Phenanthrene; CASRN 85-01-8

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 Phenanthrene

File First On-Line 12/01/1990

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	not evaluated	
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 — Phenanthrene
CASRN — 85-01-8

Not available at this time.

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

Substance Name — Phenanthrene
CASRN — 85-01-8

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Phenanthrene
CASRN — 85-01-8
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 a single gavage study in rats and skin painting and injection studies in mice.

II.A.2. Human Carcinogenicity Data

None.

II.A.3. Animal Carcinogenicity Data

Inadequate. Data from a rat gavage study and mouse skin application and injection studies are not adequate to assess the carcinogenicity of phenanthrene. Ten female Sprague-Dawley rats received a single oral dose of 200 mg phenanthrene in sesame oil (Huggins and Yang, 1962). No mammary tumors occurred. The observation period was not specified; however, based on the discussion of other experiments in the report it was probably at least 60 days. Controls were not reported.

Complete carcinogenic activity was not shown in two skin painting assays. Kennaway (1924) reported no tumors in 100 mice (strain and sex not specified) treated with phenanthrene (purity not specified) in 90% benzene (dose not reported) for 9 months. Roe and Grant (1964) reported in an abstract that mice (number, sex and strain not specified) did not develop tumors after dermal exposure to 5% phenanthrene (purity not specified, vehicle not specified) 3 times/week for 1 year.

Five studies of cancer-initiating activity in skin painting assays in mice have yielded one positive result. Groups of 30 female CD-1 mice received a single dermal application of 1.8 mg phenanthrene in benzene, followed by twice-weekly applications of tetradecanoylphorbol acetate (TPA, 3 mg), a promoter, for 35 weeks (Scribner, 1973). Phenanthrene used in the study was purified by preparative thin-layer chromatography (TLC) and determined to be homogeneous on TLC. It is stated in the report that the dose of TPA was 3 mg (5 umol); however, it is not clear whether this refers to the twice weekly or total dose. Controls were treated with TPA (6 mg); it is not clear whether controls received benzene (vehicle). The tumor incidence (skin papilloma) at 35 weeks was 12/30 (40%) in treated mice and 0/30 in TPA controls.

Tumor-initiating activity was not shown in the four other mouse skin painting studies. In the first study, male Swiss albino (Ha/ICR) mice (15 to 20/group) received 10 applications of a 0.1% solution of phenanthrene in acetone (total dose 1 mg) or acetone alone, followed by repeated applications of TPA (2.5 ug in acetone) 3 times/week for 20 weeks (LaVoie et al., 1981). Phenanthrene was >99.5% pure as determined by high pressure liquid chromatography (HPLC). No tumors occurred in treated or control mice. Wood et al. (1979) exposed female CD-1 mice (30/group) to a single application of 1.8 mg phenanthrene in acetone:ammonium hydroxide (1000:1) or vehicle alone, followed by TPA (10 ug) twice weekly for 35 weeks. Phenanthrene used in this study was >98% pure and homogeneous on HPLC. Tumor incidence (skin papillomas) out of 27-29 survivors in each group was 17% in treated mice and 7% in vehicle controls (not statistically different). In another study, albino mice (10/sex/dose, strain not specified) received four dermal applications of phenanthrene (total dose 1.2 mg, purity not specified) in acetone or to acetone alone, followed by croton oil once each week for 20 weeks (Roe, 1962). Tumor incidence (skin papillomas) was 4/19 (21%) in treated mice and 2/20 (10%)

in vehicle controls. In the last study (Salaman and Roe, 1956), groups of 20 "S" strain mice (sex unspecified) received 10 dermal applications (3 times/week) of 18% phenanthrene (total dose 0.54 g, purity not specified) in acetone, followed by 18 weekly applications of croton oil. Controls were treated with 18 applications of croton oil; 10 controls survived until termination. The tumor incidence (skin papillomas) was 5/20 (25%) in treated mice and 4/10 (40%) in croton oil controls.

Parenterally administered phenanthrene was not shown to have tumorigenic activity in three studies. In the first (Buening et al., 1979), groups of Swiss Webster BLU:Ha ICR mice (100/group, approximately 50% of each sex) received intraperitoneal injections of phenanthrene (total dose 0.25 mg) in dimethyl sulfoxide (DMSO) or DMSO alone on days 1, 8, and 15 after birth. Phenanthrene was >98% pure and homogeneous on HPLC. Incidence of pulmonary tumors (adenomas) at 38 to 42 weeks was 1/18 (6%) and 5/17 (30%) in female and male treated mice and 7/38 (18%) and 2/10 (19%) in female and male controls; the apparent differences were not statistically significant. No hepatic tumors occurred in treated or control mice. One treated female mouse developed malignant lymphoma. In the second study (Grant and Roe, 1963), albino mice (sex, strain and group size not specified) received single subcutaneous injections of phenanthrene (40 ug, purity not specified) in an acetone/gelatin vehicle or only the vehicle. Incidence of pulmonary adenomas after 52-62 weeks was 3/39 (6%) in treated mice and 8/34 (24%) in vehicle controls. Other tumors reported were 4 hepatomas and 2 skin papillomas in treated mice, and 1 mammary adenocarcinoma, 1 hepatoma and 1 hemangioma in control mice. Finally in the Steiner (1955) study, groups of 40 to 50 male and female C57BL mice (numbers per sex not specified) received single subcutaneous injections of 5 mg phenanthrene (purity not specified) in tricaprylin. No tumors were reported in 27 surviving mice after 4 months. Vehicle controls were not reported.

II.A.4. Supporting Data for Carcinogenicity

Phenanthrene has not yielded positive results in assays for DNA damage in Bacillus subtilis and Escherichia coli (Rosenkrantz and Poirier, 1979; McCarroll et al., 1981). Tests for mutagenicity in Salmonella typhimurium have yielded positive (Oesch et al., 1981; Sakai et al., 1985; Bos et al., 1988) and negative results (Wood et al., 1979; McCann et al., 1975; LaVoie et al., 1981; Kaden et al., 1979; Bos et al., 1988). The results of phenanthrene in a fungi recombination assay (Simmon, 1979) and in tests for DNA damage in several mammalian cell cultures were not positive (Lake et al., 1978; Probst et al., 1981; Rice et al., 1984). A test for forward mutation in Chinese hamster ovary cells exposed to 1 ug/mL was not positive (Huberman and Sachs, 1976), whereas a test in human lymphoblast TK6 cells incubated with rat liver S9 (Arochlor) and 9 ug/mL phenanthrene yielded positive results (Barfknecht et al., 1981). Phenanthrene did not yield positive results in sister chromatid exchange and chromosome aberration assays in mammalian cell cultures (Popescu et al., 1977) or in cell transformation assays in several types

of mammalian cells (5-40 ug/mL) (Marquardt and Heidelberger, 1972; Kakunaga, 1973; Evans and DiPaolo, 1975; Pienta et al., 1977).

Current theories regarding the mechanisms of metabolic activation of polycyclic aromatic hydrocarbons lead to predictions of a carcinogenic potential for phenanthrene. Jerina et al. (1978) considered phenanthrene to have a "bay-region" structure. It is metabolized by mixed function oxidases to reactive diol epoxides (Nordqvist et al., 1981; Vyas et al., 1982) that have been shown to be weakly mutagenic in some bacterial and mammalian cell assays (Wood et al., 1979). Evidence from in vivo assays indicates, however, that phenanthrene metabolites have a relatively low tumorigenic potential. The 1,2-, 3,4- and 9,10-dihydrodiol metabolites of phenanthrene did not show tumor initiating activity in mouse skin painting assays (Wood et al., 1979). The 1,2-diol-3,4-epoxides of phenanthrene did not produce lung tumors when injected into newborn mice (Buening et al., 1979). The relatively weak mutagenic and tumorigenic activity of phenanthrene diol epoxides is inconsistent with the "bay region theory" of PAH carcinogenesis. The reason for the inconsistency has not been elucidated. Phenanthrene epoxides have a relatively small molecular size (relative to other more active PAH epoxides such as chrysene diol epoxides) and as a result may have a lower affinity for DNA or may be transported less efficiently into the mammalian nucleus (Wood et al., 1979). While some studies have considered phenanthrene to have a "bay- region" structure, it may not clearly fall into this category.

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)

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

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, 05/03/1990

Verification Date — 05/03/1990

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 — Phenanthrene
CASRN — 85-01-8

VI.A. Oral RfD References

None

VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References

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VII. Revision History

Substance Name — Phenanthrene
CASRN — 85-01-8

Date	Section	Description
12/01/1990	II.	Carcinogen assessment on-line

VIII. Synonyms

Substance Name — Phenanthrene
CASRN — 85-01-8
Last Revised — 12/01/1990

- 85-01-8
- Phenanthrene
- HSDB 2166
- NSC 26256
- Phenanthren [German]
- Phenanthrene