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Provisional Peer Reviewed Toxicity Values for

Benzo[b]fluoranthene
(CASRN 205-99-2)

Derivation of an Oral RfD

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
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 BENZO[b]FLUORANTHENE (CASRN 205-99-2)
Derivation of an Oral RfD

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.

INTRODUCTION

An RfD for benzo[b]fluoranthene (B[b]F) is not available on IRIS (U.S. EPA, 2001), in the HEAST (U.S. EPA, 1997), or in the Drinking Water Regulations and Health Advisory list (U.S. EPA, 2000), and the chemical was never reviewed by the RfD/RfC Work Group (U.S. EPA, 1995). A HEA for Polycyclic Aromatic Hydrocarbons (PAH) (U.S. EPA, 1984), a Drinking Water Criteria Document for Polycyclic Aromatic Hydrocarbons (U.S. EPA, 1991a) and a Multimedia Document for Polycyclic Aromatic Hydrocarbons (U.S. EPA, 1992) did not derive an RfD for B[b]F. No other pertinent EPA documents were located in the CARA lists (U.S. EPA, 1991b, 1994). The ATSDR (1995) Toxicological Profile for PAHs and the ATSDR (1987) Toxicological Profile for Benzo[b]fluoranthene declined to derive oral MRLs for B[b]F due to lack of suitable data. The NTP (2001) Management Status Report, WHO (1997), the IARC monograph series (IARC, 1973, 1983, 1987), and Patty's Toxicology (Warshawsky, 2001) were searched for relevant information. Literature searches of the following databases were conducted from 1989 to April 2001 for relevant studies: TOXLINE, MEDLINE, TSCATS,

GENETOX, HSDB, CANCERLIT, CCRIS, EMIC/EMICBACK, DART/ETICBACK, and RTECS.

REVIEW OF THE PERTINENT LITERATURE

Human Studies

The most recent reviews (ATSDR, 1995; IARC, 1983, 1987; U.S. EPA, 1984, 1991a, 1992; WHO, 1997) found no available human data regarding the toxicity of B[b]F following oral exposure. The literature search identified no new studies regarding the toxicity of B[b]F in humans following oral exposure.

Animal Studies

The most recent reviews (ATSDR, 1995; IARC, 1983, 1987; U.S. EPA, 1984, 1991a, 1992; WHO, 1997) found no available animal data that could be used as the basis for derivation of an RfD for B[b]F. B[b]F suppressed the antibody response in a dose-related manner in an acute study in which male C57BL/6J mice (2/group) were administered B[b]F in corn oil as a single oral gavage at 0.1, 1.0, 10 or 100 mg/kg (Silkworth et al., 1995). Twelve hours after treatment, the mice were immunized i.v. with sheep erythrocytes. The splenic primary direct (IgM) antibody response was evaluated 5 days after immunization using a plaque assay. At the highest dose, B[b]F suppressed the immune response by approximately 84% of control. However, this study is not adequate for derivation of an RfD, because it only addresses one endpoint and is of inadequate duration.

FEASIBILITY OF DERIVING A PROVISIONAL RfD FOR BENZO[b]FLUORANTHENE

A provisional RfD for B[b]F cannot be derived because of the lack of human and adequate animal oral data.

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11-30-2001

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Derivation of an Oral Slope Factor

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Acronyms and Abbreviations

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HEC	human equivalent concentration
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IRIS	Integrated Risk Information System
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p-RfD	provisional oral reference dose
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SDWA	Safe Drinking Water Act
sq.cm.	square centimeters
TSCA	Toxic Substances Control Act
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INTRODUCTION

A carcinogenicity assessment for benzo[b]fluoranthene (B[b]F) is available on IRIS (U.S. EPA, 2001). 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 (PAH) (U.S. EPA, 1991a). B[b]F was assigned to weight-of-evidence Group B2, probable human carcinogen, based on increased incidences of epidermoid carcinomas and pleomorphic sarcomas in a lung implantation study in rats (Deutsch-Wenzel et al., 1983), injection site sarcomas in a subcutaneous injection assay in mice (Lacassagne et al., 1963), liver adenomas and hepatomas in male mice following intraperitoneal injection (LaVoie et al., 1987), and skin tumors in dermal application studies in mice (Amin et al., 1985; LaVoie et al., 1982; Wynder and Hoffmann, 1959). Supporting data from genotoxicity tests included positive results mutations in bacteria (Amin et al., 1985; Hecht et al., 1980; Hermann, 1981; LaVoie et al., 1979). It was noted that B[b]F is a component of mixtures that are known to produce cancer in humans, although there are no human data that specifically link B[b]F with

human cancers. However, due to the lack of adequate oral data for B[b]F, an oral slope factor was not included on IRIS (U.S. EPA, 2001).

U.S. EPA (1991a) explored the use of a relative potency factor approach to derive slope factors for B[b]F and other PAHs from the existing slope factor for benzo[a]pyrene. However, the CRAVE Work Group decided not to include relative potency information for PAHs on IRIS because the methodology was not sufficiently developed, the underlying database had not been sufficiently reviewed, and surrounding issues (e.g., route-to-route extrapolation) had not received sufficient peer review (U.S. EPA, 1994a). 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 B[b]F, but does not include additional cancer risk information. A Health Effects Assessment for Polycyclic Aromatic Hydrocarbons (U.S. EPA, 1984b) was located, but no relevant documents specific to B[b]F were found in the CARA lists (U.S. EPA, 1991b, 1994b).

The International Agency for Research on Cancer (IARC, 1973, 1983, 1987) evaluated B[b]F for carcinogenicity and placed the chemical in Group 2B (possible human carcinogen), finding that there is sufficient evidence that B[b]F is carcinogenic to experimental animals, that the chemical was mutagenic to *Salmonella typhimurium* in the presence of an exogenous metabolic system, and induced sister chromatid exchange in bone-marrow cells of hamsters treated *in vivo*. CalEPA derived an oral slope factor for B[b]F, but it is based on a relative potency factor approach (CalEPA, 1999). ACGIH (2000) has classified B[b]F as A2-suspected human carcinogen. The NTP (2001) Management Status Report, WHO (1997), Patty's Toxicology (Warshawsky, 2001), the ATSDR (1995) Toxicological Profile for Polycyclic Aromatic Hydrocarbons, the ATSDR (1987) Toxicological Profile for Benzo(b)fluoranthene, and a Multimedia Document for Polycyclic Aromatic Hydrocarbons (U.S. EPA, 1992) were searched for relevant information. Literature searches of the following databases were conducted from 1989 to April 2001 for relevant studies: TOXLINE, MEDLINE, TSCATS, GENETOX, HSDB, CANCERLIT, CCRIS, EMIC/EMICBACK, DART/ETICBACK, and RTECS.

REVIEW OF THE PERTINENT LITERATURE

Human Studies

The most recent reviews (ATSDR, 1995; IARC, 1983, 1987; U.S. EPA, 1984b, 1991a, 1992; WHO, 1997) found no available human data regarding the carcinogenic potential of B[b]F. The literature search identified no new studies regarding carcinogenicity of B[b]F in humans following oral exposure.

Animal Studies

The most recent reviews (ATSDR, 1995; IARC, 1983, 1987; U.S. EPA, 1984b, 1991a, 1992; WHO, 1997) found no available animal oral data regarding the carcinogenic potential of B[b]F. The literature search identified no new studies regarding carcinogenicity of B[b]F in animals following oral exposure.

Other Studies

The literature search identified the following supporting data for carcinogenicity of B[b]F not included on IRIS. Reddy et al. (1991) reported that oral treatment of mice with B[b]F induced clastogenic responses in the gastrointestinal tract. Groups of 10 male B6C3F1 mice were given single gavage doses of 0 (control) or 0.76 mmol/kg B[b]F and sections of the gastrointestinal tract (forestomach, duodenum, proximal colon) were examined for nuclear anomalies 24 hours after dose administration. Statistically increased ($p<0.05$) numbers of nuclear anomalies were observed in the duodenum and proximal colon of treated animals, but not in the forestomach, compared with control mice. No statistically significant increase in sister chromatid exchange (SCE) or micronucleus induction was observed in mice orally gavaged with B[b]F suspended in sunflower oil (100 mg/kg), whereas the number of SCEs/metaphase (but not micronucleus induction) was statistically significantly increased in animals given a single intraperitoneal injection of B[b]F (100 mg/kg) (Bryant et al., 1993). Male A/J mice, given a single intraperitoneal injection of 0, 10, 50, 100, or 200 mg/kg B[b]F dissolved in tricaprylin, were evaluated for lung adenomas 8 months after treatment (Mass et al., 1996; Nesnow et al., 1995, 1998a,b; Ross et al., 1995). Lung adenoma incidence, with mutation types TGT, CGT, GAT, and GTT induced in the Ki-*ras* oncogene codon 12, was dose-related and significantly greater ($p<0.05$) than the tricaprylin control for B[b]F doses $\geq$50 mg/kg. B[b]F formed DNA adducts *in vitro* in rat hepatocytes and the tumor cell line NCI-H322 derived from human lung, but not in V79NH cells (<0.05 adducts/10^8 nucleotides), a subclone of the Chinese hamster lung derived cell line V79 (Topinka et al., 1998). B[b]F-DNA adducts also occurred *in vivo* in the lungs of mice (Nesnow et al., 1995, 1998b; Ross et al., 1995) and in the lungs, livers, and peripheral blood lymphocytes of rats (Ross et al., 1992) given B[b]F by intraperitoneal injection. Sister chromatid exchanges from whole blood cultures from rats administered B[b]F (100 mg/kg by i.p. injection) were significantly increased relative to controls (Ross et al., 1992). Dermally applied B[b]F initiated dose-related tumor activity with TPA promotion in mouse skin (Weyland et al., 1990, 1993). B[b]F induced a dose-unrelated transformation from anchorage-dependent to independent growth *in vitro* in hamster (M3E3/C3) and rat (WRBK3) lung cells (Knebel et al., 1994). B[b]F suspended in corn oil, administered to male C57BL/6J mice as a single oral gavage at 0.1, 1.0, 10 or 100 mg/kg, suppressed the antibody response to sheep erythrocyte immunization in a dose-related manner; at the highest dose, suppression was approximately 84% of control response (Silkworth et al., 1995).

FEASIBILITY OF DERIVING A PROVISIONAL ORAL SLOPE FACTOR FOR BENZO[b]FLUORANTHENE

A provisional oral slope factor for B[b]F cannot be derived because human and animal oral cancer data are lacking.

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