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Provisional Peer Reviewed Toxicity Values for

Prussian Blue (Ferric Ferrocyanide)
(CASRN 14038-43-8)

Derivation of Subchronic and Chronic Oral RfDs

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
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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
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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
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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

Prussian Blue, also known as Iron Blue or Berlin Blue, refers to the colored complexes of hexacyanoferrate compounds represented by the formula $Fe_4[Fe(CN)_6]_3$ or as a complex represented by the formula $M^*Fe[Fe(CN)_6]$ where M may be one of the following cations: Li, Na, K, Rb, Cs, or NH_4. Prussian Blue acts as an ion exchanger for univalent cations and its affinity increases with increasing ionic radius of the cation (e.g., alkali metals: Li, Na, K, Rb, Cs) (Stevens et al., 1974). The common forms of Prussian Blue include: the insoluble ferric ferrocyanide $Fe_4[Fe(CN)_6]_3$ used in the decorporation of internal radiocesium contamination, the soluble potassium ferric hexacyanoferrate(II) $KFe[Fe(CN)_6]$ used as a therapeutic antidote to thallium poisoning, or the soluble ammonium ferric cyanoferrate $NH_4Fe[Fe(CN)_6]$ used as a food additive in animal feed to prevent the transfer of dietary radiocesium to milk (Pearce, 1994).

Potassium ferrocyanide $K_4[Fe(CN)_6)]$ and Cu^-, Co^-, Ni^-, and Zn^- hexacyanoferrates are included in the group of Prussian Blue compounds as experimental therapeutic agent complexes.

A subchronic or chronic RfD for Prussian Blue is not available on IRIS (U.S. EPA, 2005), 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

Prussian Blue has been used as a therapeutic agent in patients with radiocesium or thallium poisoning. According to the National Council on Radiation and Protection (NCRP) (1980), Prussian Blue is not absorbed by the gastrointestinal tract, but after oral or intraduodenal treatment, is distributed in colloidal form over the intestinal lumen, where it acts as an ion exchange substance for some monovalent cations by binding the metal cation in a lattice, preventing reabsorption, and increasing fecal excretion of the metal.

Medical case studies of patients administered Prussian Blue as treatment for radiocesium or thallium poisoning have reported only minor gastrointestinal side effects. "Severe constipation associated with intestinal obstruction" was the only side effect reported in 2 male subjects, previously exposed to radiocesium, who received 3 g (43 mg/kg-day, assuming a reference human body weight of 70 kg) of Prussian Blue daily for 20 days (Madshus et al., 1966). No effect on potassium levels was found. Results were similar in another group of 6 male subjects that had been exposed to radiocesium and then treated with 1.5 or 3.0 g of Prussian Blue/day (21 or 43 mg/kg-day, assuming 70 kg body weight) for 22 days (Madshus and Strömme, 1968). Farina et al. (1991) treated 46 patients from a radiological accident in Goiania, Brazil with doses of 1 to 10 g/day (up to 143 mg/kg-day, assuming 70 kg body weight) of Prussian Blue for up to 3 weeks and monitored for side effects. Low serum potassium levels in 3 cases were attributed to acute radiation syndrome. Intestinal constipation in 10 patients (alleviated by consumption of high fiber diet or laxatives) was considered to be possibly associated with Prussian Blue treatment. At the 6 month follow-up examination, 11 patients

reported light to moderate epigastralgia (pain in the upper abdominal area) and one patient had developed a duodenal ulcer. However, it is not clear that these observations have any relation to Prussian Blue treatment. The researchers cited stress from the accident and intestinal parasites as other potential causes. (Almost all of the patients had intestinal parasites, for which they were treated during their hospitalization, but which they may have re-acquired upon return to their home environments.) No side effects were reported among 11 acute thallium poisoning victims treated with Prussian Blue at acute doses as high as 20 g (286 mg/kg, assuming 70 kg body weight) (Stevens et al., 1974), or among 9 thallium poisoning patients treated with 2 g of Prussian Blue 3 times per day (86 mg/kg-day, assuming 70 kg body weight) for 6 weeks (Pai, 1987). No side effects and no effect on potassium content of the body were found in 2 male subjects that had ingested radiocesium and were treated with 2.2 g/day (31 mg/kg-day, assuming 70 kg body weight) of nickel ferrocyanide for 9 days (Inuma et al., 1971).

Nielsen et al. (1990a) administered 500 mg soluble Prussian Blue in capsule form containing radiolabeled ^{59}Fe in either the ferrous or ferric positions and ^{14}C in the cyanide group to three male volunteers in 3 sequential trials at 14 day intervals. Urine and feces were collected for 7 days post ingestion of capsule and radioactivity monitored. Minimal amounts of [^{59}Fe] ferric (0.03%) or [^{59}Fe] ferrous (0.22%) iron were absorbed by the intestinal tract, as calculated from [^{59}Fe]-whole body retention and [^{59}Fe]-urine excretion. After the 7 day period, 0.15% of ^{59}ferrous iron was excreted as ferrocyanide; the ferrocyanide fraction in the urine was 0.42% of the total dosage administered in capsule form, as indicated by increased radioactivity counts. The assumed free cyanide (0.42 -0.15 = 0.27%) adjusted for dose and body weight shows an estimated value of 0.01 mg CN^-/kg body weight in a 70kg man that will be absorbed. Both species of radio-labeled iron were administered in the bound cyanide form and are expressed as percentage of the total radioactive dosage. The authors indicated that this estimated CN level is about 2 orders of magnitude lower than the lethal dose in humans of 0.5 to 3.5 mg CN^-/kg and compares to other anthropogenic exposure levels.

Animal Studies

A few studies have been performed to determine the efficacy of Prussian Blue therapy for radiocesium and thallium poisoning in animals. No side effects of Prussian Blue therapy were noted in studies of radiocesium-treated rats given Prussian Blue by gavage at 100 mg/day (286 mg/kg-day, assuming rat body weight of 0.35 kg) for 3-11 days (Nigrovic, 1963, 1965), thallium-treated rats given Prussian Blue by gavage at doses as high as 1000 mg/kg-day for 1-4 days (Kamerbeek et al., 1971; Heydlauf, 1969), radiocesium-exposed dogs given up to 160 mg/kg-day of Prussian Blue in drinking water for 6 weeks (Melo et al., 1996), or radiocesium-exposed cows fed a diet containing 3 g/day of Prussian Blue (Unsworth et al., 1989). Although no obvious side effects of Prussian Blue were reported in these studies, there was no systematic effort to monitor toxicological endpoints in any of them.

Studies that included some more detailed evaluation of toxic effects reported no impairment of growth and no toxic side effects in young rats fed a diet containing 1% ferric cyanoferrate (estimated dose = 500 mg/kg-day) for 120 days (Nigrovic et al., 1966). Further analysis of Nigrovic et al. (1966) indicated antidote effect of orally administered prussian blue on elimination of radioactive cesium as compared to intraperitoneal effect of prussian blue. Other studies reported no toxic effects in male Sprague-Dawley rats treated with up to 226 m/kg-day of ferric cyanoferrate in the drinking water for 60 days (Richmond and Bunde, 1966), no toxic effects in rats exposed to 2% ferric hexacyanoferrate (estimated dose = 2800 mg/kg-day) in the drinking water for 12 weeks (Dvorak et al., 1971), no effect on growth or histopathology of the major organs in weanling Wistar rats fed a diet containing 2% nickel ferrocyanide (estimated dose = 1000 mg/kg-day) for 152 days (Inuma et al., 1971), no effect on body weight or general well-being in 3-month old German Shepherd dogs administered up to 400 mg/kg-day of ferric cyanoferrate for 10 days (Madshus et al., 1966), no effect on body weight in lactating ewes exposed to 1% ferric ferrocyanide in the drinking water for 23 days (Ioannides et al., 1991), no adverse effects on behavior, food intake, body weight, or milk production in lactating ewes that received up to 2 g of ammonium ferric cyanoferrate/day in the diet for 90-100 days (Daburon et al., 1991), no effect on histopathology of the major organs in sheep given 5 g of ammonium ferric cyanoferrate/day for 15 days (Giese, 1988), and no effect on histopathology of the major organs or milk cyanide levels or milk or plasma thiocyanate levels in lactating cows given 20 g of ammonium ferric cyanoferrate/day for 15 days (Giese, 1988).

Two studies in which ferric cyanoferrate was administered to rats as part of a mixture, along with calcium alginate, potassium iodide, calcium-DTPA (diethylenetriamine pentaacetate), and/or Zn-DTPA, found minor effects consistent with the known action of other mixture components (slight decreases in hemoglobin, hematocrit, erythrocyte count, and liver iron content consistent with inhibition of iron absorption by alginate; very mild histopathological changes in kidney consistent with calcium-DTPA exposure), and, therefore, not attributed by the researchers to Prussian Blue (Kostial et al., 1981; Kargacin et al., 1985). An earlier study, summarized by Pearce (1994), reported decreased growth, reduced hemoglobin and hematocrit, enlarged kidney, and histological changes in the kidney in rats treated with 5000 or 50,000 ppm (5.0, 10.0 g/kg-day) of sodium ferrocyanide in the diet for 90 days, with no effects at 500 ppm (2.5 g/kg-day). However, methods and results were not reported in sufficient detail to evaluate the study.

A very low bioavailability of iron and cyanide from ferric hexacyanoferrates was demonstrated in rats administered a single or five sequential daily doses of radiolabeled [^{59}Fe] soluble or insoluble forms of Prussian Blue (Nielsen et al., 1990b). Oral administration of 10 mg of potassium ferric hexacyanoferrate or ferric hexacyanoferrate on 5 subsequent days resulted in 0.3-0.7% absorption and retention of ferric iron, as measured by [^{59}Fe]-whole body retention, or 0.06-0.18% absorption of ferrous iron, most of which (0.05-0.15%) was excreted via the kidneys for a body retention of 0.01-0.03% after 7-10 days. The researchers estimated that approximately

16-60 ug free cyanide/kg body weight in rats is absorbed from a single dose of hexacyanoferrate(II), which is well below the lethal dose of 4.3 mg CN^-/kg body weight in rats.

Other Studies

In vitro studies designed to investigate release of cyanide from Prussian Blue compounds under gastrointestinal conditions have found that little or no cyanide is released from these compounds under these conditions (Kamerbeek, 1971; Verzijl et al., 1993).

FEASIBILITY OF DERIVING PROVISIONAL SUBCHRONIC AND CHRONIC RfDs FOR PRUSSIAN BLUE

Prussian Blue has six cyanide radicals covalently bound to iron, thus primarily making it inert and insoluble in dilute mineral acids and polar and non-polar solvents. This compound is soluble in concentrated acid. Due to its lack of toxicity, Prussian Blue is found in cosmetics and used as a medical antidote to radioisotope and heavy metal poisoning (Pearce, 1994). The available data are not adequate for derivation of subchronic or chronic p-RfDs for Prussian Blue. Human case studies examined the therapeutic effects of Prussian Blue in humans poisoned with ^{137}Cs or thallium, but were not designed to assess the toxicological effects of Prussian Blue. Individually, these case studies reported either no effects or minor gastrointestinal effects that were not clearly related to Prussian Blue treatment. There was no systematic evaluation of Prussian Blue toxicity in any of them. The available animal studies are also inadequate to serve as the basis for a p-RfD. Most studies found no effects, but looked at very few endpoints. Two studies that found effects administered other compounds in addition to Prussian Blue, and the minor hematological and renal effects noted were attributed to other compounds in the mixture. One study of sodium ferrocyanide included multiple dose levels, was of a subchronic exposure duration, investigated multiple toxic endpoints, and apparently identified NOAEL and minimal LOAEL values (5000 and 50,000 ppm, respectively), but methods and results were not reported in sufficient detail to permit independent evaluation of the data.

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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.

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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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3-21-05

Provisional Peer Reviewed Toxicity Values for

Prussian Blue (Ferric Ferrocyanide)
(CASRN 14038-43-8)

Derivation of a Carcinogenicity Assessment

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

3-21-05

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR PRUSSIAN BLUE (FERRIC FERROCYANIDE, CASRN 14038-43-8)
Derivation of a Carcinogenicity Assessment

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.

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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.

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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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