Fluorene; CASRN 86-73-7

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 Fluorene

File First On-Line 11/01/1990

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	11/01/1990
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	yes	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 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 **Mouse Subchronic Study** **U.S. EPA, 1989**	NOAEL: 125 mg/kg/day LOAEL: 250 mg/kg/day	3000	1	4E-2 mg/kg/day

*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 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 database 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 (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 — Fluorene
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Not available at this time.

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).

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

None.

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

None.

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 (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 — Fluorene
CASRN — 86-73-7

VI.A. Oral RfD References

Morris, H.P., C.A. Velat, B.P. Wagner, M. Dahlgard and F.E. Ray. 1960. Studies of carcinogenicity in the rate of derivatives of aromatic amines related to N-2-fluorenyl acetamide. J. Natl. Cancer Inst. 24: 149-180.

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U.S. EPA. 1989. 13-Week Mouse Oral Subchronic Toxicity Study. Prepared by Toxicity Research Laboratories, Ltd., Muskegon, MI for the Office of Solid Waste, Washington, DC.

VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References

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McCann, J.E., E. Choi, E. Yamasaki and B.N. Ames. 1975. Detection of carcinogens as mutagens in the Salmonella/microsome test: Assay of 300 chemicals. Proc. Natl. Acad. Sci. USA. 72(12): 5135-5139.

Morris, H.P., C.A. Velat, B.P. Wagner, M. Dahlgard and F.E. Ray. 1960. Studies of carcinogenicity in the rate of derivatives of aromatic amines related to N-2-fluorenylacetamide. J. Natl. Cancer Inst. 24(1): 149-180.

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Sakai, M., D. Yoshida and S. Mizusdki. 1985. Mutagenicity of polycyclic aromatic hydrocarbons and quinones on Salmonella typhimurium TA97. Mutat. Res. 156: 61-67.

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VII. Revision History

Substance Name — Fluorene
CASRN — 86-73-7

Date	Section	Description
11/01/1990	I.A.	Oral RfD summary on-line
12/01/1990	II.	Carcinogen assessment on-line

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