Fomesafen; CASRN 72178-02-0

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 Fomesafen

File First On-Line 08/22/1988

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	not evaluated	
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 — Fomesafen
CASRN — 72178-02-0

Not available at this time.

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

Substance Name — Fomesafen
CASRN — 72178-02-0

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Fomesafen
CASRN — 72178-02-0
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 — Fomesafen produced liver adenomas and carcinomas in both sexes of Charles River CD-1 mice.

II.A.2. Human Carcinogenicity Data

None.

II.A.3. Animal Carcinogenicity Data

Limited. Sixty-four Charles River CD-1 mice/sex/dose group were dosed for 2 years with fomesafen at 0, 1, 5, 100 and 1000 ppm by dietary incorporation. A double-size control group was used. At 12 months, 24 mice/sex from the controls and 12 mice/sex from the treated groups were killed. In male mice at termination, the incidence of liver adenomas was significantly increased at 1, 100 and 1000 ppm when compared with controls. The incidences of liver carcinomas and a combination of liver adenomas and carcinomas were significantly increased at 1000 ppm. In the females, the incidence of adenomas was increased at 100 and 1000 ppm and carcinomas were increased at 1000 ppm when compared with controls. The incidence of adenomas and carcinomas combined was significantly increased at 100 and 1000 ppm. Both sexes, therefore, showed a progression from benign to malignant tumors with increased dose. Some liver tumors (adenomas and carcinomas) were apparent at the 52-week interval kill. There was increased mortality in the males at 100 and 1000 ppm and in the females at 1000 ppm, due to liver toxicity forcing termination of the study. The 1000 ppm animals were killed at 79 weeks (males) or 89 weeks (females). The MTD appeared to be exceeded at 100 ppm in the males and 1000 ppm in the females. The tumor increases occurred at dose levels of fomesafen that were both below and above the MTD (Huntingdon, 1985).

Fomesafen was administered in the diet to Wistar rats for 106 weeks using 52 rats/sex/dose at 0, 1, 5, 100 or 1000 ppm (ICI Central Toxicology Laboratory, 1984). No oncogenic effects were noted in either sex at any dose. The 1000 ppm dose exceeded the MTD for the males but approximated an MTD in females.

II.A.4. Supporting Data for Carcinogenicity

The primary target organ of toxicity in various nonchronic studies in rats and dogs was the liver (U.S. EPA, 1986). No metabolic studies were conducted on mice but studies conducted on rats demonstrated a preferential concentration in the liver, to the exclusion of other tissues. Some evidence of genotoxic potential was provided by in vitro and in vivo cytogenetic tests using rat bone marrow. It was negative in several reverse mutation assays (Ames) with Salmonella typhimurium and a transformation test using baby hamster kidney fibroblasts; furthermore, fomesafen did not bind to DNA in vivo (U.S. EPA, 1986). Fomesafen is structurally related to several chemicals shown to produce hepatocellular adenomas and carcinomas in mice (e.g., nitrofen, oxyfluoren, acifloren).

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

II.B.1. Summary of Risk Estimates

Oral Slope Factor — 1.9E-1/mg/kg/day

Drinking Water Unit Risk — 5.4E-6/ug/L

Extrapolation Method — Linearized multistage procedure, extra risk

Drinking Water Concentrations at Specified Risk Levels:

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

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

Tumor Type — liver adenomas and carcinomas
Test animals — mice/CD-1; males
Route — diet
Reference — Huntingdon, 1985

Administered Dose (ppm)	Human Equivalent Dose (mg/kg)/day	Tumor Incidence
0	0	30/127
1	0.01	26/63
5	0.06	17/64

Administered Dose (ppm)	Human Equivalent Dose (mg/kg)/day	Tumor Incidence
100	1.3	27/64
1000	5.6	42/64

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

Data from animals that died before observation of the first tumor were not used in the quantitative risk model. Adjustments were also made to account for early termination of the highest dose group. The human equivalent dose was calculated by use of Lehman's tables (1959) such that 1 ppm in mouse diet equals 7 mg/kg/day. A human weight of 60 kg, a mouse weight of 0.03 kg and a lifespan of 104 weeks for the mouse was assumed. The duration of the experiment was 106 weeks for all dose groups except the high-dose group for which an experimental duration of 80 weeks was assumed.

The unit risk should not be used if the water concentration exceeds 2E+3 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 observed in both sexes at the MTD or lower. The incidence and degree of the effect increased with the dose. There was evidence of progression of tumors from benign to malignancy. The survival adjustment was approximate.

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, 1986

The Toxicology Branch Peer Review Committee received data on fomesafen.

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

Agency Work Group Review — 08/05/1987

Verification Date — 08/05/1987

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 Fomesafen 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.

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 — Fomesafen
CASRN — 72178-02-0

VI.A. Oral RfD References

None

VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References

Huntingdon Research Centre. 1985. Two-year feeding study of fomesafen in mice. Huntingdon Research Centre, Huntingdon, Cambridgeshire, England. (Cited in U.S. EPA, 1986)

ICI Central Toxicology Laboratory. 1984. Two-year feeding study of fomesafen in rats. (Cited in U.S. EPA, 1986)

Lehman, A.J. 1959. Appraisal of the safety of chemicals in foods, drugs and cosmetics. Association of Food and Drug Officials in the United States. p. 1.

U.S. EPA. 1986. Toxicology Branch Peer Review Committee, Office of Pesticide Programs, Office of Pesticides and Toxic Substances, memorandum on Fomesafen, July 24.

VII. Revision History

Substance Name — Fomesafen
CASRN — 72178-02-0

Date	Section	Description
08/22/1988	II.	Carcinogen summary on-line
12/03/2002	II.D.2.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Fomesafen
CASRN — 72178-02-0
Last Revised — 08/22/1988

- 72178-02-0
- BENZAMIDE, 5-(2-CHLORO-4-(TRIFLUOROMETHYL)PHENOXY)-N-(METHYLSULFONYL)-2-NITRO-
- 5-(2-CHLORO-4-(TRIFLUOROMETHYL)PHENOXY)-N-(METHYLSULFONYL)-2-NITROBENZAMIDE
- FLEX
- Fomesafen
- FOMESAFENE
- PP021
- REFLEX