TOXICITY SUMMARY FOR FLUORANTHENE

August 1993

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Prepared for:

OAK RIDGE RESERVATION ENVIRONMENTAL RESTORATION PROGRAM

*Managed by Martin Marietta Energy Systems, Inc., for the U.S. Department of Energy under Contract No. DE-AC05-84OR21400

EXECUTIVE SUMMARY

Fluoranthene is a polycyclic aromatic hydrocarbon (PAH) that can be derived from coal tar. Occurring ubiquitously in products of incomplete combustion of fossil fuels, fluoranthene has been identified in ambient air, surface, drinking, and waste water, and in char-broiled foods. Currently, there is no commercial production or use of this compound (IARC, 1983).

Fluoranthene can be absorbed through the skin following dermal exposure (Storer et al., 1984) and, by analogy to structurally-related PAHs, would be expected to be absorbed from the gastrointestinal tract and lungs (U.S. EPA, 1988). An *in vitro* study identified 2-methylfluoranthene and 3-methylfluoranthene and their dihydrodiols as metabolites of fluoranthene (La Voie et al., 1982).

Although a large body of literature exists on the toxicity and carcinogenicity of PAHs, primarily benzo[*a*]pyrene, toxicity data for phenanthrene are very limited. No human data were available that addressed the toxicity of fluoranthene. Acute toxicity data for animals include an oral LD_{50} of 2000 mg/kg for rats; a dermal LD_{50} of 3180 mg/kg for rabbits (Smyth et al., 1962); and an intravenous LD_{50} of 100 mg/kg for mice (RTECS, 1993). Subchronic oral exposure to fluoranthene at doses of $250 mg/kg produced nephropathy, increased liver weights, and increased liver enzyme levels in rats (U.S. EPA, 1988). A single intraperitoneal injection of fluoranthene to pregnant rats caused an increased rate of embryo resorptions (Irvin and Martin, 1987). Fluoranthene was photosensitizing, enhancing erythema elicited by ultraviolet radiation in guinea pig skin (Kochevar et al., 1982) and was irritating to the eyes of rabbits (Grant, 1986).

A Reference Dose (RfD) of 4.00E-01 mg/kg/day for subchronic oral exposure and 4.00E-02 mg/kg/day for chronic oral exposure to fluoranthene was calculated from a no-observed-adverse-effect level (NOAEL) of 125 mg/kg/day and a lowest-observed-adverse-effect level (LOAEL) of 250 mg/kg/day derived from a 13-week gavage study with mice (U.S. EPA, 1993a,b). The critical effects were nephropathy, increased liver weights, and changes in clinical and hematological parameters. Data were insufficient to derive an inhalation Reference Concentration (RfC) for fluoranthene (U.S. EPA, 1993a,b).

No oral or inhalation bioassays were available to assess the carcinogenicity of fluoranthene. Bioassays by other exposure routes generally gave negative results. Studies involving topical application to the skin of mice (Horton and Christian, 1974; Hoffmann, 1972; Wynder and Hoffmann, 1959; Suntzeff et al., 1957) and subcutaneous injection in mice (Shear, 1938) provided no evidence of carcinogenicity. Fluoranthene was also inactive in mouse skin initiation and promotion assays (Van Duuren and Goldschmidt, 1976; Hoffmann, et al., 1972). However, fluoranthene has been shown to be active as a cocarcinogen when applied with benzo[*a*]pyrene to mice by skin application (Van Duuren and Goldschmidt, 1976) and was active as a complete carcinogen in a short-term lung tumor assay with newborn mice (Busby et al., 1984).

Based on no human data and inadequate data from animal bioassays, U.S. EPA (1993a,b) has placed fluoranthene in weight-of-evidence group D, not classifiable as to human carcinogenicity.

1. INTRODUCTION

Fluoranthene (CAS Reg. No. 206-44-0), also known as 1,2-benzacenaphthene, benzo(j,k)fluorene, idryl, 1,2-(1,8-naphthalenediyl)benzene, or 1,2-(1,8-naphthylene)benzene, is a polycyclic aromatic hydrocarbon (PAH) with a chemical formula of $C_{16}H_{10}$ and a molecular weight of 202.26 (ATSDR, 1990; IARC, 1983). It exists as pale yellow needles or plates, has a boiling point of 375°C, a melting point of 111°C, and a density of 1.252 at 0/4°C (Lide, 1991; ATSDR, 1990). Fluoranthene is almost insoluble in water (IARC, 1983), but is soluble in alcohol, ether, benzene, and acetic acid (Lide, 1991). It has a vapor pressure of 1.91×10^{-3} mm Hg at 25°C and a log octanol/water coefficient of 5.2 (U.S. EPA, 1987).

Fluoranthene can be produced by the pyrolysis of organic raw materials such as coal and petroleum at high temperatures; it is also known to occur naturally as a product of plant biosynthesis (U.S. EPA, 1980). It is a constituent of coal tar and petroleum-derived asphalt (HSDB, 1993). Currently, there is no known production or use of this compound (IARC, 1983). Fluoranthene is a common environmental pollutant that has been found in products of incomplete combustion of fossil fuels, main stream cigarette smoke, and in char-broiled foods. It has been identified in surface, drinking, and waste water, in lake sediments, and in ambient air (IARC, 1983). Fluoranthene is one of a number of PAHs on EPA's priority pollutant list (ATSDR, 1990).

2. METABOLISM AND DISPOSITION

2.1. ABSORPTION

Data regarding the gastrointestinal or pulmonary absorption of fluoranthene in humans or animals were not available. However, data from structurally-related PAHs suggest that fluoranthene would be absorbed readily from the gastrointestinal tract and lungs (U.S. EPA, 1988). The presence of fluoranthene in the blood of humans following dermal application of 2% crude coal tar on two consecutive days provides evidence of percutaneous absorption of fluoranthene (Storer et al., 1984).

2.2. DISTRIBUTION

Very limited human data and no animal data were available concerning the tissue distribution of fluoranthene. In humans, fluoranthene was detected in the lipid collected from forehead skin of roofing workers (Wolff et al., 1982) and in the blood of individuals who were treated with topical applications of 2% crude tar (Storer et al., 1984).

2.3. METABOLISM

2-Methylfluoranthene and 3-methylfluoranthene and their dihydrodiols were identified as *in vitro* metabolites of fluoranthene following incubation of fluoranthene with rat liver homogenates (LaVoie et al., 1982).

2.4. EXCRETION

Fluoranthene has been detected in human urine and feces (HSDB, 1993). Additional data concerning the excretion of fluoranthene in humans or animals were not available.

3. NONCARCINOGENIC HEALTH EFFECTS

3.1. ORAL EXPOSURES

3.1.1. Acute Toxicity

3.1.1.1. Human

Information on the acute oral toxicity of fluoranthene in humans was not available.

3.1.1.2. Animal

The oral LD_{50} is 2000 mg/kg for rats (Smyth et al., 1962).

3.1.2. Subchronic Toxicity

3.1.2.1. Human

Information on the subchronic oral toxicity of fluoranthene in humans was not available.

3.1.2.2. Animal

In a subchronic gavage study, male and female CD-1 mice were administered 0, 125, 250, or 500 mg/kg/day of fluoranthene for 13 weeks (U.S. EPA, 1988). All fluoranthene-treated mice exhibited nephropathy, increased salivation, and increased liver enzyme levels in a dose-dependent manner. However, these effects were not considered statistically significant or adverse at 125 mg/kg/day. Mice exposed to 250 and 500 mg/kg/day had statistically significant increased serum glutamic pyruvate transaminase (SGPT) levels and increased absolute and relative liver weights. Compound-related microscopic liver lesions were observed in 65 and 87.5% of the mid- and high-dosed mice, respectively. Based on increased SGPT levels, kidney and liver pathology, and clinical and hematological changes, the lowest-observed-adverse-effect level (LOAEL) was considered 250 mg/kg/day and the no-observed-adverse-effect level (NOAEL) was 125 mg/kg/day.

3.1.3. Chronic Toxicity

Information on the chronic oral toxicity of fluoranthene in humans or animals was not available.

3.1.4. Developmental and Reproductive Toxicity

Information on the developmental and reproductive toxicity of fluoranthene in humans or animals following oral exposure was not available.

3.1.5. Reference Dose

3.1.5.1. Subchronic

ORAL RfD: 4.00E-01 mg/kg/day (U.S. EPA, 1993a)
NOAEL: 125 mg/kg/day
LOAEL: 250 mg/kg/day
UNCERTAINTY FACTOR: 300

PRINCIPAL STUDY: U.S. EPA, 1988

COMMENTS: The same study, described in Section 3.1.2.2, was used for the derivation of the subchronic and chronic RfD. An uncertainty factor of 300 reflects 10 each for intra- and interspecies variability and 3 for lack of supporting reproductive/developmental toxicity and toxicity data in a second species.

3.1.5.2. Chronic

ORAL RfD: 4.00E-02 mg/kg/day (U.S. EPA, 1993a,b)
NOAEL: 125 mg/kg/day
LOAEL: 250 mg/kg/day
UNCERTAINTY FACTOR: 3000

CONFIDENCE:
Study: Medium
Data Base: Low
RfD: Low

VERIFICATION DATE: 11/15/89

PRINCIPAL STUDY: U.S. EPA, 1988

COMMENTS: The RfD is based on a 13-week gavage study with mice described in Section 3.1.2.2, with nephropathy, increased liver weights, and changes in clinical and hematological

parameters as critical effects. An uncertainty factor of 3000 reflects 10 each for intra- and interspecies variability, 10 for the use of a subchronic study for the derivation of a chronic RfD, and 3 for lack of supporting reproductive/developmental toxicity and toxicity data in a second species.

3.2. INHALATION EXPOSURES

3.2.1. Acute Toxicity

3.2.1.1. Human

Information on the acute toxicity of fluoranthene in humans following inhalation exposure was not available.

3.2.1.2. Animal

Exposure of male and female albino rats to concentrated vapors of fluoranthene for 8 hours produced no mortality (Smyth et al., 1962).

3.2.2. Subchronic Toxicity

Information on the subchronic toxicity of fluoranthene in humans or animals following inhalation exposure was not available.

3.2.3. Chronic Toxicity

Information on the chronic toxicity of fluoranthene in humans or animals following inhalation exposure was not available.

3.2.4. Developmental and Reproductive Toxicity

Information on the developmental and reproductive toxicity of fluoranthene in humans or animals following inhalation exposure was not available.

3.2.5. Reference Concentration

Data were insufficient to derive a subchronic or chronic inhalation reference concentration (RfC) for fluoranthene (U.S. EPA, 1993a,b).

3.3. OTHER ROUTES OF EXPOSURE

3.3.1. Acute Toxicity

3.3.1.1. Humans

Information on the acute toxicity of fluoranthene in humans by other routes of exposure was not available.

3.3.1.2. Animals

The intravenous LD_{50} is 100 mg/kg for mice (RTECS, 1993); the dermal LD_{50} resulting from 24-hour contact with fluoranthene is 3180 mg/kg for rabbits (Smyth et al., 1962).

All mice survived intraperitoneal injections of 500 mg fluoranthene administered daily for 7 days (Gerarde, 1960). A single intraperitoneal injection of 30 mg fluoranthene had no adverse effect on body weight gain of rats over a 24-day observation period (Haddow et al., 1937). By comparison, several other PAHs caused an initial weight decrease followed by resumption of growth at a reduced rate.

In common with several other PAHs present in coal tar, fluoranthene was highly phototoxic, causing erythema in guinea pig skin when applied topically at concentrations of 5 µM - 5 mM, followed by ultraviolet radiation exposure (Kochevar et al., 1982). A single topical application of 1 mg fluoranthene/10 g body weight to newborn rats caused induction of liver aryl hydrocarbon hydroxylase (AHH) activity, but had no effect on skin enzymes (Mukhtar et al., 1982).

When applied to the eyes of rabbits, fluoranthene was rated 7 on a scale of 1 to 10 according to the degree of injury observed after 24 hours (Grant, 1986).

3.3.2. Subchronic Toxicity

Information on the subchronic toxicity of fluoranthene by other routes of exposure in humans or animals was not available.

3.3.3. Chronic Toxicity

Information on the chronic toxicity of fluoranthene by other routes of exposure in humans or animals was not available.

3.3.4. Developmental and Reproductive Toxicity
3.3.4.1. Human

Information on the developmental or reproductive toxicity of fluoranthene by other routes of exposure in humans was not available.

3.3.4.2. Animal

A single intraperitoneal injection (dose not reported) of fluoranthene to pregnant C57/B6 mice on gestational day 6, 7, 8, or 9 produced an increased rate of embryo resorptions (Irvin and Martin, 1987). Embryotoxic effects that included decreased crown-rump length, deformities of the telencephalon, and absence of red blood cell circulation through the yolk sac were also observed in an *in vitro* study in which postimplantation rat embryo cultures were exposed to fluoranthene (Irvin and Martin, 1987).

3.4. TARGET ORGANS/CRITICAL EFFECTS
3.4.1. Oral Exposures
3.4.1.1. Primary Target Organs

1. Kidney. Subchronic oral exposure to fluoranthene produced nephropathy in rats.

2. Liver. Subchronic oral exposure of rats to fluoranthene produced increased liver weights and increased liver enzyme levels, resulting in microscopic lesions.

3.4.1.2. Other Target Organs

Information concerning other target organs following oral exposure was not available.

3.4.2. Inhalation Exposures

Information on target organs for inhalation exposure to fluoranthene was not available.

3.4.3. Other Routes of Exposure

Skin: Fluoranthene is photosensitizing, enhancing erythema elicited by ultraviolet radiation in guinea pig skin.

4. CARCINOGENICITY
4.1. ORAL EXPOSURES

Information on the carcinogenicity of fluoranthene in humans or animals following oral exposure was not available.

4.2. INHALATION EXPOSURES

Information on the carcinogenicity of fluoranthene in humans or animals following inhalation exposure was not available.

4.3. OTHER ROUTES OF EXPOSURE

4.3.1. Human

Information on the carcinogenicity of fluoranthene in humans by other routes of exposure was not available.

4.3.2. Animal

Fluoranthene has been tested for carcinogenicity in several skin painting assays in mice with consistently negative results. Application of a 0.1% solution of fluoranthene in acetone, 3 times/week for life, did not induce tumors in female Swiss mice (Wynder and Hoffmann, 1959). All female Swiss mice treated 3 times/week for 12 months with a 1% solution of fluoranthene survived; no tumors were observed (Hoffmann et al., 1972). Twice weekly application of 50 mg fluoranthene in decalin or in decalin-*n*-dodecane to the skin of male C3H mice for 82 weeks also did not produce tumors (Horton and Christian, 1974). No tumors were found in CAF, Jackson, Swiss, and Millerton mice 13 months after they were administered a 10% solution of fluoranthene in acetone by topical application 3 times/week (Suntzeff et al., 1957).

Fluoranthene did not exhibit tumor-initiating activity in Swiss mice that received 10 topical administrations of 0.1 mg fluoranthene followed by promotion with croton oil (Hoffmann et al., 1972). Van Duuren and Goldschmidt (1976) tested fluoranthene for tumor-promoting and cocarcinogenic activity. In the promotion study, benzo[*a*]pyrene was applied to the skin of female Swiss mice; after 14 days, 40 mg fluoranthene was applied 3 times/week for the duration of the study (440 days). No tumor-promoting activity was observed. In the cocarcinogenicity study, benzo[*a*]pyrene was applied simultaneously with 50 mg fluoranthene in acetone, 3 times/week for 440 days. The number of mice with papillomas and carcinomas more than doubled with fluoranthene compared with benzo(*a*)pyrene controls. Fluoranthene also increased the number of tumors/mouse and decreased the days to the appearance of the first tumor. Coapplication of a single dose of a mixture of benzo[*a*]pyrene and fluoranthene to the skin of female CD-1 mice increased the formation of DNA adducts compared with benzo[*a*]pyrene treatment alone (Rice et al., 1984).

Because some chemical carcinogens have shown to induce melanogenesis in melanoblasts of skin, several PAHs including fluoranthene, were examined for their ability to induce melanocyte activation (Iwata et al., 1981). Topical application of 200 µg of fluoranthene to the backs of mice on 1 or 2 consecutive days produced no increases in the number of active melanocytes.

Although several skin painting assays gave negative results, a short-term *in vivo* lung tumor assay suggests that fluoranthene is a complete carcinogen (Busby et al., 1984). Male and female mice received intraperitoneal injections of fluoranthene in dimethyl sulfoxide on days 1, 8, and 15 after birth at total doses of 0, 700, or 3500 µg fluoranthene. After 24 weeks, there was a statistically significant increase in the incidence of lung adenomas and adenocarcinomas (combined) in the combined male and female high-dosed group (28/48) compared with vehicle controls (5/55). In the combined high-dosed groups, 80% of the lung tumors were adenomas and 20% adenocarcinomas. The lung tumor response in the combined low-dosed groups was not statistically different from controls.

Shear (1938) administered four doses of 10 mg fluoranthene in glycerol by subcutaneous injection to strain A mice. Six of 14 mice survived for 18 months; no tumors were found by 18 months.

4. EPA WEIGHT-OF-EVIDENCE

Classification D -- Not classifiable as to human carcinogenicity (U.S. EPA, 1993a,b) Basis -- Based on no human data and inadequate data from animal bioassays (U.S. EPA, 1993b)

4.5. CARCINOGENICITY SLOPE FACTORS

None were calculated.

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