES

Substance Name: Trifluralin
CASRN: 1582-09-8

Status: empty

U.S. EPA REGULATORY ACTIONS

Substance Name: Trifluralin
CASRN: 1582-09-8

EPA risk assessments may be updated as new data are published and as assessment methodologies evolve. Regulatory actions are frequently not updated at the same time. Compare the dates for the regulatory actions in this section with the verification dates for the risk assessments in the Oral RfD, Inhalation RfC and Carcinogen Assessment Sections, as this may explain inconsistencies. Also note that some regulatory actions consider factors not related to health risk, such as technical or economic feasibility. Such considerations are indicated for each action. In addition, not all of the regulatory actions listed in this section involve enforceable federal standards. Please direct any questions you may have concerning these regulatory actions to the U.S. EPA contact listed for that particular action. Users are strongly urged to read the background information on each regulatory action in the Regulatory Action Background Document.

FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTCIDE ACT (FIFRA)

Pesticide Active Ingredient Registration Standard

Status: Issued 1987
Reference: Trifluralin Pesticide Registration Standard. April, 1987 (NTIS No. PB87-201935).
Contact: Registration Branch / OPP / (703)305-5447

Pesticide Active Ingredient Special Review

Action: Final Regulatory Decision - PD 4
Year: 1982
Econ/Tech?: No, does not consider economic or technical feasibility
Reference: 47 FR 33777 (08/04/82) [NTIS# PB82-263252]
Contact: Special Review Branch / OPP / (703)308-8010

Summary of Regulatory Actions: Registration allowed to continue if total N-nitrosamine contamination is kept below 0.5 ppm for technical products, and below a figure based on trifluralin content for formulated products. Criterion of concern: oncogenicity and mutagenicity.

REVISION HISTORY

01/92 Reg Data: Regulatory Action section on-line

Trifluralin

Suppl-1

SUPPLEMENTARY DATA

Substance Name: Trifluralin
CASRN: 1582-09-8

Status: empty