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Provisional Peer-Reviewed Toxicity Values for

Phenanthrene
(CASRN 85-01-8)

Superfund Health Risk Technical Support Center
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ACRONYMS AND ABBREVIATIONS

bw	body weight
cc	cubic centimeters
CD	Caesarean Delivered
CERCLA	Comprehensive Environmental Response, Compensation and Liability Act of 1980
CNS	central nervous system
cu.m	cubic meter
DWEL	Drinking Water Equivalent Level
FEL	frank-effect level
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
g	grams
GI	gastrointestinal
HEC	human equivalent concentration
Hgb	hemoglobin
i.m.	intramuscular
i.p.	intraperitoneal
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
i.v.	intravenous
kg	kilogram
L	liter
LEL	lowest-effect level
LOAEL	lowest-observed-adverse-effect level
LOAEL(ADJ)	LOAEL adjusted to continuous exposure duration
LOAEL(HEC)	LOAEL adjusted for dosimetric differences across species to a human
m	meter
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mg/kg	milligrams per kilogram
mg/L	milligrams per liter
MRL	minimal risk level
MTD	maximum tolerated dose
MTL	median threshold limit
NAAQS	National Ambient Air Quality Standards
NOAEL	no-observed-adverse-effect level
NOAEL(ADJ)	NOAEL adjusted to continuous exposure duration
NOAEL(HEC)	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional inhalation reference concentration

p-RfD	provisional oral reference dose
PBPK	physiologically based pharmacokinetic
ppb	parts per billion
ppm	parts per million
PPRTV	Provisional Peer Reviewed Toxicity Value
RBC	red blood cell(s)
RCRA	Resource Conservation and Recovery Act
RDDR	Regional deposited dose ratio (for the indicated lung region)
REL	relative exposure level
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	Regional gas dose ratio (for the indicated lung region)
s.c.	subcutaneous
SCE	sister chromatid exchange
SDWA	Safe Drinking Water Act
sq.cm.	square centimeters
TSCA	Toxic Substances Control Act
UF	uncertainty factor
µg	microgram
µmol	micromoles
VOC	volatile organic compound

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR PHENANTHRENE (CASRN 85-01-8)

Background

On December 5, 2003, the U.S. Environmental Protection Agency's (EPA's) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

1. U.S. EPA's Integrated Risk Information System (IRIS).
2. Provisional Peer-Reviewed Toxicity Values (PPRTV) used in U.S. EPA's Superfund Program.
3. Other (peer-reviewed) toxicity values, including:

   - Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR),
   - California Environmental Protection Agency (CalEPA) values, and
   - EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in U.S. EPA's Integrated Risk Information System (IRIS). PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the U.S. EPA IRIS Program. All provisional toxicity values receive internal review by two U.S. EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multi-program consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all U.S. EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a five-year basis and updated into the active database. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV manuscripts conclude that a PPRTV cannot be derived based on inadequate data.

Disclaimers

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and RCRA program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV manuscript and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other U.S. EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

Questions Regarding PPRTVs

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may be directed to the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

No RfD or RfC for phenanthrene is listed on IRIS (U.S. EPA, 2008), in the Health Effects Assessment Summary Tables (HEAST; U.S. EPA, 1997), or in the Drinking Water Standards and Health Advisories list (U.S. EPA, 2006). The Chemical Assessments and Related Activities (CARA) list (U.S. EPA 1991, 1994) includes a Health Effects Assessment (HEA) (U.S. EPA, 1984) and a Health and Environmental Effects Profile (HEEP) (U.S. EPA, 1987) for phenanthrene; it also includes a Drinking Water Criteria Document (DWCD) for polycyclic aromatic hydrocarbons (PAH) (U.S. EPA, 1992). None of these documents derive an RfD or RfC for phenanthrene because no relevant toxicity data are available for humans or animals. Similarly, because relevant data are not available, the Agency for Toxic Substances and Disease Registry (ATSDR, 1995) Toxicological Profile for PAH does not derive any oral or inhalation MRLs for phenanthrene. An Environmental Health Criteria document on PAH available from the World Health Organization (WHO, 1998) contains no subchronic or chronic oral or inhalation toxicity data for phenanthrene. The California Environmental Protection Agency (CalEPA, 2005a,b) has not derived oral or inhalation RELs for phenanthrene. There are no Occupational Safety and Health Administration (OSHA, 2008), National Institute for Occupational Safety and Health (NIOSH, 2008), or American Conference of Governmental Industrial Hygienists (ACGIH, 2007) occupational exposure limits for phenanthrene. Warshawsky (2001) also reviewed the health effects associated with PAHs.

The IRIS Summary for Phenanthrene (U.S. EPA, 2008) presents a cancer weight-of-evidence characterization of Group D, not classifiable as to human carcinogenicity, based on no human data and inadequate animal data from a single gavage study in rats and several skin application and injection studies in mice. Phenanthrene also is classified as Group D in the Drinking Water Standards and Health Advisories list (U.S. EPA, 2006). Although there is no listing for phenanthrene in the HEAST cancer table (U.S. EPA, 1997), the HEA, a HEEP, and a DWCD all designated phenanthrene a Group D chemical or otherwise indicated that insufficient data were available for a carcinogenicity assessment. The International Agency for

Research on Cancer (IARC, 1983, 1987) assigned phenanthrene to Group 3—not classifiable as to human carcinogenicity because of no adequate data in humans and inadequate evidence in animals. Documents developed more recently by ATSDR (1995) and WHO (1998) do not contain any previously unidentified carcinogenicity data for phenanthrene. The National Toxicology Program (NTP) has not tested the carcinogenicity of phenanthrene or included it in its 11th Report on Carcinogens (NTP, 2005, 2008). CalEPA (2002) has not derived a cancer potency factor for phenanthrene.

Literature searches were conducted through December 2007 for studies relevant to the derivation of provisional toxicity values for phenanthrene. Databases searched include the following: MEDLINE (including cancer subset), TOXLINE (Special), BIOSIS, TSCATS 1/TSCATS 2, CCRIS, DART/ETIC, GENETOX, HSDB, RTECS, and Current Contents. An additional PubMed Search was conducted between December 2007 and March 2009 for studies relevant to the derivation of provisional toxicity values for phenanthrene.

REVIEW OF PERTINENT DATA

Human Studies

No studies were located regarding oral or inhalation exposure of humans to phenanthrene. In a population-based case-control study, Croen et al. (1997) reported a nonsignificant increase in risk for neural tube defects associated with maternal residence near National Priority List (NPL) sites containing phenanthrene, among other pollutants. Consequently, the association cannot be attributed to phenanthrene only.

Animal Studies

Oral Exposure

No adequate studies were located regarding chronic oral toxicity of phenanthrene in animals. Rakhmanina (1964) conducted 3- and 7-month oral studies in rats and rabbits. In the 3-month study, groups of six male rabbits and six male white rats were administered 0 or 70 mg/kg of phenanthrene (strains used were not identified). The purity of phenanthrene used, the vehicle, and the frequency of test compound administration are not reported. In rabbits, treatment with phenanthrene resulted in significant ($p \leq 0.05$) increases (up to 5-fold higher than controls) in serum galactose content following i.v. injection of galactose (quantity of galactose injected and vehicle not reported) on days 45 and 90. Significantly increased (24% higher than controls, $p = 0.05$) serum sulfhydryl group content (measured after 60 days of exposure) was also reported in rabbits. No other treatment-related changes were reported for rabbits or rats in the 3-month study (data not shown). Other endpoints evaluated included hepatic protein formation, hypophyseal-adrenocortical system, blood cholinesterase and catalase activity, blood composition, oxygen consumption and body weights. Specific details regarding the actual analyses undertaken for most endpoints are unclear. While the results are reported as negative, the data from these analyses were not shown. Given the reporting limitations, the results of the 3-month study are of limited utility due to inadequate reporting of methods and results. In the 7-month study, Rakhmanina (1964) administered 0 or 0.2 mg/kg of phenanthrene to an unreported number of rabbits and white rats. The authors reported evaluating the "carbohydrate

and detoxifying functions of the liver," the sulfhydryl content of serum, clinical signs, body weight and, in rats only, conditioned reflexes. According to the study authors, no treatment-related effects were observed; however, the data were not shown. Effect levels cannot be determined from these data due to the poor reporting.

Huggins and Yang (1962) administered a single gavage dose of 200 mg phenanthrene (dissolved in sesame oil; purity not specified) to 10 female Sprague-Dawley rats (50 days old) in an effort to determine whether the compound induced mammary tumors. The authors reported that no mammary tumors were observed in the phenanthrene-treated rats (0/10), although mammary tumors occurred in 700/700 rats administered 7,12-dimethylbenz[*a*]anthracene (20 mg) and in 8/9 rats given benzo[a]pyrene (100 mg) under the same conditions. In their study, no other tissues or organs are evaluated for the presence of tumors. The authors generally describe their methods for assessing tumor formation in studies of mammary carcinogenicity, but they do not specify the methods used in the current study of phenanthrene. Thus, it is not clear whether the occurrence of mammary tumors was evaluated exclusively by palpation or whether a histologic examination was performed. In addition, the observation period is not specified. Consequently, this study is not an adequate test of the carcinogenic potential of phenanthrene.

Other Studies

Fourteen additional toxicity studies are identified and described in the following sections. These studies are not appropriate for setting PPRTVs for oral and inhalation exposures; many of these have study-design limitations or the results are poorly reported.

Other Routes

Dermal Studies—Salaman and Roe (1956) conducted a skin-tumor initiation study in mice. A total dose of 540 mg per mouse phenanthrene (18% solution in acetone) was applied to the skin of 20 S-strain mice. The total dose was applied in 10 individual doses (54 mg per dose) applied 3 times per week, followed (25 days after first initiator treatment) by 18 weekly croton oil applications. A control group received only croton oil treatment. A week after the promotion period ended, the study authors recorded the papilloma incidence; it is not clear whether any histologic examination of the skin was performed. In addition, the authors sacrificed all the mice and examined them for lung tumors. Skin papillomas were observed in 5/20 mice treated with phenanthrene and in 4/19 control mice surviving croton oil treatment (not statistically significant). The total number of papillomas in the tumor-bearing mice was higher in the phenanthrene-treated animals (a total of 12 tumors) than in controls (4). The incidence of lung tumors reportedly was not affected by phenanthrene treatment (data not shown).

Roe (1962) assessed the cocarcinogenicity of phenanthrene and benzo[a]pyrene. Groups of 10 mice/sex were given dermal applications of 300 µg phenanthrene (in 0.25 mL acetone) with or without 300 µg of benzo[a]pyrene. The applications were given on days 0, 2, 6, and 8. Beginning on day 21, the mice were treated with dermal applications of croton oil (0.1%) once each week for 20 weeks. Papillomas were recorded for 20 weeks following initiation. Papillomas were observed in 2/20, 4/19, and 9/19 mice in the control, phenanthrene-exposed, and benzo[a]pyrene-exposed groups, respectively. The average numbers of papillomas per survivor are 0.2, 0.4, and 2.5 in the control, phenanthrene-exposed, and benzo[a]pyrene-exposed mice respectively. Other groups of mice were exposed to phenanthrene (300 µg, in 3% aqueous

gelatin) by subcutaneous injection on days 0, 2, 4, 6, and 8, with or without dermal application of benzo[a]pyrene (300 µg). In the group exposed to subcutaneous phenanthrene alone, 3/17 mice developed papillomas (average of 0.6 papillomas per survivor). Although tumor incidence and the number of tumors per survivor are each higher in the group exposed to both dermal benzo[a]pyrene and subcutaneous phenanthrene, according to the study authors, coadministration of subcutaneous phenanthrene with dermal benzo[a]pyrene exposure did not result in a statistically significant increase in tumor formation when compared with the group exposed to dermal benzo[a]pyrene.

Wood et al. (1979) administered a single application of phenanthrene (10 µmol in 200 µL acetone: ammonium hydroxide [1000:1]) to the shaved backs of 30 female CD-1 mice; 30 control mice were exposed to solvent alone. (The phenanthrene was >98% pure). The study authors began promotion with twice-weekly applications of tetradecanylphorbol acetate (TPA; 16 nmol/200 µL acetone) 1 week after initiation. Two identical experiments were conducted. In the first experiment, the study authors reported papilloma incidence after 35 weeks of promotion and, in the second experiment, after 25 and 35 weeks of promotion. The numbers of animals surviving are not reported by group; however, the study authors indicated that 27−30 animals in each group were alive at 35 weeks. In the first experiment, the papilloma incidences were 7% and 17% in the control and phenanthrene-treated groups, respectively, after 35 weeks. The numbers of papillomas per mouse are 0.1 and 0.28 in the control and phenanthrene-treated groups, respectively, after 35 weeks. In the second experiment, control animals exhibited papilloma incidences of 3% and 7% after 25 and 35 weeks of promotion, respectively; the incidence in phenanthrene-treated animals is 14% at both time periods. The numbers of papillomas per mouse are 0.035 and 0.14 in the control and phenanthrene-treated groups, respectively, after 25 weeks and 0.07 and 0.14 in the control and phenanthrene-treated groups, respectively, after 35 weeks. The differences between the groups are not statistically significant in either experiment.

In the only study reporting a statistically significant increase in tumor formation associated with phenanthrene treatment, Scribner (1973) applied 10 µmol phenanthrene (in benzene) to the shaved backs of 30 female CD-1 mice, followed by twice weekly treatment with TPA (5 µmol[1]). Though the study text identifies a control group (n = 30), it does not specify the treatment of control mice. Papilloma incidence was recorded every 5 weeks from 10 to 35 weeks after initiation. All animals survived for the 35 weeks of the study in the control and treatment groups. In the control group, the study authors reported papillomas at only 25 weeks and only in 1 of 30 animals (3%); no papillomas are reported in weeks 30 or 35. In the group treated with phenanthrene, the percentage of mice with papillomas is 0%, 10%, 20%, 23%, 30%, and 40% when measured in weeks 10, 15, 20, 25, 30, and 35, respectively. The number of papillomas per mouse was 0, 0.1, 0.27, 0.37, 0.5, and 0.6 when measured in weeks 10, 15, 20, 25, 30, and 35, respectively. The incidence in phenanthrene-treated animals is statistically significantly increased ($p < 0.01$). However, the influence of the carcinogenic vehicle (benzene) is uncertain—especially given the apparent lack of a description of the treatment of the control group.

[1] It is not clear whether this was the total dose or the twice-weekly dose of TPA.

In another study of skin tumor initiation, LaVoie et al. (1981) applied a total of 1.0 mg of phenanthrene (>99.5% pure, in acetone) to the shaved backs of 20 female Swiss albino mice (Ha/ICR). The total dose was administered through 10 doses of 0.1 mg of phenanthrene applied every other day to each mouse. A control group received acetone application only. The study authors began promotion by TPA (2.5 μg) 10 days after the last subdose and continued 3 times weekly for 20 weeks. Benzo[a]pyrene was also tested at a total dose of 0.3 mg. The authors did not specify the methods used to assess skin tumor formation (e.g., palpation, histopathology, or both). No tumors were observed in the control group or in the phenanthrene-treated group. Benzo[a]pyrene induced tumors in 14/15 animals (5 animals in this treatment group died prematurely).

Siebert et al. (1981) applied a single dose of phenanthrene to the backs of 28 NMRI mice (sex not specified), followed by twice-weekly TPA treatment (dose of TPA not reported). It is not clear whether a control group is included, and no further details of the study design are reported. The study authors indicate that phenanthrene gave negative results, as assessed by the tumor incidence and average tumor yield. No other information is provided.

As part of a study of the complete carcinogenicity of PAH mixtures, Warshawsky et al. (1993) exposed groups of 20 male C3H/HeJ mice to phenanthrene (99% pure; a dose of 50 μL of a 0.1% solution in toluene) via dermal application to the interscapular region of the back twice weekly for up to 104 weeks. Both untreated and toluene-treated control groups are included. A benzo[a]pyrene-treated group was also studied, but a noncarcinogenic dose (0.001% in toluene) was intentionally used. The animals were observed twice daily for skin anomalies. Papilloma appearance and progression to malignancy were recorded. Upon autopsy (when moribund or dead, or at sacrifice at study termination), the study authors performed a gross necropsy and collected skin samples from areas with visible lesions. Of 17 phenanthrene-treated mice that survived to study termination, one animal had a tumor, appearing after 53 weeks of exposure. No control or benzo[a]pyrene-exposed mice exhibited tumors.

Intraperitoneal Studies—Phenanthrene did not induce significant increases in lung or liver tumors in a newborn mouse assay conducted by Buening et al. (1979). Phenanthrene (98% pure) was administered via three i.p. injections (for a total dose of 1.4 μmol, or 0.25 mg, per mouse over) on the first, 8th and 15th day after birth to groups of 100 Swiss-Webster BLU:Ha(ICR) mice. Control mice received i.p. injections of dimethyl sulfoxide (DMSO) on the same schedule. The animals were sacrificed between 38 and 42 weeks of age for autopsy and gross tumor count. The protocol called for microscopic examination of a "representative number" of grossly identified lung tumors, all grossly identified liver tumors, as well as tissues with "suspected pathology." No liver tumors were observed in phenanthrene-treated or control mice. There is no statistically significant increase in the incidence of pulmonary tumors in the phenanthrene-treated mice.

Lung Implantation Studies—Wenzel-Hartung et al. (1990) implanted phenanthrene (99.9% pure) in a beeswax matrix in the lungs of female Osborne-Mendel rats. Phenanthrene doses of 1, 3, and 10 mg/animal were given to groups of 35 rats per dose. Both vehicle and untreated control groups (n = 35) were used. Other groups of rats were exposed to additional PAHs, including three groups exposed to benzo[a]pyrene at 0.03, 0.1, and 0.3 mg/animal. Observations of the animals were performed twice daily, and the rats were sacrificed when moribund or when clinical signs of tumor formation were evident. The study authors gave each

rat a complete autopsy, and histologically examined the lungs, along with any grossly evident tumors. No tumors were observed in vehicle or untreated control animals. Only one tumor, a squamous-cell carcinoma, was observed in the high-dose phenanthrene-treated animals. The authors reported that the incidence of preneoplastic lesions (squamous cell metaplasias) was similar between the phenanthrene-exposed and control groups (data not shown). Benzo[a]pyrene exposure resulted in a dose-related increase in the incidence of tumors (3/35, 11/35, and 27/35 in low-, mid-, and high-dose groups).

Subcutaneous Studies—Three subcutaneous studies of the potential carcinogenicity or cocarcinogenicity of phenanthrene are identified. Steiner (1955) injected male and female C57BL mice (40−50 in total) with a single dose of phenanthrene (5 mg) dissolved in tricaprylin. The animals were sacrificed 22 to 28 months after exposure. No other study design details are given, and a control group is not reported. Benzo[a]pyrene was tested at a concentration of 0.09 mg. Phenanthrene treatment did not result in any sarcomas among the 27 mice that survived to 4 months after exposure. In contrast, sarcomas were observed in 16/21 mice exposed to benzo[a]pyrene. Given the limited number of details provided by the study authors and the route of exposure, this study is of limited value for setting PPRTVs for oral exposures.

Phenanthrene was administered by subcutaneous injection in a study by Grant and Roe (1963; Roe and Waters, 1967). Newborn albino mice (strain and group sizes not specified) were given 40-µg phenanthrene in 0.02 mL of aqueous gelatin. Controls received either 0.02 or 0.04 mL aqueous gelatin. The study authors excluded mice that died within the first 10 weeks of the study from analysis. At 52 weeks after exposure, the study authors sacrificed 10 mice/group and examined them for tumors; the remaining mice were sacrificed at 62 weeks. The extent of histologic examination is not reported. Exposure to phenanthrene did not result in an increased incidence of pulmonary adenomas (3/49) or hepatomas (4/49) when compared to incidences in the control groups. In controls receiving 0.02 mL aqueous gelatin, the incidence of pulmonary adenomas and hepatomas were 8/34 and 1/34, respectively. In controls receiving 0.04 mL aqueous gelatin, the incidence of pulmonary adenomas is 5/38 while the incidence of hepatomas is 2/38. The study authors observed skin papillomas in 2/49 rats exposed to phenanthrene; these incidences are not statistically significantly increased over controls (no skin papillomas were observed in controls).

Genotoxicity and Mutagenicity Studies

An abundance of evidence suggests that phenanthrene is either very weakly genotoxic or not genotoxic at all. Tables 1, 2, and 3 collectively summarizes the genotoxicity data for phenanthrene: Table 1—*in vitro* mutagenicity and morphological transformation studies; Table 2—*in vivo* clastogenicity studies; and Table 3—*in vitro* clastogenicity and DNA damage, repair, synthesis, and adduct studies.

The majority of the available bacterial mutagenicity assays gave results that were negative. Six of the 17 studies available provide positive results. Bos et al. (1988), Carver et al. (1986) and Sakai et al. (1985) observed weakly positive results for phenanthrene (2- to 3-fold increases in revertants) in *Salmonella typhimurium* strains TA100 and TA97. Sakai et al. (1985) reported a poor dose-response relationship for phenanthrene. Dunkel et al. (1984) reported a study in which the same experiments were conducted in four different laboratories. In mutagenicity tests conducted with or without six different metabolic

activation preparations, phenanthrene tested negative in five strains of *S. typhimurium* and in *Escherichia coli* WP-2 uvrA (Dunkel et al., 1984). Only one of the four laboratories reported a positive result for phenanthrene (in TA1538 with Aroclor 1254-induced rat liver S9). When this assay was repeated in the same laboratory, the result was negative (Dunkel et al., 1984). Verschaeve et al. (1999) tested phenanthrene in the VITOTOX assay and reported positive results—but at toxic concentrations. Finally, Oesch et al. (1981) report positive results in the Ames assay (strains TA100 and TA1537) when phenanthrene was tested in combination with rat Aroclor-induced S9 rat microsomal and cytosolic liver fractions (neither alone was active) and when epoxide hydrolase was inhibited. Phenanthrene did not induce mitotic gene conversion in *Saccharomyces cerevisiae* (Siebert et al., 1981). Phenanthrene gave negative results in four *in vitro* studies of mammalian mutagenicity and in nine *in vitro* studies of morphological cell transformation (see Table 1).

Both studies assessing clastogenicity after *in vivo* administration of phenanthrene report positive findings (Roszinsky-Kocher et al., 1979; Bayer, 1978; see Table 2); however, in the study by Bayer (1978), only the high dose gave a significant response. Negative results were obtained in four *in vitro* studies of clastogenicity using mammalian cells (see Table 3). Of 14 studies examining DNA adducts, damage, repair, or synthesis in *in vitro* systems, four gave positive results, one reported equivocal findings, and the remaining nine gave negative results (see Table 3).

Phenanthrene also is negative in the initiator tRNA acceptance assay (Hradec et al., 1990). In studies of DNA adduct formation with phenanthrene, no DNA adducts are found in calf thymus DNA (Bryla and Weyand, 1992), while a low level of DNA binding is reported by Grover and Sims (1968) when the DNA of salmon testes were assayed. In cultured hamster fibroblasts treated with tritiated phenanthrene, a low level of DNA binding has also been observed (Grover et al., 1971). In an *in vivo* study of DNA adduct formation in mice (TO strain) exposed to a topical application of 50 mM phenanthrene, no adducts were detected in the skin when tested 1 to 8 days after exposure (Ingram et al., 2000).

Table 1. *In vitro* Mutagenicity and Morphological Transformation Studies of Phenanthrene

Reference	Test system	Activation system	Result	Comments
Bacterial Mutagenicity				
Bos et al., 1988	*S. typhimurium* TA98, TA100	Rat Ar S9	Weakly positive	
Bücker et al., 1979	*S. typhimurium* TA1535, TA1537, TA1538, TA98, TA100 and *B. subtilis* H17 and M45	Mouse Ar microsomes	Negative	
Carver et al., 1986	*S. typhimurium* TA100	Ar rat and Ar hamster S9	Weakly positive	S9 concentration varied; 400 µL/plate optimal
Dunkel et al., 1984	*S. typhimurium* TA1535, TA1537, TA1538, TA98, TA100, also *E. coli* strains	Rat, mouse, hamster Ar S9	Negative	Dose-response data not provided. Positive result reported by 1/4 laboratories in 1/6 strains; repeat was negative
Gibson et al., 1978	*S. typhimurium* TA1535, TA1537, TA1538, TA98	Nonenzymatic (gamma radiation)	Inconclusive	Toxicity interfered with mutagenicity testing
Hermann, 1981	*S. typhimurium* TA98	Rat Ar S9	Negative	
Kaden et al., 1979	*S. typhimurium* TM677	Rat Ar or PB S9	Negative	
Kangsadalampai et al., 1996	*S. typhimurium* TA98, TA100	None	Negative	
LaVoie et al., 1980	*S. typhimurium* TA98, TA100	Rat Ar S9	Negative	
McCann et al., 1975	*S. typhimurium* TA1535, TA1537, TA98, TA100	Rat Ar S9	Negative	
Oesch et al., 1981	*S. typhimurium* TA1537, TA100	Rat Ar S9	Positive under conditions shown at right	Large amounts of Rat Ar S9, or microsomal + cytosolic liver fractions, or when epoxide hydrolase inhibited
Pahlman and Pelkonen, 1987	*S. typhimurium* TA100	S9 from control, MC- or TCDD-treated rats and mice	Negative	

Table 1. *In vitro* Mutagenicity and Morphological Transformation Studies of Phenanthrene

Reference	Test system	Activation system	Result	Comments
Probst et al., 1981	*S. typhimurium* TA1530, TA1535, TA1537, TA1538, TA98, TA100	Rat Ar S9	Negative	Data reported as minimum mutagenic concentration (nmol/mL)
Rosenkranz and Poirier, 1979	*S. typhimurium* TA1530, TA1535, two *E. coli* strains	Uninduced rat S9	Negative	
Sakai et al., 1985	*S. typhimurium* TA97, TA98, TA100	Rat Ar S9	Weakly positive	Toxicity observed at 250 µg/plate
Simmon, 1979a	*S. typhimurium* TA1535, TA1536, TA1537, TA1538, TA98, TA100	Rat Ar S9	Negative	
Verschaeve et al., 1999	*S. typhimurium* TA104*rec*N2-4 and TA104*pr*1	S9 (unspecified)	Positive	Toxicity observed at mutagenic doses. VITOTOX assay tests expression of *lux* bioluminescent operon
Mammalian Mutagenicity				
Barfknecht et al., 1982	TK6 human lymphoblast cells	Rat Ar S9	Negative	Trifluorothymidine resistance (TK)
Durant et al., 1996	Human B-lymphoblastoid h1A1v2 cells	Intrinsic	Negative	Trifluorothymidine resistance (TK)
Huberman and Sachs, 1976	V79 Chinese hamster cells	Hamster embryo cells	Negative	Ouabain and 8-azaguanine resistance (HPRT)
Mishra et al., 1978	Fischer rat embryo cells infected with Rauscher leukemia virus	Rat Ar S9	Negative	Ouabain resistance (HPRT)
Morphological Transformation				
DiPaolo et al., 1969	Syrian golden hamster embryo cells	Cocultivated irradiated Sprague-Dawley rat fetal cells	Negative	
DiPaolo et al., 1973	Syrian golden hamster embryo cells	*In vivo* (transplacental) exposure	Negative	Positive results confirmed with tumor induction
Dunkel et al., 1981	Balb/3T3, Syrian golden hamster embryo and Rauscher murine leukemia virus-infected F344 rat embryo cells	None	Negative	

Table 1. *In vitro* Mutagenicity and Morphological Transformation Studies of Phenanthrene

Reference	Test system	Activation system	Result	Comments
Evans and DiPaolo, 1975	Strain 2 guinea pig fetal cells	None	Negative	Positive results confirmed with tumor induction
Greb et al., 1980	BHK 21/CL 13	Rat Ar S9	Negative	
Kakunaga, 1973	BALB/3T3 subclone A31-714	None	Negative	Positive results confirmed with tumor induction
Lubet et al., 1983	C3H10T1/2CL8 mouse embryo fibroblasts	None	Negative	
Mishra et al., 1978	Rauscher leukemia virus-infected Fischer rat embryo	None	Negative	
Pienta et al., 1977	Syrian golden hamster embryo	Cocultivated X-irradiated cells of same type	Negative	

Table 2. *In vivo* Clastogenicity Studies of Phenanthrene

Reference	Species	Strain	Route of administration	Vehicle	Exposure	Hours between dosing and sacrifice	Tissue analyzed	Clastogenic endpoint	Result	Comments
Bayer, 1978	Hamsters	Chinese	Intraperitoneal	Tricaprylin	Single	24 hr for aberrations; 30 hr for micronuclei	Bone marrow	Gaps, breaks, micronuclei, SCEs	Positive at high dose	
Roszinsky-Kocher et al., 1979	Hamsters	Chinese	Intraperitoneal	Tricaprylin	2 doses 24 hr apart	24 hr after 2nd treatment	Bone marrow	SCEs, aberrations	Positive for Sister Chromatid Exchanges	Negative for aberrations

Table 3. *In vitro* Clastogenicity, DNA Adducts, DNA Damage, DNA Repair, and DNA Synthesis Studies of Phenanthrene

Reference	Test system	Metabolic activation	Endpoint	Result	Comments
Clastogenicity					
Crofton-Sleigh et al., 1993	Human lymphoblastoid MCL-5 cells	Intrinsic	Micronuclei	Negative	
Matsuoka et al., 1979	Male Chinese hamster lung (CHL)	Rat Ar S9	Aberrations and SCEs	Negative	No untreated control
Popescu et al., 1977	Chinese hamster V79-4 cells	With or without irradiated Syrian golden hamster secondary embryo feeder cells	Aberrations and SCEs	Negative	
Platt et al., 2007	Chinese hamster V79-4 cells V79 lung fibroblasts	With and without Rat Ar S9	DNA strand breaks in Comet assay	Negative	
DNA Damage, Repair, and Synthesis					
Casto, 1979	Syrian golden hamster embryo	Intrinsic	Unscheduled DNA synthesis measured by [^{3}H] thymidine uptake	Negative	
Lake et al., 1978	Human foreskin epithelial cells	None	Unscheduled DNA synthesis measured by [^{3}H] thymidine uptake	Negative	
McCarroll et al., 1981	*E. coli* WP2, WP2 uvrA, WP67, CM611, WP100, W3110polA+ and p3478pola-	Rat Ar S9	DNA damage measured by differential killing of repair-deficient strains	Negative	
Mersch-Sundermann et al., 1992, 1993	*E. coli* PQ37	Rat Ar S9	Induction of SOS system measured by SOS chromotest	Positive	
Milo et al., 1978	Human skin fibroblast NF and Detroit 550 cells	None	DNA damage measured by alkaline elution	Negative	
Probst et al., 1981	Rat hepatocyte primary culture	None	Unscheduled DNA synthesis measured by [^{3}H] thymidine uptake	Negative	

Table 3. *In vitro* Clastogenicity, DNA Adducts, DNA Damage, DNA Repair, and DNA Synthesis Studies of Phenanthrene

Reference	Test system	Metabolic activation	Endpoint	Result	Comments
Rosenkranz and Leifer, 1980	*E coli* pol A1-	Rat liver S9	DNA damage measured by differential killing of repair-deficient strains	Negative	
Rossman et al., 1991	*E coli* WP2s(λ)	Rat liver S9	DNA damage measured by Λ prophage induction	Positive	
Selden et al., 1994	Rat hepatocyte primary culture	Intrinsic	Unscheduled DNA synthesis measured by bromodeoxyuridine uptake	Negative	
Simmon, 1979b	*Saccharomyces cerevisiae* D3	Rat Ar S9	Induced recombination	Negative	
Storer et al., 1996	Rat hepatocyte primary culture	Intrinsic	DNA damage measured by alkaline elution	Equivocal	
DNA Adducts					
Bryla and Weyand, 1992	Calf thymus DNA		DNA adducts measured by [^{32}P] postlabeling	Negative	No measurable DNA adducts
Grover and Sims, 1968	Salmon testes DNA	Rat liver microsomes	DNA binding measured by [^{3}H] prelabeling	Low-level DNA binding detected	
Grover et al., 1971	BHK 21 and PyY hamster fibroblasts		DNA binding measured by [^{3}H] prelabeling	Low-level DNA binding detected	

FEASIBILITY OF DERIVING PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR PHENANTHRENE

Due to the lack of suitable human and animal data, provisional RfDs for phenanthrene cannot be derived.

FEASIBILITY OF DERIVING PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfC VALUES FOR PHENANTHRENE

Due to the lack of suitable human and animal data, provisional RfCs for phenanthrene cannot be derived

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR PHENANTHRENE

Weight-of-Evidence Descriptor

On IRIS (U.S. EPA, 2008), phenanthrene is classified as Group D—not classifiable as to human carcinogenicity—under the U.S. EPA (1986) Guidelines for Carcinogen Risk Assessment. The IRIS Summary cites a lack of human data and inadequate animal data from a single gavage study in rats and several skin application and injection studies in mice. Under the U.S. EPA (2005) Guidelines, there is "*Inadequate Information to Assess [the] Carcinogenic Potential"* of phenanthrene. As indicated in IRIS, there are no human data, and the single oral bioassay of phenanthrene (Huggins and Yang, 1962) is inadequate. Most of the studies that are available (both *in vivo* and *in vitro*) for evaluating the carcinogenicity of phenanthrene are nonpositive. Overall, the database for phenanthrene is substantial, and the weight-of-evidence suggests that this chemical is either very weakly carcinogenic or not carcinogenic at all. An abundance of data indicates that phenanthrene exhibits little or no genotoxicity. However, given the limitations of the bioassays and the absence of human data and cancer bioassays conducted in additional species, the data are inadequate to classify the human carcinogenicity of phenanthrene.

Quantitative Assessment of Carcinogenic Risk

A provisional oral slope factor and inhalation unit risk for phenanthrene cannot be derived because human data are lacking and the animal data are inadequate for developing such estimates.

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