

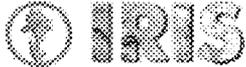
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List of IRIS Substances

Select a Substance

- Full IRIS Summary
- [QuickView](#)

Fluorene (CASRN 86-73-7)

[view QuickView](#)

MAIN CONTENTS

[Reference Dose for Chronic Oral Exposure \(RfD\)](#)

0435

Fluorene; CASRN 86-73-7

Health assessment information on a chemical substance is included in IRIS only after a comprehensive review of chronic toxicity data by U.S. EPA health scientists from several Program Offices and the Office of Research and Development. The summaries presented in Sections I and II represent a consensus reached in the review process. Background information and explanations of the methods used to derive the values given in IRIS are provided in the Background Documents.

STATUS OF DATA FOR Fluorene

File First On-Line 11/01/1990

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	11/01/1990
Inhalation RfC Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	on-line	12/01/1990

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Substance Name -- Fluorene
CASRN -- 86-73-7
Last Revised -- 11/01/1990

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

Chronic Health Hazard for Non-Carcinogenic Effects

[Chronic Health Hazard for Non-Carcinogenic Effects](#)

[Reference Dose for Chronic Oral Exposure \(RfD\)](#)

- [Oral RfD Summary](#)
- [Principal and Supporting Studies](#)
- [Uncertainty and Modifying Factors](#)
- [Additional Studies/Comments](#)
- [Confidence in the Oral RfD](#)
- [EPA Documentation and Review](#)

[Reference Concentration for Chronic Inhalation Exposure \(RfC\)](#)

- [Inhalation RfC Summary](#)
- [Principal and Supporting Studies](#)
- [Uncertainty and Modifying Factors](#)
- [Additional Studies/Comments](#)
- [Confidence in the Inhalation RfC](#)
- [EPA Documentation and Review](#)

Carcinogenicity Assessment for Lifetime Exposure

[Evidence for Human Carcinogenicity](#)

- [Weight-of-Evidence Characterization](#)
- [Human Carcinogenicity Data](#)
- [Animal Carcinogenicity Data](#)
- [Supporting Data for Carcinogenicity](#)

[Quantitative Estimate of](#)



9930

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
Decreased RBC, packed cell volume and hemoglobin	NOAEL: 125 mg/kg/day	3000	1	4E-2 mg/kg/day
	LOAEL: 250 mg/kg/day			

Mouse Subchronic Study

U.S. EPA, 1989

*Conversion Factors: None

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

U.S. EPA. 1989. Mouse oral subchronic toxicity study. Prepared by Toxicity Research Laboratories, LTD., Muskegon, MI for the Office of Solid Waste, Washington, DC.

CD-1 mice (25/sex/group) were exposed to 0, 125, 250, or 500 mg/kg/day fluorene suspended in corn oil by gavage for 13 weeks. Parameters used to assess toxicity included food intake, body weight, clinical observations, hematology and serum chemistry and gross and histopathological examinations. Increased salivation, hypoactivity, and urine-wet abdomens in males were observed in all treated animals. The percentage of mice exhibiting hypoactivity was dose-related. In mice exposed at 500 mg/kg/day, labored respiration, ptosis (drooping eyelids), and unkempt appearance were also observed. A significant decrease in red blood cell count and packed cell volume were observed in females treated with 250 mg/kg/day fluorene and in males and females treated with 500 mg/kg/day. Decreased hemoglobin concentration and increased total serum bilirubin levels were also observed in the 500 mg/kg/day group. Decreases in erythrocyte count, packed cell volume, and hemoglobin concentration were all observed at 125 mg/kg; however, these effects, although apparently dose-dependent, were not statistically significant. A significant decreasing trend in BUN and a significant increasing trend in total serum bilirubin were observed in both high-dose males and females. A dose-related increase in relative liver weight was observed in treated mice; a significant increase in absolute liver weight was also observed in the mice treated with 250 and 500 mg/kg/day fluorene. A significant increase in absolute and relative spleen and kidney weight was observed in males and females exposed to 500 mg/kg/day and males at 250 mg/kg/day. Increases in the absolute and relative liver and spleen weights in the high-dose males and females were accompanied by histopathological increases in the amounts of hemosiderin in the spleen and in the Kupffer cells of the liver. No other histopathological lesions were observed. The LOAEL is 250 mg/kg/day based on hematological effects; the NOAEL is 125 mg/kg/day.

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

UF -- An uncertainty factor of 3000 was used: 10 for use of a subchronic study for chronic RfD derivation, 10 each for inter- and intraspecies variability, and 3 for lack of adequate toxicity data in a second species and reproductive/developmental data.

MF -- None

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

Morris et al. (1960) fed 18 female Buffalo strain rats 12.3 mg fluorene/kg/day for 6 months or

[Quantitative Estimate of Carcinogenic Risk from Oral Exposure](#)

- [Summary of Risk Estimates](#)
- [Dose-Response Data](#)
- [Additional Comments](#)
- [Discussion of Confidence](#)

[Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure](#)

- [Summary of Risk Estimates](#)
- [Dose-Response Data](#)
- [Additional Comments](#)
- [Discussion of Confidence](#)

[EPA Documentation, Review and Contacts](#)

[Bibliography](#)
[Revision History](#)
[Synonyms](#)

13.1 mg fluorene/kg/day for 18 months. The diet in the 6- month study was composed of purified materials, low in protein and fat, and prepared in 3% propylene glycol. The diet in the longer study was composed of a mixture of natural foodstuffs in 3% corn oil. In the 6-month study, of 11 animals examined, the incidences of non-neoplastic reactions were reported by organ as follows: forestomach (acanthosis, hyperkeratosis), 5 animals; kidney (squamous metaplasia of pelvis), 7 animals; uterus (squamous metaplasia), 1 animal; small intestine (epithelial ulcer, acute), 1 animal; and liver (cirrhosis), 3 animals.

In the longer study using 18 rats, none of the effects seen in the 6-month study were observed. The only effect reported in this experiment was hyperplasia of the pituitary (predominantly chromophobe cells) in two animals.

It appears that the effects observed in the 6-month study were related to either dietary composition or propylene glycol, since none of these effects were observed after 18 months at a similar dosage using a different diet and vehicle. Consequently, this study is not considered acceptable as a basis for chronic RfD derivation.

No other studies on the toxicity of orally administered fluorene were located.

__I.A.5. Confidence in the Oral RfD

Study -- Medium
Database -- Low
RfD -- Low

Confidence in the principal study is medium: it is a well-designed study that examined and identified both a LOAEL and NOAEL for several sensitive endpoints using an adequate number of animals. Confidence in the data base is low; developmental, reproductive, and chronic toxicity following oral exposure to fluorene have not been tested, and a NOAEL was not identified. Confidence in the RfD is accordingly low.

__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 -- U.S. EPA, 1987

Agency Work Group Review -- 10/19/1989, 11/15/1989

Verification Date -- 11/15/1989

__I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (301)345-2870 (phone), (301)345-2876 (FAX) or Hotline.IRIS@epamail.epa.gov (internet address).

[Back to top](#)

__I.B. Reference Concentration for Chronic Inhalation Exposure (RFC)

Substance Name -- Fluorene
CASRN -- 86-73-7

Not available at this time.

[Back to top](#)

__II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name -- Fluorene
CASRN -- 86-73-7
Last Revised -- 12/01/1990

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 -- D; not classifiable as to human carcinogenicity

Basis -- Based on no human data and inadequate data from animal bioassays.

__II.A.2. Human Carcinogenicity Data

None.

__II.A.3. Animal Carcinogenicity Data

Inadequate. Morris et al. (1960) fed female buffalo rats a diet containing 0.05% fluorene in 3% corn oil for approximately 18 months or in propylene glycol for about 6 months (approximately 11 mg/kg/day). Various types of tumors occurred in controls and exposed animals at approximately the same incidences, ranging from 6 to 34%. No statistical analysis was reported.

Studies of fluorene for complete carcinogenic activity, initiating activity or co-carcinogenicity with 3-methylcholanthrene in mouse skin painting assays were not positive or were inconclusive (Kennaway, 1924; Riegel et al., 1951; LaVoie et al., 1979, 1981).

No injection site tumors occurred within 18 months in 10 strain A mice after seven subcutaneous injections of 10 mg fluorene in glycol (Shear, 1938). No control groups appear to have been utilized in this study.

Wilson et al. (1947) fed two groups of albino rats various concentrations of fluorene in the diet. One set of rats was exposed to several concentrations (number not specified) ranging from 0.062-1.0% fluorene in the diet for 104 days. These rats were maintained on diets with fluorene concentrations of 0.5 and 1.0%; they experienced significant decreases in their rate of growth, but in other aspects they appeared normal. The second set received either 0.125, 0.25 or 0.5% fluorene in the diet for 453 days. One rat exposed to 0.125% fluorene in the diet developed a small benign kidney tubular adenoma. The total number of animals treated was not indicated, nor was a control group described.

__II.A.4. Supporting Data for Carcinogenicity

Fluorene produced no positive results in reverse mutation assays in five strains of *Salmonella typhimurium* (1000 ug/plate) or in forward mutation assays in *Salmonella* strain TM677 (50 ug/mL) (McCann et al., 1975; LaVoie et al., 1979, 1981; Sakai et al., 1985; Bos et al., 1988; Kaden et al., 1979; Mamber et al., 1983). In a DNA damage assay using *S. typhimurium* TA1535, Nakamura et al. (1987) reported that fluorene at concentrations of up to 16.7 ug/mL was not positive. DNA damage assays with fluorene were not positive in *Escherichia coli* at concentrations of up to 2 mg/mL (Mamber et al., 1983, 1984) or in primary rat hepatocyte cultures at a maximum concentration of 3 mM (Sina et al., 1983). In a phage induction assay using *Escherichia coli* as a host, fluorene was not positive at concentrations of up to 1 mg/mL (Mamber et al., 1984).

In an unscheduled DNA synthesis assay the exposure of primary rat hepatocytes to 10 nmol and 100 nmol/mL fluorene did not yield positive results (Probst et al., 1981; Williams et al., 1989). Fluorene produced positive results in a DNA damage assay (strand-break assay) in L5178Y/mouse lymphoma cells at 0.15 uM in the presence of hepatic homogenates and at 0.5 uM in the absence of hepatic homogenates (Garberg et al., 1988). In forward mutation assays in L5178Y/mouse lymphoma cells, fluorene was not positive at concentrations of up to 30 and 60 ug/mL in the presence and absence of hepatic homogenates, respectively (Amacher et al., 1981; Oberly et al., 1984).

[Back to top](#)

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

None.

[Back to top](#)

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

None.

[Back to top](#)

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

__II.D.1. EPA Documentation

Source Document -- U.S. EPA, 1990

The 1990 Drinking Water Criteria Document for Polycyclic Aromatic Hydrocarbons has received Agency and external review.

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

Agency Work Group Review -- 02/07/1990

Verification Date -- 02/07/1990

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

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (301)345-2870 (phone), (301)345-2876 (FAX) or Hotline.IRIS@epamail.epa.gov (internet address).

[Back to top](#)

III. [reserved]

IV. [reserved]

V. [reserved]

VI. Bibliography

Substance Name -- Fluorene
CASRN -- 86-73-7
Last Revised -- 12/01/1990

VI.A. Oral RfD References

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[Back to top](#)

VI.B. Inhalation RfC References

None

[Back to top](#)

VI.C. Carcinogenicity Assessment References

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Kennaway, E.L. 1924. On cancer-producing tars and tar-fractions. *J. Ind. Hyg.* 5(12): 462-488.

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Williams, G., H. Mori and C. McQueen. 1989. Structure-activity relationships in the rat hepatocyte DNA-repair test for 300 chemicals. *Mutat. Res.* 221: 263-286.

Wilson, R.H., F. DeEds and A.J. Cox. 1947. The carcinogenic activity of 2- acetaminofluorene. IV. Action of related compounds. *Cancer Res.* 7: 453-458.

[Back to top](#)

_VII. Revision History

Substance Name -- Fluorene
CASRN -- 86-73-7

Date	Section	Description
11/01/1990	I.A.	Oral RfD summary on-line
11/01/1990	VI.	Bibliography on-line
12/01/1990	II.	Carcinogen assessment on-line
12/01/1990	VI.C.	Carcinogen assessment references added
01/01/1992	IV.	Regulatory Action section on-line
04/01/1997	III., IV., V.	Drinking Water Health Advisories, EPA Regulatory Actions, and Supplementary Data were removed from IRIS on or before April 1997. IRIS users were directed to the appropriate EPA Program Offices for this information.

[Back to top](#)

_VIII. Synonyms

Substance Name -- Fluorene
CASRN -- 86-73-7
Last Revised -- 11/01/1990

86-73-7
9H-Fluorene
Diphenylenemethane
Fluorene
HSDB 2165
Methane, diphenylene-
NSC 6787
o-BIPHENYLENEMETHANE
2,2'-METHYLENEBIPHENYL
9H-fluorene

[Back to top](#)

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