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Provisional Peer Reviewed Toxicity Values for Carbazole

(CASRN 86-74-8)

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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 CARBAZOLE (CASRN 86-74-8)

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. 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

No RfD, RfC, or carcinogenicity assessment for carbazole is available on IRIS (U.S. EPA, 2008). Carbazole is not included in the Drinking Water Standards and Health Advisories list (U.S. EPA, 2006). The HEAST (U.S. EPA, 1997) does not include an RfD or RfC for carbazole, but it does list carbazole as a B2 carcinogen with an oral slope factor (OSF) of 2E-02 $(mg/kg/day)^{-1}$. This OSF was derived in a Health and Environmental Effects Profile (HEEP) for carbazole (U.S. EPA, 1986) on the basis of an increased incidence of hepatocellular carcinomas and neoplastic nodules in mice chronically exposed to carbazole through diet (Tsuda et al., 1982). IARC (1983, 1999), however, considers the study by Tsuda et al. (1982) to provide "limited evidence" of carcinogenicity in animals but assigned an overall classification of Group 3, "not classifiable," for the carcinogenicity of carbazole to humans. IARC uses the classification of *limited evidence of carcinogenicity* when there is credible evidence of a positive association between exposure to the chemical and cancer, but the occurrence of chance, bias, or confounding influences cannot be ruled out with reasonable confidence, as is the case with carbazole. The carcinogenicity of carbazole has not been assessed by NTP (2005, 2008). Additionally, Cal EPA (2008a, 2008b, 2008c) has not derived a REL or cancer potency factor for carbazole.

The CARA list (U.S. EPA, 1991, 1994) includes no relevant documents besides the previously mentioned HEEP (U.S. EPA, 1986). ATSDR (2008) has not published a Toxicological Profile for carbazole and did not include it in the profile for polycyclic aromatic hydrocarbons (PAH) (ATSDR, 1995). In the Toxicological Profile for creosote (ATSDR, 2002), carbazole is mentioned as a constituent of a blended creosote oil that tested positively for dermal carcinogenicity, but it is not mentioned in the context of oral toxicity. The World Health Organization (WHO) (2008) has not published an Environmental Health Criteria document for carbazole, and there is no discussion of carbazole toxicity in the WHO (1998) PAH document.

OSHA (2008), NIOSH (2008), and ACGIH (2007) have not established occupational exposure limits for carbazole.

Carbazole, and several of its derivatives, are polycyclic aromatic hydrocarbons (PAHs) derived from fossil fuels and their incomplete combustion. The chemical shows inconsistent toxicity data. It is negative in the Ames test, with or without activation; negative in short term carcinogenicity tests in rats, negative in cultured hepatocytes (Weyland et al., 1993), and negative in the CHO cell assay. However, it is positive in chromosome aberration test in Swiss mice (Jha et al 2002), and in Syrian Hamster sperm. In two long-term studies in the same lab (Hagiwara, et al 1979 and Tsuda et al 1982), significant increases in liver cancers were found in mice exposed to carbazole in the diet that were somewhat dose dependent. An additional study in Syrian Hamsters found it carcinogenic in that system (Moore et al, 1987). Unlike the well known dibenzo and other derivatives, carbazole itself is negative in the Ames test, though the chemical does intercalate in DNA. There is evidence for aromatic hydrocarbon receptor (AhR) binding and P4501A1 induction in several systems, as well as peroxysome proliferation through the PPAR. The interaction with AhR however, may be noncompetitive, as there is some antagonism with better ligands like benzopyrene.

Literature searches were conducted from the 1960s through December 2007 for studies relevant to the derivation of provisional toxicity values for carbazole. Databases searched include MEDLINE, TOXLINE (Special), BIOSIS (from August 2000), TSCATS 1/TSCATS 2, CCRIS, DART/ETIC, GENETOX, HSDB, RTECS, and Current Contents (July through December 2007).

FEASIBILITY OF DERIVING A PROVISIONAL RfD FOR CARBAZOLE

The data are inadequate to derive a p-RfD for carbazole. No dose-response information pertinent to any target organs is available in the current database; thus, the database lacks a study that could serve as a suitable basis for the derivation of a p-RfD for carbazole.

FEASIBILITY OF DERIVING A PROVISIONAL RfC FOR CARBAZOLE

No inhalation toxicity data in humans or animals is identified; thus, no p-RfC could be derived for carbazole.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR CARBAZOLE

Because of the lack of carcinogenic data in humans or animals, under the 2005 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), this PPRTV document classifies carbazole as having "*Inadequate Information to Assess Carcinogenic Potential*."

FEASIBILITY OF DERIVING A PROVISIONAL ORAL SLOPE FACTOR OR INHALATION UNIT RISK FOR CARBAZOLE

Neither a p-OSF nor a p-IUR could be derived for carbazole because of the lack of suitable oral or inhalation data in both humans and animals.

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