

Provisional Peer Reviewed Toxicity Values for
Prussian Blue (Ferric Ferrocyanide)
(CASRN 14038-43-8)

Derivation of Subchronic and Chronic Inhalation RfCs

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

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-RfD - provisional Oral Reference Dose
p-RfC - provisional Inhalation Reference Concentration
p-OSF - provisional Oral Slope Factor
p-IUR - provisional Inhalation Unit Risk
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
RGDR - Regional deposited dose ratio (for the indicated lung region)
REL - relative exposure level
RGDR - Regional gas dose ratio (for the indicated lung region)
RfD - Oral Reference Dose
RfC - Inhalation Reference Concentration
s.c. - subcutaneous
SCE - sister chromatid exchange
SDWA - Safe Drinking Water Act
sq.cm. - square centimeters
TSCA - Toxic Substances Control Act
UF - uncertainty factor
ug - microgram
umol - micromoles
VOC - volatile organic compound

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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 science and available information evolve, PPRTVs are initially derived with a three-year life-cycle. However, EPA Regions or the EPA Headquarters Superfund Program sometimes request that a frequently used PPRTV be reassessed. 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

A subchronic or chronic RfC for Prussian Blue is not available on IRIS (U.S. EPA, 2003) or in the HEAST (U.S. EPA, 1997). No relevant documents were located in the CARA list (U.S. EPA, 1991, 1994). ACGIH (2002), NIOSH (2002) and OSHA (2002) have not recommended occupational exposure limits for Prussian Blue. Neither ATSDR (2002), NTP (2002), IARC (2002), nor WHO (2002) have produced documents regarding Prussian Blue. Literature searches of the following databases were conducted from 1965 through December 2002 in order to locate relevant studies: TOXLINE, CANCERLIT, MEDLINE, CCRIS, GENETOX, HSDB, DART/ETICBACK, EMIC/EMICBACK, RTECS and TSCATS. A recent review by Pearce (1994) was also consulted. Additional literature searches from January 2003 through May 2004 were conducted by NCEA-Cincinnati using MEDLINE, TOXLINE, Chemical and Biological Abstracts databases.

REVIEW OF PERTINENT DATA

Human Studies

No data regarding the toxicity of Prussian Blue to humans following chronic or subchronic inhalation exposure were located.

Animal Studies

No data regarding the toxicity of Prussian Blue to animals following chronic or subchronic inhalation exposure were located.

FEASIBILITY OF DERIVING PROVISIONAL SUBCHRONIC AND CHRONIC RfCs FOR PRUSSIAN BLUE

The lack of chronic or subchronic inhalation data for humans or animals precludes derivation of a subchronic or chronic p-RfC for Prussian Blue.

REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 2002. 2002 Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices. Cincinnati, OH.

ATSDR (Agency for Toxic Substances and Disease Registry). 2002. Toxicological Profile Information Sheet. Online. <http://www.atsdr.cdc.gov/toxpro2.html>

IARC (International Agency for Research on Cancer). 2002. IARC Agents and Summary Evaluations. Online. http://193.51.164.11/cgi/iHound/Chem/iH_Chem_Frames.html

NIOSH (National Institute for Occupational Safety and Health). 2002. NIOSH Pocket Guide to Chemical Hazards. Online. <http://www.cdc.gov/niosh/npg/.html>

NTP (National Toxicology Program). 2002. Management Status Report. Online. <http://ntp-server.niehs.nih.gov/>

OSHA (Occupational Safety and Health Administration). 2002. OSHA Standard 1910.1000 TableZ-1. Part Z, Toxic and Hazardous Substances. Online. http://www.osha-slc.gov/OshStd_data/1910_1000_TABLE_Z-1.html

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U.S. EPA. 1991. Chemical Assessments and Related Activities (CARA). Office of Health and Environmental Assessment, Washington, DC. April.

U.S. EPA. 1994. Chemical Assessments and Related Activities (CARA). Office of Health and Environmental Assessment, Washington, DC. December.

U.S. EPA. 1997. Health Effects Assessment Summary Tables. FY-1997 Update. Prepared by the Office of Research and Development, National Center for Environmental Assessment, Cincinnati OH for the Office of Emergency and Remedial Response, Washington, DC. July. EPA/540/R-97/036. NTIS 97-921199.

U.S. EPA. 2003. Integrated Risk Information System (IRIS). Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Online. <http://www.epa.gov/iris/>

WHO (World Health Organization). 2002. Online Catalogs for the Environmental Criteria Series. Online. http://193.51.164.11/cgi/iHound/Chem/iH_Chem_Frames.html

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Derivation of a Carcinogenicity Assessment

Superfund Health Risk Technical Support Center
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INTRODUCTION

A carcinogenicity assessment of Prussian Blue is not available on IRIS (U.S. EPA, 2003), the HEAST (U.S. EPA, 1997), or the Drinking Water Standards and Health Advisories list (U.S. EPA, 2002). No relevant documents were located in the CARA list (U.S. EPA, 1991, 1994). Neither ATSDR (2002), NTP (2002), IARC (2002), nor WHO (2002) have produced documents regarding Prussian Blue. Literature searches of the following databases were conducted from 1965 through December 2002 in order to locate relevant studies: TOXLINE, CANCERLIT, MEDLINE, CCRIS, GENETOX, HSDB, DART/ETICBACK, EMIC/EMICBACK, RTECS and TSCATS. A recent review by Pearce (1994) was also consulted. Additional literature searches from January 2003 through May 2004 were conducted by NCEA-Cincinnati using MEDLINE, TOXLINE, Chemical and Biological Abstracts databases.

REVIEW OF PERTINENT DATA

Human Studies

No data regarding the possible carcinogenicity of Prussian Blue in humans were located.

Animal Studies

No reports of animal studies examining the carcinogenicity of Prussian Blue by any route of exposure were located.

Other Studies

Data regarding the genotoxicity of Prussian Blue are limited to bacterial assays. Iron Blue (CI77510), a ferric ferrocyanide print dye, did not induce an increase in revertant colony counts with or without an S-9 metabolic activation system in *Salmonella typhimurium* tester strains TA98, TA1535, or TA1538 exposed in reaction mixture of 0.01 mg Prussian Blue/ml DMSO (Milvy and Kay, 1978). Recombinant-repair-deficient assays were negative for ferric ferrocyanide compounds in *Bacillus subtilis* using the cold incubation procedure for increased sensitivity. Ferric ferrocyanide did not induce reverse mutations in *Escherichia coli* strains B/rWP2 *try* and WP2 *hcr try* (Kanematsu et al., 1980) and no mutagenic activity was detected when potassium ferrocyanide was tested in the *E. coli* strain PQ37 (Olivier and Marzin, 1987).

PROVISIONAL WEIGHT-OF-EVIDENCE CLASSIFICATION

There are no data on the carcinogenicity of Prussian Blue in humans or animals. Limited data in bacteria indicate that Prussian Blue is not mutagenic. Under the proposed U.S. EPA (1999) cancer guidelines, the available data are inadequate for an assessment of human carcinogenic potential.

QUANTITATIVE ESTIMATES OF CARCINOGENIC RISK

Derivation of quantitative estimates of cancer risk for Prussian Blue is precluded by the lack of data demonstrating carcinogenicity associated with Prussian Blue exposure.

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- ATSDR (Agency for Toxic Substances and Disease Registry). 2002. Toxicological Profile Information Sheet. Online. <http://www.atsdr.cdc.gov/toxpro2.html>
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