1-31-2002

Provisional Peer Reviewed Toxicity Values for

Indeno[1,2,3-cd)pyrene
(CASRN 193-39-5)

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 INDENO(1,2,3-cd)PYRENE (CASRN 193-39-5) 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 indeno(1,2,3-cd)pyrene (IP) 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 1984 HEA for Polycyclic Aromatic Hydrocarbons (PAHs) did not derive an RfD for IP because the chemical was designated a probable human carcinogen, and noncancer toxicity values were not derived for carcinogens at that time (U.S. EPA, 1984). A Drinking Water Criteria Document for Polycyclic Aromatic Hydrocarbons (PAHs) (U.S. EPA, 1990) declined to derive an RfD for IP due to lack of suitable data. No other pertinent EPA documents were located in the CARA list (U.S. EPA, 1991, 1994). The ATSDR Toxicological Profile for PAHs (ATSDR, 1995) declined to derive oral MRLs for IP due to lack of suitable data. Other review documents used were IARC (1973, 1983, 1987) and WHO (1997). The NTP (2001) management status report was checked for relevant studies. Literature searches of the following databases were conducted from 1989 to December 2000 for relevant studies: TOXLINE,

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

REVIEW OF THE PERTINENT LITERATURE

Human Studies

The available reviews (ATSDR, 1995; IARC, 1983, 1987; U.S. EPA, 1984, 1990) reported no data regarding the toxicity of IP to humans following oral exposure. No relevant data were found in the literature search.

Animal Studies

No oral animal studies of IP suitable for derivation of an RfD were located in either the literature search or available reviews (ATSDR, 1995; IARC, 1983, 1987; U.S. EPA, 1984, 1990).

FEASIBILITY OF DERIVING A PROVISIONAL RfD FOR INDENO(1,2,3-cd)PYRENE

A provisional RfD for IP cannot be derived because of the lack of human and animal oral data.

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INTRODUCTION

A carcinogenicity assessment for indeno(1,2,3-cd)pyrene (IP) 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 (PAHs) (U.S. EPA, 1990). IP was assigned to weight-of-evidence Group B2, probable human carcinogen, based on increased incidences of epidermoid carcinomas 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) and skin tumors in dermal application studies in mice (Hoffman and Wynder, 1966; Rice et al., 1985a, 1986). Supporting data from genotoxicity tests included positive results for mutations in bacteria (LaVoie et al., 1979; Hermann et al., 1980; Rice et al., 1985b) and human lymphocytes (Durant et al., 1996). It was noted that IP is a component of mixtures that are known to produce cancer in humans, although there are no human data that specifically link IP with human cancers.

However, due to the lack of adequate oral data for IP, an oral slope factor was not included on IRIS (U.S. EPA, 2001).

U.S. EPA (1990) explored the use of a relative potency factor approach to derive slope factors for IP 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 IP, 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 IP were found in the CARA database (U.S. EPA, 1991, 1994b).

The International Agency for Research on Cancer (IARC, 1973, 1983, 1987) evaluated IP for carcinogenicity and placed the chemical in Group 2B (possible human carcinogen), finding that there is sufficient evidence that IP is carcinogenic to experimental animals and that the chemical was mutagenic to *Salmonella typhimurium* in the presence of an exogenous metabolic system. CalEPA derived an oral slope factor for IP, but it is based on a relative potency factor approach (CalEPA, 1999). ACGIH (2000) has not assessed the carcinogenicity of IP. WHO (1997), the ATSDR (1995) Toxicological Profile for Polycyclic Aromatic Hydrocarbons (PAHs) and the NTP (2001) management status report were searched for relevant information. Literature searches of the following databases were conducted from 1989 to December 2000 for relevant studies: TOXLINE, MEDLINE, TSCATS, GENETOX, HSDB, CANCERLIT, CCRIS, EMIC/EMICBACK, DART/ETICBACK, and RTECS.

REVIEW OF THE PERTINENT LITERATURE

Human Studies

Available reviews reported no human data regarding the carcinogenic potential of IP by oral exposure (ATSDR, 1995; IARC, 1983, 1987; U.S. EPA, 1984b, 1990). No relevant data were located in the literature search.

Animal Studies

No oral animal studies of IP suitable for derivation of an oral slope factor were located in either the literature search or available reviews (ATSDR, 1995; IARC, 1983, 1987; U.S. EPA, 1984b, 1990).

Other Studies

A dose-related statistically significant increase in incidence of epidermoid carcinomas in the lung and thorax occurred in rats receiving lifetime lung implants of IP (Deutsch-Wenzel et al., 1983). Mice receiving intraperitoneal injections (580 µg/mouse) of IP did not exhibit a significant tumor incidence (LaVoie et al., 1987). Lacassagne et al. (1963) reported 10 of 14 (71%) male mice and 1 of 14 (7%) female mice developed sarcomas following subcutaneous injection of 0.6 mg of IP. Hoffman and Wynder (1966) reported that skin painting of mice with IP at concentrations of 0.5 and 0.1% resulted in skin carcinomas in 5 of 20 (25%), and 3 of 20 (15%) animals, respectively, after 12 months of exposure. Similar treatment with IP at concentrations of 0.05% and 0.01% produced no skin tumors in mice. Chronic topical application of up to 9.2 µg of IP in acetone to the backs of mice for a lifetime resulted in no tumor induction (Habs et al., 1980). Positive results for DNA adduct formation (Rice et al., 1990) and tumor initiation with TPA promotion (Rice et al., 1985a, 1986, 1990) were obtained with IP. Genotoxicity studies indicate positive results for mutations in bacteria (only in the presence of metabolic activation) (LaVoie et al., 1979; Hermann et al., 1980; Rice et al., 1985b) and human B-lymphoblastoid cells (Durant et al., 1996).

FEASIBILITY OF DERIVING A PROVISIONAL ORAL SLOPE FACTOR FOR INDENO(1,2,3-cd)PYRENE

A provisional oral slope factor for IP cannot be derived because human and animal oral cancer data are lacking.

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