FINAL
12-12-2012

Provisional Peer-Reviewed Toxicity Values for

Cyanogen Bromide
(CASRN 506-68-3)

Superfund Health Risk Technical Support Center
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This document was externally peer reviewed under contract to
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COMMONLY USED ABBREVIATIONS

BMC	benchmark concentration
BMCL	benchmark concentration lower bound 95% confidence interval
BMD	benchmark dose
BMDL	benchmark dose lower bound 95% confidence interval
HEC	human equivalent concentration
HED	human equivalent dose
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
POD	point of departure
p-OSF	provisional oral slope factor
p-RfC	provisional reference concentration (inhalation)
p-RfD	provisional reference dose (oral)
RfC	reference concentration (inhalation)
RfD	reference dose (oral)
UF	uncertainty factor
UF_A	animal-to-human uncertainty factor
UF_C	composite uncertainty factor
UF_D	incomplete-to-complete database uncertainty factor
UF_H	interhuman uncertainty factor
UF_L	LOAEL-to-NOAEL uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
WOE	weight of evidence

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR CYANOGEN BROMIDE (CASRN 506-68-3)

BACKGROUND

A Provisional Peer-Reviewed Toxicity Value (PPRTV) is defined as a toxicity value derived for use in the Superfund Program. PPRTVs are derived after a review of the relevant scientific literature using established Agency guidance on human health toxicity value derivations. All PPRTV assessments receive internal review by a standing panel of National Center for Environment Assessment (NCEA) scientists and an independent external peer review by three scientific experts.

The purpose of this document is to provide support for the hazard and dose-response assessment pertaining to chronic and subchronic exposures to substances of concern, to present the major conclusions reached in the hazard identification and derivation of the PPRTVs, and to characterize the overall confidence in these conclusions and toxicity values. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of this substance.

The PPRTV review process provides needed toxicity values in a quick turnaround timeframe while maintaining scientific quality. PPRTV assessments are updated approximately on a 5-year cycle for new data or methodologies that might impact the toxicity values or characterization of potential for adverse human health effects and are revised as appropriate. It is important to utilize the PPRTV database (http://hhpprtv.ornl.gov) to obtain the current information available. When a final Integrated Risk Information System (IRIS) assessment is made publicly available on the Internet (http://www.epa.gov/iris), the respective PPRTVs are removed from the database.

DISCLAIMERS

The PPRTV document provides toxicity values and information about the adverse effects of the chemical and the evidence on which the value is based, including the strengths and limitations of the data. All users are advised to review the information provided in this document to ensure that the PPRTV used is appropriate for the types of exposures and circumstances at the site in question and the risk management decision that would be supported by the risk assessment.

Other U.S. Environmental Protection Agency (EPA) programs or external parties who may choose to use PPRTVs are advised that Superfund resources will not generally be used to respond to challenges, if any, of PPRTVs used in a context outside of the Superfund program.

QUESTIONS REGARDING PPRTVs

Questions regarding the contents and appropriate use of this PPRTV assessment should 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).

INTRODUCTION

Cyanogen bromide, CAS Number 506-68-3, is an inorganic cyanide compound with a pungent odor and occurs as colorless or white crystals at room temperature (see Figure 1). CNBr has applications in industry and in the laboratory, acting as potential sources for exposure. In industry, it has been used in gold extraction, organic synthesis, cellulose technology, textile treatment, and as a fumigant and pesticide/parasiticide. In the laboratory, it has been used to immobilize proteins for chromatography, for protein structure analysis, and as a reagent in the Niacin production test for identifying strains of *Mycobacterium tuberculosis*. CNBr decomposes upon heating or contact with acids, producing toxic HCN gas and corrosive hydrogen bromide (International Labour Organization, 2000). It reacts slowly with water and moisture to produce hydrogen bromide and HCN. Consistent with the pKa for HCN listed below, HCN exists primarily in its nondissociated form at pH values less than 7, and the concentration of CN^- increases as pH increases above 7. A table of physicochemical properties for CNBr is provided below (see Table 1).

Figure 1. Cyanogen Bromide Structure

Table 1. Physicochemical Properties of Cyanogen Bromide (CASRN 506-68-3)

Property (unit)	Value
Boiling point (ºC)	61.5[a]
Melting point (ºC)	52[a,b]
Density (g/cm^3)	2.0[b]
Vapor pressure (at 25ºC)	16.2 kPa[b], 122 mm Hg[a]
pKa (at 25ºC)	HCN, 9.22[b]
Solubility in water (g/100 mL at 25ºC)	10.8[a]
Relative vapor density (air = 1)	3.6[b]
Molecular weight (g/mol)	105.9[a,b]

[a]ChemIDPlus (2011).
[b]International Labour Organization (2000).

Although no Reference Concentration (RfC) or cancer assessment for CNBr are included on U.S. EPA IRIS, a Reference Dose (RfD) value of 9×10^{-2} mg/kg-day, based on HCN toxicity, is provided (U.S. EPA, 2010). This online IRIS document state that a subsequently conducted comprehensive review of toxicological studies published prior to 2004 found no new relevant data for CNBr. A more recent revision of the IRIS summary for HCN and cyanide salts (i.e., U.S. EPA, 2010) includes chronic RfD and RfC values for HCN of 6×10^{-4} mg/kg-day and 8×10^{-4} mg/m^3, respectively. The justification for using HCN to derive values for CNBr is stated as follows (U.S. EPA, 1988):

> *Despite the lack of studies that evaluate the toxicity of chronic oral exposure to cyanogen bromide specifically, the available data indicate that cyanogen bromide is soluble in water and dilute acid, that full dissociation would result in a maximum of one mole equivalent of cyanide and that of the three possible breakdown products of cyanogen bromide (cyanide, bromide and cyanogen bromide), cyanide is probably the most toxic to mammals. Therefore, until specific data on cyanogen bromide become available, the RfD for cyanogen bromide is derived by analogy to cyanide.*

However, current risk assessment practices for using information on analogy and uncertainty in mode of action do not provide sufficient scientific support for the approach used in the IRIS assessment for CNBr (U.S. EPA, 1988) to derive a subchronic p-RfD or provisional inhalation toxicity values.

A summary of available toxicity values for cyanogen bromide from U.S. EPA and other agencies/organizations is provided in Table 2.

Table 2. Summary of Available Toxicity Values for Cyanogen Bromide (CASRN 506-68-3)

Source/Parameter[a]	Value (Applicability)	Notes	Reference	Date Accessed
Cancer				
IRIS	NV	"Inadequate Information to Assess Carcinogenic Potential"	U.S. EPA, 2010	1-18-2011
HEAST	NV	NA	U.S. EPA, 2011b	1-18-2011
IARC	NV	NA	IARC, 2010	1-18-2011
NTP	NV	NA	NTP, 2011	1-18-2011
CalEPA	NV	NA	CalEPA, 2008	1-18-2011
Drinking Water Standards and Health Advisories	Cancer designation "D"	"Not Classifiable as to Human Carcinogenity"	U.S. EPA, 2011a	5-5-2011
Drinking Water Criteria	Cancer designation "D"	"Not Classifiable as to Human Carcinogenity"	U.S. EPA, 1992	5-5-2011
Noncancer				
ACGIH	TLV-TWA: 5 mg/m^3 (4.7 ppm) TLV-TWA: 0.6 mg/m^3 (0.3 ppm)	DEL (Cyanides) EL (Cyanogen chloride)	ACGIH, 2008	1-18-2011
ATSDR	NV	NA	ATSDR, 2011	1-18-2011
CalEPA	PHG: 0.15 mg/L MCL: 0.2 mg/L	(Cyanide) (Cyanide)	CalEPA, 2009	1-18-2011
NIOSH	REL-TWA: 5 mg/m^3 (4.7 ppm) REL-TWA: 0.6 mg/m^3 (0.3 ppm)	DEL 10-minute ceiling (cyanides) EL (Cyanogen chloride)	NIOSH, 2010	1-18-2011
OSHA	PEL-TWA: 5 mg/m^3 (4.7 ppm)	DEL: 8-hour TWA (cyanides)	OSHA, 2004	1-18-2011
IRIS	RfD: 9×10^{-2} mg/kg-day	(Hydrogen cyanide)	U.S. EPA, 2010	1-18-2011
Drinking Water Standards and Health Advisories	0.05 mg/L RfD: 0.05 mg/kg-day DWEL: 2 mg/L	1- and 10-day exposure limits (cyanogen chloride) (Cyanogen chloride) Value for a 10-kg child (cyanogen chloride)	U.S. EPA, 2011a	5-5-2011

Table 2. Summary of Available Toxicity Values for Cyanogen Bromide (CASRN 506-68-3)

Source/Parameter[a]	Value (Applicability)	Notes	Reference	Date Accessed
Drinking Water Criteria	0.2 mg/L DWEL: 0.7 mg/L	1- and 10-day exposure limits for a 10-kg child (Cyanide)	U.S. EPA, 1992	5-5-2011
DOE Protective Action Criteria (PAC)	TEEL-0: 20.4 mg/m^3	Threshold concentration below which most people will experience no adverse health effects	ChemIDPlus, 2011	
HEAST	RfD: 9×10^{-2} mg/kg-day	(Hydrogen cyanide)	U.S. EPA, 2011b	1-18-2011
CARA HEEP	NV	NA	U.S. EPA, 1994	1-18-2011
WHO	NV	NA	WHO, 2011	1-18-2011

[a]Sources: Integrated Risk Information System (IRIS) database; Health Effects Assessment Summary Tables (HEAST); International Agency for Research on Cancer (IARC); National Toxicology Program (NTP); California Environmental Protection Agency (CalEPA); American Conference of Governmental Industrial Hygienists (ACGIH); Agency for Toxic Substances and Disease Registry (ATSDR); National Institute for Occupational Safety and Health (NIOSH); Occupational Safety and Health Administration (OSHA); Department of Energy (DOE); Chemical Assessments and Related Activities (CARA) list; Health and Environmental Effects Profile (HEEP); World Health Organization (WHO).

IDLH= immediately dangerous to life or health; NA = not applicable; NV = not available; PEL-TWA = permissible exposure level-time weighted average; REL-TWA = recommended exposure level-time weighted average; TLV-TWA = threshold limit value-time weighted average; PHG = Public Health Goal; MCL = Maximum Contaminant Level; DWEL = lifetime drinking water equivalent level; DEL = dermal exposure limits; EL = exposure limit; PAC = Protective Action Criteria; TEEL-0 = Temporary Emergency Exposure Limit value (no effects).

Literature searches were conducted on sources published from 1900 through September 2012, for studies relevant to the derivation of provisional toxicity values for CNBr, CAS Number 506-68-3. Searches were conducted using U.S. EPA's Health and Environmental Research Online (HERO) database of scientific literature. HERO searches the following databases: AGRICOLA; American Chemical Society; BioOne; Cochrane Library; DOE: Energy Information Administration, Information Bridge, and Energy Citations Database; EBSCO: Academic Search Complete; GeoRef Preview; GPO: Government Printing Office; Informaworld; IngentaConnect; J-STAGE: Japan Science & Technology; JSTOR: Mathematics & Statistics and Life Sciences; NSCEP/NEPIS (EPA publications available through the National Service Center for Environmental Publications [NSCEP] and National Environmental Publications Internet Site [NEPIS] database); PubMed: MEDLINE and CANCERLIT databases; SAGE; Science Direct; Scirus; Scitopia; SpringerLink; TOXNET (Toxicology Data Network): ANEUPL, CCRIS, ChemIDplus, CIS, CRISP, DART, EMIC, EPIDEM, ETICBACK, FEDRIP, GENE-TOX, HAPAB, HEEP, HMTC, HSDB, IRIS, ITER, LactMed, Multi-Database Search, NIOSH, NTIS, PESTAB, PPBIB, RISKLINE, TRI, and TSCATS; Virtual Health Library; Web of Science (searches Current Content database among others);WHO; and Worldwide Science. The following databases outside of HERO were searched for relevant health information: ACGIH, ATSDR, CalEPA, U.S. EPA IRIS, U.S. EPA HEAST, U.S. EPA HEEP, U.S. EPA OW, U.S. EPA TSCATS/TSCATS2, NIOSH, NTP, OSHA, and RTECS.

REVIEW OF POTENTIALLY RELEVANT DATA (CANCER AND NONCANCER)

CNBr can enter the bloodstream via oral, inhalation, or dermal absorption and then be broken down into bromide and cyanide (Luttrell, 2009). CNBr possesses some of the same properties as HCN and its soluble salts regarding effects on the central nervous system (CNS), although CNBr is also a highly irritating vesicant gas, producing severe lacrimatory effects and pulmonary irritation and edema (Hartung, 1982). However, other than data from acute exposures (see Table 3), no studies investigating the toxicity of CNBr were located. In the absence of any directly relevant data, and based on the argument presented above, data from studies on HCN and cyanide salts are not considered for the derivation of reference values for CNBr.

Table 3 provides an overview of the relevant database for CNBr.

Table 3. Summary of Potentially Relevant Data for Cyanogen Bromide (CASRN 506-68-3)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry	Critical Effects	NOAEL	BMDL/ BMCL	LOAEL	Reference[a] (Comments)	Notes[b]
Human								
1. Oral (mg/kg-d)								
Acute[c]	ND							
Short-term[d]	ND							
Long-term[e]	ND							
Chronic[f]	ND							
2. Inhalation (mg/m^3)								
Acute[c]	Numbers and sex unspecified	6, 35, 85,400	400, fatal after 10 min; 85, intolerable after 1 min; 35, intolerable after 10 min; 6, lowest irritant concentration after 10 min	NA	NA	NA	Hartung (1982) as cited in IRIS (2010)	NA
Short-term[d]	ND							

[a]Unless otherwise stated, study summaries are available in *Toxicological Review of HCN and Cyanide Salts in Support of IRIS* (U.S. EPA, 2010).
[b]Notes: IRIS = Utilized by IRIS, date of last update; PS = principal study, PR = peer reviewed, NPR = not peer reviewed. The form of CN^- used for dosing is reported.
[c]Acute = Exposure for 24 hr or less (U.S. EPA, 2002).
[d]Short-term = Repeated exposure for >24 h ≤30 d (U.S. EPA, 2002).
[e]Long-term = Repeated exposure for >30 d ≤10% lifespan (based on 70 yr typical lifespan) (U.S. EPA, 2002).
[f]Chronic = Repeated exposure for ≥10% lifespan (U.S. EPA, 2002).

DU = data unsuitable; NA = not applicable; NV = not available; ND = No data; NDr = Not determinable; NI = not identified; NP = not provided; NR = not reported; NR/Dr = not reported but determined from data; NS = not selected.

HUMAN STUDIES

Oral Exposures

No studies were identified.

Inhalation Exposures

Aside from acute exposures (Hartung, 1982), no studies examining the effects of inhalation exposure to CNBr in humans were located.

Acute Studies

Hartung (1982)

In a book chapter by Hartung (1982) cited by IRIS (U.S. EPA, 1988), human responses to inhalation of CNBr were described as follows: "0.4 mg/L, fatal after 10 minutes; 0.085 mg/L, intolerable concentration, 1-minute exposure; 0.035 mg/L, intolerable concentration, 10-minute exposure; 0.006 mg/L, lowest irritant concentration, 10-minute exposure." No further information was provided.

Short-Term Studies

No studies were identified.

Long-Term Studies

No studies were identified.

ANIMAL STUDIES

Oral Exposures

Acute Studies

In acute oral toxicity studies using CNBr, 20 rats and 24 mice (sex and strain not specified) were dosed with CNBr at 1−100 mg/kg bw for rats and 0.5−100 mg/kg bw for mice (Eastman Kodak Co., 1992). Toxic symptoms included weakness, rapid prostration, squirming, ataxia, tremors, convulsions, and rough coat. Mortality data were not provided; however, the study report included an LD_{50} value between 25−50 mg/kg bw CNBr (approximately 6−12 mg/kg bw CN^-) for both species. This LD_{50} range for CNBr, in CN^- equivalents (6−12 mg/kg bw), is similar to the LD_{50} range for CN^- (3−8 mg/kg bw) reported in U.S. EPA (2010).

Subchronic-Duration Studies

IRIS (U.S. EPA, 2010) has provided a chronic RfD based on analogy to HCN toxicity data. However, lack of data pertinent to the mode of action of CNBr and available information on CNBr raise several uncertainties using the approach previously considered by the IRIS (1988) to derive a subchronic p-RfD.

Inhalation Exposure

Acute Studies

In an acute inhalation toxicity study, Dow Chemical Company (1992, as cited in U.S. EPA, 2010) exposed S-D rats (8−10 per sex per group) via whole body inhalation to CNBr at 10, 35, 45, 56, or 65 ppm for 6 hours or at 112 ppm for 2.5 hours. Chamber concentrations of CNBr were verified by gas chromatography. Rats were observed prior to and during exposure, and for up to 2 weeks after exposure. Two rats per sex from the 10-, 35-, 45-, and 56-ppm groups were sacrificed for gross pathologic examination 24 hours after exposure. Gross

pathological examinations were also performed on any rats that died and all rats remaining alive at the end of the 2-week observation period. No mortality was observed in the 10- and 35-ppm groups following the 6-hour exposure; however, substantial mortality was observed at 45 ppm (8/8 M, 2/8 F), 56 ppm (5/8 M, 2/8 F), 65 ppm (8/10 M, 10/10 F), and 112 ppm (10/10 M, 10/10 F). Transient nasal irritation was observed at 35 ppm, and moderate-to-severe respiratory tract irritation was observed at ≥45 ppm, with rats gasping for breath during and after exposure, and "severe weight loss with a slow recovery." Necropsy revealed severe respiratory tract irritation, congested lungs and liver, and distended stomachs due to mouth breathing. The LC_{50} was reported to be 39.3 ppm (170.3 mg/m^3) for males and 52.7 ppm (228.3 mg/m^3) for females (equivalent to 43.4 and 58.3 mg/m^3 HCN, respectively). The LC_{50} for CNBr in HCN equivalents is similar in magnitude to the range of LC_{50} values for HCN (151−579 mg/m^3) reported in U.S. EPA (2010).

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

No studies were identified with regard to the genotoxicity of CNBr.

DERIVATION OF PROVISIONAL VALUES

DERIVATION OF ORAL REFERENCE DOSES

Because CNBr dissociates to cyanide, IRIS (U.S EPA, 1988) used cyanide data for derivation of an RfD for CNBr by analogy to HCN. Thyroid toxicity was the critical effect used for developing the RfD, with a POD of 12.5 mg/kg-day. However, further evaluation of data presented in the revised assessment for HCN, IRIS (U.S. EPA, 2010) presented a much lower POD (BMDL = 1.9 mg/kg-day) based on reproductive effects reported in the same NTP (1993a,b) study. Associated reproductive effects at this POD (BMDL = 1.9 mg/kg-day), were not evaluated in the earlier IRIS assessment. Furthermore, human male fertility is established to be at doses lower than the rodent test species, suggesting that effects on human fertility may be more susceptible than rodents following exposure to toxic substances (Working, 1988). Additionally, available data discussed earlier indicated major differences in acute toxicity of cyanides and CNBr, as well as dermal and respiratory effects produced by CNBr resulting from direct interaction with proteins and slow dissociation of cyanogen bromide in water, raising debate as to how quickly dissociation may take place in vivo. Furthermore, given the absence of pharmacokinetic information on CNBr, the issues surrounding the linkage between CNBr and simple cyanides introduces incertitude in the prudence of deriving a subchronic p-RfD.

Because of the aforementioned uncertainties and unavailability of toxicity data specifically for CNBr, derivation of a subchronic p-RfD value is precluded at present.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

Derivation of Subchronic and Chronic Provisional RfC

IRIS (U.S. EPA, 2010) recommended that the RfC for HCN should not be used to estimate an RfC for cyanide salts due to considerations of inhalation uncertainties. Specifically, exposure to HCN occurs as a gas, whereas the extremely high boiling points and vapor pressure of cyanide salts (e.g., CNBr) predict inhalation exposure as aerosols. Thus, lack of data on inhalation exposure to CNBr precludes the derivation of provisional inhalation toxicity values.

CANCER WOE DESCRIPTOR

Limitations in the available data preclude development of a WOE descriptor.

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

No long-term studies were found examining the effects of CNBr via oral or inhalation exposure in humans or rats.

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