09-30-02

Provisional Peer Reviewed Toxicity Values for

Picric acid (2,4,6-Trinitrophenol)

(CASRN 88-89-1)

Derivation of a Chronic 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
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-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

09-30-02

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR PICRIC ACID (2,4,6-TRINITROPHENOL) (CASRN 88-89-1)
Derivation of a Chronic 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 picric acid is not listed on IRIS (U.S. EPA, 2002), in the HEAST (U.S. EPA, 1997), or in the Drinking Water Standards and Health Advisories list (U.S. EPA, 2000). The CARA list (U.S. EPA, 1991, 1994) includes a Health and Environment Effects Profile for Trinitrophenols (U.S. EPA, 1984) that did not derive an ADI for picric acid because adequate data were lacking. The toxicity of picric acid has not been reviewed by ATSDR (2001), IARC (2001), or the WHO (2001). A toxicity review on aromatic nitro and amino compounds (Weisburger and Hudson, 2001), a review of the occupational hazards of nitrophenols, prepared by the Syracuse Research Corporation (SRC, 1981) for the National Institute for Occupational Safety and Health, and the NTP (2001a, 2001b) management status report and chemical repository summary were consulted for relevant information. Literature searches were conducted in TOXLIT (1965-1991), TOXLINE (1965-1992), MEDLINE (1980-1992), RTECS and HSDB

in 1991/1992. Updated literature searches were conducted from 1983 to October 2001 in TOXLINE (plus NTIS and BIOSIS updates), CANCERLIT, MEDLINE, CCRIS, GENETOX, HSDB, EMIC/EMICBACK, DART/ETICBACK, RTECS and TSCATS.

REVIEW OF PERTINENT INFORMATION

Human Studies

The following effects have been reported after acute oral exposure to ≥28 mg/kg of picric acid: headache, vertigo, nausea, vomiting, diarrhea, yellow coloration of the skin, hematuria, albuminuria, and, at high doses, destruction of erythrocytes, hemorrhagic nephritis, and hepatitis (NIOSH, 1981; ACGIH, 1992). No quantitative data were located regarding the toxicity of picric acid to humans following chronic or subchronic oral exposure.

Animal Studies

No relevant data were located regarding the toxicity of picric acid to animals following chronic or subchronic oral exposure.

POTENTIAL SURROGATES

Since relevant toxicological data for picric acid are lacking, it may be possible to choose another chemical as a surrogate for the purpose of health risk assessment. In selecting a chemical related structurally to picric acid, particular attention should be given to both the nitro substitution and the phenol group. The absence of either of these moieties would weaken any comparison made between an analog and picric acid. In this regard, the phenolic group is essential because of the acidic hydrogen (methyl groups do not have acidic hydrogens), and the nitro groups are essential because of their chemical behavior. Based on these chemical considerations, 2,4-dinitrophenol appears to be an appropriate choice for a surrogate.

Both 2,4-dinitrophenol and picric acid (2,4,6-trinitrophenol) are readily absorbed by the oral route of exposure (SRC, 1981; U.S. EPA, 1984). Also, both chemicals undergo similar metabolic reactions involving reduction of the nitro group to amino. In the case of picric acid, the main metabolic product is picramic acid (2-amino-4,6-dinitrophenol), whereas 2,4-dinitrophenol gives rise to 2-amino-4-nitrophenol (4-amino-2-nitrophenol is also formed). 2,4-Dinitrophenol (or metabolites) is rapidly excreted in the urine and does not accumulate in the body; picric acid and picramic acid have been identified in the urine of humans and picric acid in the urine of dogs following picric acid exposure or administration, but the rate of excretion is unknown.

Acute data indicate that 2,4-dinitrophenol has a higher lethal potency than picric acid (SRC, 1981). Oral and parenteral lethal doses (and/or LD50s) for 2,4-dinitrophenol in mice, rats, dogs, and rabbits of 15-100 mg/kg were reported; those reported for picric acid are approximately one order of magnitude higher.

The effects of acute exposure to 2,4-dinitrophenol include increased body temperature, oxygen consumption, respiratory rate, blood pressure, heart rate, glycogenolysis, thyroxin and bile secretion, and altered neuromuscular transmission. Many of these effects result from the chemical's ability to uncouple oxidative phosphorylation. Acute studies show reversible cataract formation in chickens, ducks and immature rabbits. Long-term ingestion of 2,4-dinitrophenol has been associated with elevated body temperature, weight loss, skin rashes and irreversible cataract formation in humans; the effects of occupational exposure are similar to those of ingestion, with the exception that cataracts have not been reported as an effect of occupational exposure (SRC, 1981; U.S. EPA, 1983, 2002).

The toxicity of picric acid has received little study. Some of the effects of picric acid (such as elevated body temperature, excessive perspiration, and skin rashes in humans exposed occupationally) are similar to those of 2,4-dinitrophenol in humans exposed orally or occupationally, but whether or not picric acid uncouples oxidative phosphorylation is not clear from the limited evidence. Acute administration of picric acid to chickens did not produce cataracts, but cataract formation in animals given 2,4-dinitrophenol appears to be different than in humans because cataracts may appear in animals within an hour of acute administration and are readily reversible. To what extent this transient cataract formation in animals is predictive of results in humans is unknown.

Given the paucity of toxicity and pharmacokinetic information on picric acid, the selection of a suitable surrogate must rest primarily on the chemical properties noted above, which support the selection of 2,4-dinitrophenol as a surrogate. However, the relevance of cataract formation in humans due to 2,4-dinitrophenol is unrelated to the target organ specificity of picric acid as discussed in the preceding paragraphs. Therefore, based on available data, no p-RfD for picric acid could be recommended.

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09-30-02

Provisional Peer Reviewed Toxicity Values for

Picric acid (2,4,6-Trinitrophenol)

(CASRN 88-89-1)

Derivation of a Chronic Inhalation RfC

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
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Acronyms and Abbreviations

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CERCLA	Comprehensive Environmental Response, Compensation and Liability Act of 1980
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cu.m	cubic meter
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MF	modifying factor
mg	milligram
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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)
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SCE	sister chromatid exchange
SDWA	Safe Drinking Water Act
sq.cm.	square centimeters
TSCA	Toxic Substances Control Act
UF	uncertainty factor
µg	microgram
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   - Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR),
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   - EPA Health Effects Assessment Summary Table (HEAST) values.

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INTRODUCTION

Picric acid is not listed on IRIS (U.S. EPA, 2002) or the HEAST (U.S. EPA, 1997). The CARA list (U.S. EPA, 1991, 1994) includes a Health and Environment Effects Profile (HEEP) for Trinitrophenols that contained no quantitative data regarding long-term inhalation toxicity of picric acid in humans or animals (U.S. EPA, 1984). The ACGIH (2001) established a TWA-TLV of 0.1 mg/m^3 for picric acid to protect against dermatitis, irritation, ocular effects and sensitization; however, the supporting document indicated that the TLV was intended to protect against systemic effects (headache, vertigo, gastrointestinal effects) and might not protect unusually sensitive individuals from dermal sensitization (ACGIH, 1992). NIOSH (2001) established a REL-TWA of 0.1 mg/m^3 and a 15-minute STEL of 0.3 mg/^{3} with a skin notation to protect against irritation, sensitization dermatitis, headache, urinary abnormalities, and gastrointestinal and renal effects. OSHA (2001) established a PEL-TWA of 0.1 mg/m^3 with a

skin notation for picric acid based on dermal irritation and sensitization, cumulative hepatic, renal, and erythrocyte damage, and mutagenicity. The toxicity of picric acid has not been reviewed by ATSDR (2001), IARC (2001) or the WHO (2001). A toxicity review on aromatic nitro and amino compounds (Weisburger and Hudson, 2001), a review of the occupational hazards of nitrophenols, prepared by the Syracuse Research Corporation (SRC, 1981) for the National Institute for Occupational Safety and Health, and the NTP (2001a, 2001b) management status report and chemical repository summary were consulted for information relevant to the inhalation toxicity of picric acid. Literature searches were conducted from 1983 to October 2001 in TOXLINE (plus NTIS and BIOSIS updates), CANCERLIT, MEDLINE, CCRIS, GENETOX, HSDB, EMIC/EMICBACK, DART/ETICBACK, RTECS and TSCATS.

REVIEW OF PERTINENT INFORMATION

Human Studies

Irritation of the eyes and dermal sensitization have been observed following occupational exposure to picric acid dust (ACGIH, 1992). Acute inhalation of high concentrations of the dust caused temporary coma followed by weakness, myalgia, anuria, and later polyuria in one worker (NIOSH, 1981). No relevant data were located regarding the toxicity of picric acid to humans following chronic or subchronic inhalation exposure.

Animal Studies

No relevant data were located regarding the toxicity of picric acid to animals following chronic or subchronic inhalation exposure.

FEASIBILITY OF DERIVING AN RfC FOR PICRIC ACID

The lack of suitable inhalation data for humans or animals precludes the derivation of a p-RfC for picric acid.

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09-30-02

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(CASRN 88-89-1)

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

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REL	relative exposure level
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SCE	sister chromatid exchange
SDWA	Safe Drinking Water Act
sq.cm.	square centimeters
TSCA	Toxic Substances Control Act
UF	uncertainty factor
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µmol	micromoles
VOC	volatile organic compound

09-30-02

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR PICRIC ACID (2,4,6-TRINITROPHENOL) (CASRN 88-89-1)
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 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

Picric acid is not listed on IRIS (U.S. EPA, 2002), the HEAST (U.S. EPA, 1997) or the Drinking Water Standards and Health Advisories list (U.S. EPA, 2000). The CARA list (U.S. EPA, 1991, 1994) includes a Health and Environment Effects Profile (HEEP) for Trinitrophenols (U.S. EPA, 1984) that reported inadequate data for carcinogenicity (negative results in a deficient oral bioassay) and some evidence for mutagenicity of picric acid. Picric acid has not been reviewed by ATSDR (2001), IARC (2001) or the WHO (2001). A toxicity review on aromatic nitro and amino compounds (Weisburger and Hudson, 2001), a review of the occupational hazards of nitrophenols, prepared by the Syracuse Research Corporation (SRC, 1981) for the National Institute for Occupational Safety and Health, and the NTP (2001a, 2001b) management status report and chemical repository summary were consulted for information relevant to the carcinogenicity of picric acid. Literature searches were conducted from 1983 to October 2001 in

TOXLINE (plus NTIS and BIOSIS updates), CANCERLIT, MEDLINE, CCRIS, GENETOX, HSDB, EMIC/EMICBACK, DART/ETICBACK, RTECS and TSCATS.

REVIEW OF PERTINENT INFORMATION

Human Studies

No relevant data were located regarding the carcinogenicity of picric acid to humans by any route of exposure.

Animal Studies

U.S. EPA (1984) reported negative results for carcinogenicity in male and female Wistar rats given a dietary concentration of 500 ppm of picric acid for 2.5 years (van Esch et al., 1957). U.S. EPA (1984) characterized this study as inconclusive because of small group sizes and unusually high incidence of mammary tumors in the control group. No additional data were located regarding the carcinogenicity of picric acid to animals following oral or inhalation exposure.

Genotoxicity Studies

The available evidence suggests that the genotoxicity of picric acid is increased by metabolic activation. Picric acid did not induce reverse mutations in *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1538 unless a metabolic activation system was present (U.S. EPA, 1984). Feeding of picric acid to adult *Drosophila melanogaster* significantly increased the incidence of sex-linked recessive lethal mutations in offspring (U.S. EPA, 1984). Picric acid did not induce micronucleus formation in mouse marrow bone cells (U.S. EPA, 1984).

Picramic acid, a major metabolite of picric acid, appears to be genotoxic (U.S. EPA, 1984; CIREPS, 1992; NTP, 2001a). With or without metabolic activation, picramic acid yielded positive results for reverse mutation in *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1538, but negative results in *Saccharomyces cerevisiae* strain D4. Picramic acid was not mutagenic at the TK locus in cultured L5178Y mouse lymphoma cells, nor was it mutagenic or clastogenic in the mouse dominant lethal assay. With or without metabolic activation, there was some evidence of weak mutagenic activity of picramic acid with extremely toxic treatments (2-4% relative growth) in the mouse bone marrow cytogenetic assay.

PROVISIONAL WEIGHT-OF-EVIDENCE CLASSIFICATION

There are no data available regarding the carcinogenicity of picric acid in humans. U.S. EPA (1984) considered the only available oral bioassay in rats to be inadequate because of small group sizes, the use of a single dose, and an unusually high incidence of mammary tumors in the control group. No adequate studies were available that examined the carcinogenicity of picric acid to humans or animals exposed by any route. There is some evidence that a metabolite of picric acid is genotoxic in bacteria and mammalian cells (U.S. EPA, 1984). Following the U.S. EPA (1999) proposed guidelines for carcinogen risk assessment, the data for picric acid are considered inadequate for an assessment of human carcinogenic potential.

QUANTITATIVE ESTIMATES OF CARCINOGENIC RISK

Derivation of quantitative estimates of cancer risk for picric acid is precluded by the absence of data demonstrating carcinogenicity associated with picric acid exposure.

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