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Provisional Peer Reviewed Toxicity Values

Benz[a]anthracene
(CASRN 56-55-3)

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

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
i.v.	intravenous
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
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 BENZ[a]ANTHRACENE (CASRN 56-55-3)

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. EPA's Integrated Risk Information System (IRIS).

2. Provisional Peer-Reviewed Toxicity Values (PPRTV) used in 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 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 EPA IRIS Program. All provisional toxicity values receive internal review by two 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 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 EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other 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.

This document has passed the STSC quality review and peer review evaluation indicating that the quality is consistent with the SOPs and standards of the STSC and is suitable for use by registered users of the PPRTV system.

INTRODUCTION

IRIS (U.S. EPA 1990b) reports that an RfD for benz[a]anthracene is not available at this time. Neither the HEAST (U.S. EPA, 1997) nor the Drinking Water Regulations and Health Advisory list (U.S. EPA, 2000) report an RfD for benz[a]anthracene. ATSDR (2000) has not published a Toxicological Profile for benz[a]anthracene, though a discussion of benz[a]anthracene is included in the profile for polycyclic aromatic hydrocarbons (PAH) (ATSDR, 1995). No oral MRLs were derived for benz[a]anthracene. IARC (1973, 1983) monographs on benz[a]anthracene and the NTP status report (NTP, 2000) were consulted for relevant information. The World Health Organization (WHO, 2000) has not published an Environmental Health Criteria document for benz[a]anthracene.

The CARA lists (U.S. EPA, 1991, 1994b) report no relevant documents specific for benz[a]anthracene. A Drinking Water Criteria Document (U.S. EPA, 1990a) for PAH exists, but an RfD for benz[a]anthracene was not derived.

Literature searches were conducted from 1989 to June, 2000 for studies relevant to the derivation of an RfD. The databases searched were: TOXLINE, MEDLINE, CANCERLIT, RTECS, GENETOX, HSDB, CCRIS, TSCATS, EMIC/EMICBACK, and DART/ETICBACK.

A carcinogenicity assessment for benz[a]anthracene is available on IRIS (U.S. EPA, 1990b). This assessment, verified 02/07/1990, was based on a Carcinogen Assessment of Coke Oven Emissions (U.S. EPA, 1984a) and a Drinking Water Criteria Document for Polycyclic Aromatic Hydrocarbons (PAHs) (U.S. EPA, 1990). Benz[a]anthracene was assigned to weight-of-evidence Group B2, probable human carcinogen, based on increased incidences of pulmonary and hepatic tumors in mice exposed by gavage (Klein, 1963) or intraperitoneal injection (Wislocki et al., 1986), positive results in tests for complete carcinogenicity and initiating activity in skin painting assays in mice (multiple studies reviewed by IARC, 1973), and injection site sarcomas in mice injected subcutaneously (Steiner and Edgecomb, 1952; Steiner and Falk, 1951). Supporting data from genotoxicity tests included positive results for mutations in bacteria and mammalian cells, and transformed mammalian cells in culture. It was noted that benz[a]anthracene is a component of mixtures that are known to produce cancer in humans, although there are no human data that specifically link benz[a]anthracene with human cancers. However, due to the lack of adequate oral data for benz[a]anthracene, an oral slope factor was not included on IRIS (U.S. EPA, 1990b).

The HEAST (U.S. EPA, 1997) reports the availability of the weight-of-evidence assessment on IRIS, but contains no additional information. The Drinking Water Standards and Health Advisories list (U.S. EPA, 2000) includes the cancer group B2 designation for benz[a]anthracene, but does not include additional cancer risk information. A Health Effects Assessment for Polycyclic Aromatic Hydrocarbons (PAHs) (U.S. EPA, 1984b) was located, but no relevant documents specific to benz[a]anthracene were found in the CARA database (U.S. EPA, 1991, 1994b).

The International Agency for Research on Cancer (IARC, 1973, 1983, 1987) evaluated benz[a]anthracene for carcinogenicity and placed the chemical in Group 2A (probable human carcinogen), finding that there is sufficient evidence that benz[a]anthracene is carcinogenic to experimental animals and that the chemical is active in short-term genotoxicity tests. CalEPA derived an oral slope factor for benz[a]anthracene which is based on a relative potency factor approach (CalEPA, 1999). The ATSDR (1995) Toxicological Profile for Polycyclic Aromatic Hydrocarbons (PAHs) and the NTP (2000) management status report were searched for relevant information. Updated literature searches for cancer data were conducted from 1989 to 2000. The databases searched were TOXLINE, MEDLINE, CANCERLIT, CCRIS, TSCATS, HSDB, RTECS, GENETOX, DART/ETICBACK, and EMIC/EMICBACK.

REVIEW OF THE PERTINENT LITERATURE

Human Studies

No studies were located regarding oral exposure of humans to benz[a]anthracene.

No studies were located regarding the carcinogenicity of benz[a]anthracene in humans following oral exposure.

Animal Studies

No oral studies in animals suitable for derivation of an RfD were located. The majority of available studies examined mixtures of PAHs containing benz[a]anthracene, rather than the pure compound. A study by Klein (1963) examined the carcinogenic effects of benz[a]anthracene in mice following gavage exposure (3 exposures/week, ~1.5 mg/exposure in 0.05 mL volume, for durations between 344 and 600 days). However, the study examined only one exposure level and only reported tumor incidence; noncancer endpoints were not evaluated.

Klein (1963) observed increased incidence of pulmonary adenoma and hepatoma in male mice treated with 3% benz[a]anthracene solution by gavage for 5 weeks. This study is not suitable for quantitative cancer risk assessment due to the short exposure duration and use of a single dose level (U.S. EPA, 1990a). No other studies were located that could be used as the basis for derivation of an oral slope factor for benz[a]anthracene.

Other Studies

A number of genotoxicity studies (reviewed by ATSDR, 1995; IARC, 1973; U.S. EPA, 1984b, 1990a) indicate that benz[a]anthracene is genotoxic to bacteria and mammalian cells.

DERIVATION OF A PROVISIONAL RfD FOR BENZ[a]ANTHRACENE

A provisional RfD for benz[a]anthracene cannot be derived due to the lack of suitable human and animal data.

DERIVATION OF A PROVISIONAL RfC FOR BENZ[a]ANTHRACENE

A provisional RfC for benz[a]anthracene cannot be derived due to the lack of suitable human and animal data.

DERIVATION OF A PROVISIONAL ORAL SLOPE FACTOR FOR BENZ[a]ANTHRACENE

A provisional oral slope factor for benz[a]anthracene cannot be derived because human data are lacking and the oral cancer data in animals are inadequate. However, the Appendix to this document contains a screening value that may be useful in certain instances. Please see the attached Appendix for details. A provisional unit risk is not developed because of lack of available data.

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APPENDIX

DERIVATION OF A SCREENINGVALUE FOR BENZ[a]ANTHRACENE

For reasons noted in the main PPRTV document, it is inappropriate to derive provisional toxicity values for benz[a]anthracene, oral slope factor. However, information is available for this chemical which, although insufficient to support derivation of a provisional toxicity value, under current guidelines, may be of limited use to risk assessors. In such cases, the Superfund Health Risk Technical Support Center summarizes available information in an Appendix and develops a "Screening Value." Appendices receive the same level of internal and external scientific peer review as the PPRTV documents to ensure their appropriateness within the limitations detailed in the document. In the OSRTI hierarchy, Screening Values are considered to be below Tier 3, "Other (Peer-Reviewed) Toxicity Values."

Screening Values are intended for use in limited circumstances when no Tier 1, 2, or 3 values are available. Screening Values may be used, for example, to rank relative risks of individual chemicals present at a site to determine if the risk developed from the associated exposure at the specific site is likely to be a significant concern in the overall cleanup decision. Screening Values are not defensible as the primary drivers in making cleanup decisions because they are based on limited information. Questions or concerns about the appropriate use of Screening Values should be directed to the Superfund Health Risk Technical Support Center.

In this appendix, we briefly examine the Agency's development of a quantitative cancer dose-response analysis for benz(a)anthracene (B[a]A), a polycyclic aromatic hydrocarbon (PAH). In 1993, the U.S. EPA developed an estimated order of potency value of 0.1 for B[a]A, relative to the carcinogenicity of a second PAH, benzo(a)pyrene (B[a]P). We then examine the development of this estimated order of potency value considering the relative potency factor method developed in the U.S. EPA's Supplementary Chemical Mixtures Guidance (U.S. EPA, 2000). We conclude that there is uncertainty in applying an RPF value, which was developed in a rodent bioassay, to an oral slope factor. We identify uncertainties regarding the application of this value in risk assessments. The discussion focuses on animal bioassay data rather than *in vitro* methods, because we do not know whether such studies provide relevant measures of relative potency for humans. We also do not discuss studies that have compared potencies for non-cancer effects because the IRIS database does not quantify an oral RfD for B[a]P; other sources of variability associated with the development of RfD estimates complicate the application of relative potency approaches.

In 1992, the U.S. EPA published the 'Drinking Water Criteria Document for Polycyclic Aromatic Hydrocarbons (U.S. EPA, 1992), which details the development of an oral cancer slope factor (OSF) for a PAH, B[a]P. This document also classified seven other PAHs including B[a]A as probable human carcinogens, but, citing limited dose-response information, did not develop cancer slope factor estimates for these seven PAHs. In 1993, the Agency published the 'Provisional Guidance for Quantitative Risk Assessment of Polycyclic Aromatic Hydrocarbons' (U.S. EPA, 1993), which describes the development of an approach for quantifying the cancer risk associated with these seven PAHs by comparing the relative carcinogenic potency of each

compound to that of B[a]P. The Agency's approach was mathematically equivalent to the toxicity equivalence factor (TEF) approach (U.S. EPA, 1989). The TEF approach as applied to dioxins assumed that a single TEF value could be developed for each dioxin congener and that this same value could be used for different health endpoints, different routes of exposure and different durations of exposure. However, the underlying scientific data for B[a]A and B[a]P did not satisfy all of the criteria recommended for implementing the TEF method (Barnes, et al., 1991). The Agency acknowledged that this approach did not meet all of the criteria for TEF development and coined an alternative term, "estimated order of potency" to distinguish this approach from TEFs citing the following additional reasons:

- approach applied to a small subset of the PAHs, instead of all PAHs
- approach limited to the cancer endpoint, instead of all health endpoints
- slope factor derivation based on B[a]P exposure only from an oral pathway, instead of deriving this value based on multiple exposure routes
- uncertainty about such an application given the current understanding of the toxicodynamics associated with PAH carcinogenicity

The Agency approach assumed that the human carcinogenicity of the seven PAHs could be predicted using an oral cancer slope factor that was developed for B[a]P. To analyze the carcinogenicity of B[a]A relative to B[a]P, the Agency utilized the results of a chronic mouse dermal bioassay reported by Bingham and Falk (1969), which relied on the bioassay methods published by Horton et al. (1965). In the bioassay, groups of mice were treated with either B[a]P or B[a]A. B[a]P or B[a]A was applied to an area of shaved skin on the back of each mouse twice weekly until the animal developed a tumor or died. We note that Bingham and Falk (1969) did not report solvent control tumor incidences.

The ability of B[a]A to elicit rodent skin tumors then was quantitatively compared to that of B[a]P (Equation 1). U.S. EPA (1992) describes a potency analysis by T. Thorslund of ICF-Clement Associates under contract with U.S. EPA. In the application of these models it was assumed that carcinomas can develop from papillomas. The relative potency of each PAH was calculated as the ratio of the estimated times-to-tumor with the potency of BAP indexed as 1. Point estimates (maximum likelihood estimates) were compared rather than upper bound estimates. Based on this approach the U.S. EPA (1993) recommended an "estimated order of potency" value for B[a]A of 0.1, relative to B[a]P. This was described as an interim recommendation. Time-to-tumor analyses rely on measures of response time and dose. Consequently, this integrated measure of response time is an imperfect measure upon which to base an estimate of the relative potency of one chemical to another.

$$RPF = \frac{TT_{B[A]P}}{TT_{B[A]A}}$$ Equation 1

Where:
RPF Relative Potency Factor (unitless)
TT Time-to-tumor (days)
B[A]A Benz[a]Anthracene
B[A]p Benz[a]Pyrene

U.S. EPA (1993) also analyzes the relative potency of B[a]A based on several other bioassays. Based on an intraperitoneal injection study (Wislocki et al. 1986), US EPA (1993) reported a range of "estimated order of potency" values of 0.06-0.52 for B[a]A. Wislocki et al. (1986) administered B[a]P and B[a]A intraperitoneally to newborn CD-1 mice on postnatal days 1, 8, and 15 and the mice were sacrificed after 1 year. The range of potency values was calculated using liver and lung tumor incidence data. The relevance of this exposure route to environmental exposures is questionable and the applicability of relative potency comparisons to such exposures is not known. The US EPA (1993) also discusses a manuscript by Nisbet and Lagoy, which recommends a relative potency value of 0.1 for B[a]A based on comparisons of tumorigenic potencies with B[a]P (essentially the same as those reviewed by Clement Associates, 1988). The RPFs were derived from previously reported review papers (Nisbet and LaGoy, 1992; Rugen et al., 1989; Clement Associates, 1988; Chu and Chen, 1984), as well as the primary literature describing pulmonary implant, skin painting, subcutaneous injection, and mouse skin DNA binding studies. The relative potency values of B[a]A were comparable across multiple testing modalities.

In 2000, the Agency published the 'Supplementary Guidance for Chemical Mixtures,' which describes the relative potency factor method. Similar to the TEFs and estimated order of potency methods, this method is based on the concept of dose addition. The fundamental assumption of dose additive mixture methods is that the components' toxicity is mediated through the same toxic mode of action; then, the toxicity of mixtures consisting of components that act through a common mode of toxic action can be predicted by the component compounds' toxicity. The toxicity of the marginally studied components of the mixture can be estimated by scaling to the toxicity of a well-studied component of the chemical mixture (referred to as the index chemical). To implement this approach, the index chemical must have adequate toxicologic dose-response data for relevant routes of exposure. The toxicity of each of the other components of the mixture is predicted by scaling its exposure level by its toxicity relative to the index chemical. This scaling factor, called the Relative Potency Factor (RPF), is based on a comparison of the results of toxicologic assays with those results for the index chemical. The product of the measured exposure concentration of each mixture component and its RPF is considered to be an equivalent dose in units of the index chemical (i.e., dose of Chemical I X RPF_I = Index Chemical Equivalent Dose of Chemical I). The index chemical exposure equivalents of all the mixture components are summed to express the total mixture exposure in terms of an equivalent exposure to the index chemical. The risk posed by the mixture is quantified by comparing the mixture's index chemical equivalent dose to the dose-response function of the index chemical. A key advantage of this mixture component method is that, based on the available data, the application of an RPF can be limited to specific toxicologic effects, exposure routes, exposure durations, or dose ranges. The EPA stated that RPF applications that have no such limitations are called toxicity equivalence factors (TEFs).

Based on this application of the RPF method and the OSF listed on IRIS for B[a]P, 7.3 per mg/kg-day, we provide a **screening oral slope factor of 0.7 per mg/kg-day (0.1 x 7.3).** Screening level values should be used only for screening and after consultation with the Superfund Health Risk Assessment Center.

The following should be considered in the application of the B[a]A RPF value to the OSF for B[a]P.

- The B[a]A RPF value of 0.1 was developed using chronic exposure data, applications to other exposure durations should include analyses of toxicokinetics and toxicodynamics.
- The B[a]A RPF value of 0.1 was developed using cancer data, applications to other toxicity endpoints should include analyses of toxicokinetics and toxicodynamics.
- The B[a]A RPF value of 0.1 was developed based on a small number of exposure routes, applications to other routes of exposure should compare toxicokinetics and toxicodynamics of B[a]A across relevant routes of exposure.
- Use of the maximum likelihood estimates to develop the RPF value (U.S. EPA, 1992) of 0.1 for B[a]A is appropriate

A number of additional uncertainties are identified:

- The Bingham and Falk study does not report a vehicle control. The lack of such a control increases the uncertainty in the quantitative interpretation of the results.
- The limited review of the toxicological literature on B[a]A failed to identify data that characterize whether the carcinogenicity of B[a]A and B[a]P results from a common toxic mode of action. Evidence presented here is based on gross observations of benign and malignant tumor development in rodents. Additional toxicodynamic analyses are needed to characterize whether these compounds share a common toxic mode of action in rodents. Information is also needed to determine if this mode of action is relevant to humans. We emphasize that this assumption of common toxic mode of action is *critical* to application of a dose additive method such as the RPF method and that the molecular evidence supporting this assumption for carcinogenicity of B[a]A and B[a]P is not evaluated here.
- The RPF value for B[a]A is based primarily on a point of contact exposure with shaved dermis. Although other similar RPF values have been derived based on other exposure pathways (U.S. EPA, 1993), the applicability of the exposure routes used in these studies to environmentally relevant RPFs estimates is not known. The OSF for B[a]P is based on the increased incidences of squamous cell papillomas and carcinomas in the forestomachs of mice, rats and hamsters administered BAP via the diet or by gavage (Neal and Rigdon, 1967; Knauf and Rice, 1992). These were likely point of contact tumors. Additional data are needed to characterize the absorption, distribution, metabolism and elimination of B[a]A; such data need to be compared with similar studies in B[a]P as well as toxicodynamic studies to assess the uncertainty in cross-route applications of this RPF. Again, in addition to such studies in rodents, an evaluation of the kinetics of both compounds in humans would be useful in the evaluation of the RPF value to other routes of exposure.
- Applications of this RPF value for B[a]A to other types of risks (e.g., non-cancer) should be considered carefully. In this analysis, we did not survey the literature to evaluate whether

data are available to evaluate the relative potency of B[a]A to B[a]P for other health endpoints.

- Additional empirical data are needed on the additivity of carcinogenic effects of PAHs. Results of testing simple mixtures of PAHs and mixture components must be compared to assessments made from bioassays of complex PAH environmental mixtures. The conduct of such studies, while not critical to the development of this RPF value, could improve the overall confidence in the results of cancer risk estimates derived from dose-additive models of PAH carcinogenicity.

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