

Provisional Peer-Reviewed Toxicity Values for

Anthracene
(CASRN 120-12-7)

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COMMONLY USED ABBREVIATIONS

BMD	Benchmark Dose
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
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
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
RfC	inhalation reference concentration
RfD	oral reference dose
UF	uncertainty factor

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Background

On December 5, 2003, the U.S. Environmental Protection Agency's (U.S. EPA) 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 (PPRTVs) 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 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 multiprogram 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 5-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 documents 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 Resource Conservation and Recovery Act (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 document 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 U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

IRIS (U.S. EPA, 2008) reports a RfD of 0.3 mg/kg-day for anthracene based on a NOEL of 1000 mg/kg-day in mice given gavage doses for 90 days (Wolfe, 1989). A UF of 3000 was applied (10 for interspecies extrapolation, 10 for intraspecies variability, and 30 for both the lack of a chronic toxicity study and also the lack of reproductive/developmental toxicity data or adequate toxicity data in a second species). The Drinking Water Criteria Document (DWCD) for Polycyclic Aromatic Hydrocarbons (PAHs) (U.S. EPA, 1990) includes the same chronic RfD of 0.3 mg/kg-day for anthracene as does the Drinking Water Standards and Health Advisories list (U.S. EPA, 2006). The Health Effects Assessment Summary Tables (HEAST; U.S. EPA, 1997) lists a subchronic RfD of 3 mg/kg-day based on the same principal study (Wolfe, 1989) as used for the IRIS (U.S. EPA, 2008) chronic RfD; however, a UF of 300 (UF components were not specified in HEAST but presumably include 10 for interspecies extrapolation, 10 for intraspecies variability, and 3 for database deficiencies [including the lack of reproductive/developmental toxicity studies]) was applied to the NOEL. The Chemical Assessments and Related Activities (CARA) list (U.S. EPA, 1991, 1994) includes a Health and Environmental Effects Profile (HEEP) for Anthracene (U.S. EPA, 1987) in addition to the previously mentioned DWCD. Due to the lack of relevant toxicity data at that time, the HEEP (U.S. EPA, 1987) did not derive an RfD. The Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profile for Polycyclic Aromatic Hydrocarbons (PAH; ATSDR, 1995) used the Wolfe (1989) study to derive an intermediate-duration MRL for anthracene of 10 mg/kg-day by dividing the NOEL of 1000 mg/kg-day by a UF of 100 (10 for extrapolation from animals-to-humans and 10 for human variability).

IRIS (U.S. EPA, 2008) and the HEAST (U.S. EPA, 1997) do not report a chronic RfC, and the ATSDR (ATSDR, 1995) does not report an inhalation MRL for anthracene. No standards or guidelines for occupational exposure to anthracene have been promulgated by the American Conference of Governmental Industrial Hygienists (ACGIH, 2007), the National Institute for Occupational Safety and Health (NIOSH, 2008), or the Occupational Safety and Health Administration (OSHA, 2008).

Based on the lack of human data and inadequate animal data, IRIS (U.S. EPA, 2008) identifies anthracene as a classification D carcinogen—"not classifiable as to human carcinogenicity." The National Toxicology Program (NTP, 2008) has not assessed the carcinogenicity of this compound (NTP, 2005, 2008). The International Agency for Research on

Cancer (IARC) Monograph for Anthracene (IARC, 1983) categorizes anthracene as a Group 3 carcinogen—“*available data provide no evidence that anthracene is carcinogenic to experimental animals.*”

To identify toxicological information pertinent to the derivation of provisional toxicity values for anthracene, literature searches were conducted in December 2007 using the following databases: MEDLINE, TOXLINE, and DART/ETIC (1960s–December 2007); BIOSIS (January 2000–June 2007); Current Contents (prior 6 months); and TSCATS1/2, GENETOX, CCRIS, HSDB, and RTECS (not limited by date). The Environmental Health Criteria for Selected Non-Heterocyclic Polycyclic Aromatic Hydrocarbons (WHO, 1998) and the Priority Substances List Assessment Report on Polycyclic Aromatic Hydrocarbons (Health Canada, 1994) were also consulted for relevant information. Finally, an updated search for recently published studies was conducted for the period from January, 2008 thru March, 2009.

REVIEW OF PERTINENT DATA

Human Studies

No adequate human studies that address oral or inhalation exposures to anthracene were located.

Badiali et al. (1985) reported melanosis of the rectum in patients taking laxatives containing anthracene for chronic constipation. Eighty-four patients (25 males, 59 females) seeking medical advice for constipation were examined for melanosis of the colon and rectum. Melanosis was present in 73.4% of the patients consuming anthracene laxatives and in 26.6% of patients not taking such laxatives ($p < 0.01$). Other possible effects of anthracene were not reported.

There were three cases of epithelioma (hand, cheek, and wrist) that were reported in men who routinely handled 40% crude anthracene in an alizarin factory (Kennaway, 1924a,b). Two of these workers handled anthracene for 30–32 years and had never worked with any other coal-tar product. Workers in the same factory who had contact with only purified anthracene did not develop tumors or other skin lesions (i.e., acne, keratoses, telangiectases, and pigmentation) that had been observed in the workers who had contact with the crude material. The crude anthracene was not chemically characterized and additional information regarding these observations was not reported.

Animal Studies

Oral Exposure

Subchronic Studies—In a subchronic study conducted by Hazleton Laboratories America for the U.S. EPA (according to TSCA Guidelines, 40CFR 798.2650), Groups of CD-10 (ICR) BR mice (20/sex/dose) were administered anthracene (5 mL/kg; 100% purity) by gavage (in corn oil), for 7 days/week, at doses of 0, 250, 500, or 1000 mg/kg-day for 90 days (Wolfe, 1989). In addition to ophthalmoscopic and physical examinations prior to testing, all mice were observed daily for signs of toxicity and twice daily for mortality and morbidity. Body weight and food consumption were recorded weekly. Ophthalmoscopic examinations were again made during week thirteen of exposure. Clinical pathology examinations (hematology and clinical chemistry) were conducted on an additional group of 10 randomly selected mice of each sex

prior to initiation of the study and on 10 randomly selected mice of each sex from each of the control and treatment groups during week thirteen of exposure. Hematology variables included cell counts (red, white, platelets, reticulocytes, differential white) and determination of hemoglobin, hematocrit, and cell morphology. Clinical chemistry variables included sodium, potassium, chloride, total protein, albumin, calcium, phosphorus, total bilirubin, urea nitrogen, creatinine, glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), globulin, alkaline phosphatase, cholesterol, albumin/globulin ratio, and lactate dehydrogenase. All animals were necropsied after 13 weeks of exposure, along with animals that died—or were sacrificed—prior to the end of the study. Organs, including the heart, liver, kidneys, spleen, testis, brain, ovaries, and adrenal glands, were weighed at the terminal sacrifice of each animal. Comprehensive histological examinations were conducted on all control and high-dose animals. Histological evaluations of lung, liver, kidney, and any grossly observable lesions were made for all low- and mid-dose animals.

There was no treatment-related mortality (Wolfe, 1989). Two control mice (one male, one female) and one low-dose female died as a result of gavage errors. Very few clinical signs were observed both during the weekly evaluations and the postdosing cage-side evaluations; none appeared to be treatment related. Both males and females in the low-, mid-, and high-dose groups gained weight that was comparable to the controls' throughout the study, and there were no significant differences between any treatment groups during any weekly evaluation or at the end of the study. Similarly, food consumption did not vary between treatment groups.

There were no treatment-related effects on ophthalmoscopic examination or on any of the hematological variables reported (Wolfe, 1989). The only clinical chemistry variable that differed from controls with statistical significance was decreased total protein in all anthracene-treated males but not females. However, this effect was not dose related; values were 5.8 ± 0.40 , 5.2 ± 0.28 , 5.4 ± 0.35 , and 5.4 ± 0.42 for male control, 250-, 500-, and 1000-mg/kg-day groups, respectively. Both absolute and relative ovary weights were statistically significantly elevated among 500-mg/kg-day females relative to controls but not in the low-dose or the higher 1000-mg/kg-day group. No other effects on absolute or relative organ weights are evident from the data.

Cysts were observed in the mouse ovaries upon gross necropsy in 1/19, 3/19, 5/20, and 2/20 females in the control, 250-, 500-, and 1000-mg/kg-day treatment groups, respectively. Of the cysts observed, histopathologic examinations confirmed the presence of ovarian cysts in 1, 0, 3, and 1 females examined in the control, low-, mid- and high-dose groups, respectively. The uterus was distended and fluid-filled in 0/19, 1/19, 1/20, and 2/20 females in the control, 250-, 500-, and 1000-mg/kg-day groups, respectively. Cystic endometrial hyperplasia of the uterus was histologically identified in 3/19, 0/1, 0/3, and 3/20 females examined in the control, low-, mid- and high-dose groups. Wolf (1989) provided no explanation for examining fewer animals in the middle dose groups. There were no other notable or treatment-related histopathologic changes. None of the observations were statistically significant ($p < 0.05$) and no other grossly observable pathological changes were remarkable or treatment related. Both Wolfe (1989) and U.S. EPA (1990, 2008) identify 1000 mg/kg-day (highest dose tested) as the NOEL for the study.

Chronic Studies—No adequate chronic oral studies were identified for anthracene. A group of twenty-eight 14-week-old BDI or BDIII rats of unspecified sex were fed diets that initially contained 5 mg and later (timing not specified) 15 mg of “highly purified” anthracene in

oil, 6 days/week, for a total of 550 treatment days (Schmahl, 1955). The total dose administered was 4.5 grams/rat (28 mg/kg-day per U.S. EPA, 2008). All rats were observed until natural death. The authors noted no toxic symptoms during treatment or recovery and reported a mean survival time of 700 days. The authors do not describe their postmortem procedures, but they report that malignant tumors were observed in only two of the treated rats: a liver sarcoma developed in one rat after 18 months of treatment and a uterine adenocarcinoma with numerous metastases developed in another rat after 25 months of treatment. The authors did not believe these tumors were related to anthracene administration and reported a control incidence of 0.5% (presumably historical controls, because no controls were used in the experiment). No other data regarding oral exposure are presented by the authors. Effect levels cannot be determined from this study.

Reproductive/Developmental Studies—No oral-route reproductive or developmental toxicity studies were identified for anthracene. The observed changes on the ovaries and uteri of mice in the Wolfe (1989) study were not statistically significant ($p < 0.05$) and do not appear to be dose related. In the oral subchronic toxicity study, Wolfe (1989) noted no changes in the reproductive tissues of the male mice.

Inhalation Exposure

No subchronic, chronic, reproductive, or developmental studies of anthracene conducted by the inhalation route of exposure in animals were identified.

Other Studies

Immunotoxicity

In a study of structure-activity relationships (White et al., 1985), 10 PAHs—including anthracene (160 $\mu\text{mol/kg-day}$)—were subcutaneously injected into female B6C3F1 mice (8 per chemical) daily for 14 days. Immunosuppression in the mice was evaluated by determining the ability of the PAHs to inhibit the induction of splenic antibody-forming cells (AFCs) 4 days after immunization with sheep erythrocytes. The spleen weights of mice treated with anthracene were not statistically significantly ($p < 0.05$) different from the vehicle-treated control mice. Further, treatment with anthracene failed to significantly ($p < 0.05$) reduce the number of IgM-AFCs in the mice spleens in comparison with the control mice. The study authors concluded that PAH immunosuppression closely parallels the structure-activity relationship for carcinogenesis and that simple PAHs, including anthracene, do not suppress the AFC response.

Parenteral Carcinogenicity

Groups of 60 female 3- to 6-month-old Osborne-Mendel rats were observed for 55–81 weeks after receiving a single lung-implanted pellet of anthracene (0.5 mg/rat, approximately 2 mg/kg by injection) dissolved in a 1:1 by volume (v/v) mixture of beeswax and trioctanoin (0.1 mL) (Stanton et al., 1972). Controls received an implant of the vehicle. No tumors were observed.

Dermal Carcinogenicity

Anthracene has been tested for carcinogenicity by skin application with and without ultraviolet radiation in mice, in skin initiation-promotion assays with mice, by subcutaneous and intraperitoneal injection in rats, and by implantation into the brain or eyes in rabbits (U.S. EPA, 1987). The results of the skin application studies with anthracene do not provide evidence of carcinogenicity, but contradictory results were obtained when anthracene was applied to skin

together with exposure to ultraviolet radiation. Initiating activity was not indicated in the mouse skin initiation-promotion assays.

Skin-painting experiments were conducted on groups of 20 male C3H/HeJ mice (Warshawsky et al., 1993). Anthracene dissolved in toluene was applied to areas of shaved skin twice weekly for 6 months at a dose of 0.05 mg. Tumor incidence was determined at the end of the study. In 14 treated animals, anthracene administered alone produced no tumors (0%). With coadministration of 0.05 mg benzo[a]pyrene, 1/13 (8%) had a papilloma, with a mean latency period of 85 weeks. Anthracene was negative as a complete carcinogen following chronic dermal exposure (Habs et al., 1980). Swiss mice receiving 10% anthracene in acetone topically applied to their backs three times a week throughout their lifetime did not develop any skin tumors after 20 months of exposure (Wynder and Hoffmann, 1959).

No tumors were observed in an assay of initiating activity in which Crl:CD/1 (ICR)BR female albino mice were exposed to 1 mg anthracene in acetone and then treated with 12-*O*-tetradecanoyl-phorbol-13 acetate (TPA) as the promoting agent three times/week for 20 weeks (LaVoie et al., 1985). In another study with TPA (Scribner, 1973), a single dermal application of 10 μ M anthracene (purity not stated) in benzene was administered to 30 female CD-1 mice; this initial application was followed 7 days later by twice-weekly applications of 5 μ M TPA for 35 weeks. Survival in the group was 93% after 35 weeks. By week 20 of the test, 2/28 (7%) mice had developed skin tumors; this increased to 4/28 (14%) by week 35. In the control group, in which 30 mice received only the TPA applications, a mouse developed a skin tumor at week 25.

Kennaway (1924a) administered anthracene (purity unknown) as a 40% solution dissolved either in lanolin or as an ether extract to two groups of 100 mice each (sex and strain not stated). In the lanolin-group, 44% of the mice survived 131 days and in the ether-extract group only 6% survived until day 160. In the lanolin-group, 1/44 (2%) surviving mice developed a papilloma by day 131; no mice developed tumors in the ether-extract group by day 160. No information pertaining to the use of a control group was given.

Genotoxicity

With a single exception (Sakai et al., 1985), anthracene did not cause mutations or chromosomal damage in bacteria, yeast, or mammalian cells. Most of the available studies employed metabolic activation. Anthracene was negative in mutagenicity assays with *Salmonella typhimurium* (McCann et al., 1975; Simmon, 1979a; LaVoie et al., 1978, 1985; Kaden et al., 1979; Salamone et al., 1979; Ho et al., 1981; DeFlora et al., 1984); and was negative in mutation assays with Chinese hamster V79 cells (Knapp et al., 1981; Langenbach et al., 1983), rat liver epithelial cells (Ved Brat et al., 1983), human lymphoblastoid TK6 cells (Barfknecht et al., 1981), and mouse lymphoma cells (Amacher and Turner, 1980; Amacher et al., 1980). Sakai et al. (1985) reported positive results in a mutation assay with *Salmonella typhimurium* strain TA97 at concentrations of 5 and 10 μ g/plate in the presence of rat liver S9. No other studies tested this strain. Anthracene did not induce sister chromatid exchange in Chinese hamster D6 cells (Abe and Sasaki, 1977) or rat liver epithelial cells (Tong et al., 1981; Ved Brat et al., 1983), nor did it cause strand breakage in DNA from rat liver hepatocytes (Sina et al., 1983). Anthracene did not cause DNA damage in *Escherichia coli* (Rosenkrantz and Poirier, 1979; DeFlora et al., 1984) or *Bacillus subtilis* (McCarroll et al., 1981), and it did not induce mitotic combination in *Saccharomyces cerevisiae* (Simmon, 1979b).

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR ANTHRACENE

Subchronic p-RfD

The subchronic toxicity study by Wolfe (1989) is the only oral toxicity study for anthracene that is suitable for the basis of a subchronic p-RfD for anthracene because a variety of toxicologic endpoints were examined in three dose groups and one control group of mice by gavage dosing. This study defines a NOEL of 1000 mg/kg-day (highest dose tested) and is the basis for U.S. EPA's verified chronic RfD of 0.3 mg/kg-day for anthracene on IRIS (U.S. EPA, 2008). The Benchmark Dose approach was not applied because a dose-response relationship was not identified in the critical study. Using the NOEL from Wolfe (1989) as the point of departure and a composite UF of 1000, a **subchronic p-RfD of 1 mg/kg-day** is derived as follows:

$$\begin{aligned}\text{Subchronic p-RfD} &= \text{NOEL} \div \text{UF} \\ &= 1000 \div 1000 \\ &= \mathbf{1 \text{ or } 1 \times 10^0 \text{ mg/kg-day}}\end{aligned}$$

The composite UF of 1000 is composed of the following:

- A full UF of 10 was applied for interspecies extrapolation to account for potential pharmacokinetic and pharmacodynamic differences between rats and humans.
- A full UF of 10 was applied for intraspecies differences to account for potentially susceptible individuals in the absence of information on the variability of response in humans.
- A full uncertainty factor of 10 was applied to account for database uncertainty. The database lacks developmental toxicity or multigeneration reproduction studies.

Confidence in the principal study is medium. The study examined a variety of toxicological endpoints but the failure to identify a LOAEL precludes a higher level of confidence. Confidence in the database is low because of the lack of adequate toxicity data in a second species and developmental/reproductive studies. Low confidence in the subchronic p-RfD follows.

Chronic p-RfD

IRIS (U.S. EPA, 2008) currently posts a verified (11/15/89) chronic RfD of 0.3 mg/kg-day for anthracene based on the study by Wolfe (1989). The basis for the chronic RfD is a NOEL of 1000 mg/kg-day divided by a UF of 3000 (10 for interspecies extrapolation, 10 for intraspecies variability, and 30 for lack of a chronic toxicity study, reproductive/developmental toxicity data or adequate toxicity data in a second species).

FEASIBILITY OF DERIVING PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION p-RfC VALUES FOR ANTHRACENE

There are no data available from which to derive p-RfC values for anthracene.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR ANTHRACENE

Weight-of-Evidence Descriptor

Under the 2005 Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005), “*inadequate information is available to assess the carcinogenic potential*” of anthracene. This is reflected in IRIS (U.S. EPA, 2008) where anthracene is classified as a Group D carcinogen—“*not classifiable as to human carcinogenicity,*” based on a lack of human data and inadequate data from animal bioassays. As discussed previously, oral, dermal, parenteral, and lung-injection routes of exposure have failed to provide evidence of carcinogenicity, although some of the studies are limited in terms of design and reporting. Numerous genotoxicity studies were overwhelmingly negative.

Quantitative Estimates of Carcinogenic Risk

Due to the lack of adequate data, it is neither possible nor appropriate to derive quantitative estimates of carcinogenic risk for anthracene for either oral or inhalation exposures.

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