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Provisional Peer Reviewed Toxicity Values for

Nicotinonitrile
(CASRN 100-54-9)

Superfund Health Risk Technical Support Center
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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

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PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR NICOTINONITRILE (CASRN 100-54-9)

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 HQ 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

The HEAST (U.S. EPA, 1997) does not list subchronic or chronic reference dose (RfD) or reference concentration (RfC) values for nicotinonitrile (3-cyanopyridine; $C_6H_4N_2$), noting that data were inadequate for quantitative risk assessment, and does not include any cancer assessment for the chemical. A Health and Environmental Effects Document (HEED) for Selected Nitriles (U.S. EPA, 1987), that was listed in the HEAST as a reference for subchronic and chronic toxicity, reported no chronic or subchronic toxicity studies of nicotinonitrile and assigned the chemical to U.S. EPA (1999) cancer weight-of-evidence Group D (*not classifiable as to human carcinogenicity*) based on no human or animal cancer data. Nicotinonitrile is not listed on IRIS (U.S. EPA, 2003) or the Drinking Water Standards and Health Advisories list (U.S. EPA, 2002). No relevant documents, other than the previously mentioned HEED, were located in the CARA list (U.S. EPA, 1991, 1994). IARC (2003), NTP (2003), and ACGIH

(2002) have not assessed the carcinogenicity of nicotinonitrile. ACGIH (2002), NIOSH (2003) and OSHA (2003a,b) have not established occupational exposure limits for nicotinonitrile. ATSDR (2003) and WHO (2003) have not published toxicological review documents on nicotinonitrile. Patty's Toxicology (2001) was consulted for relevant information. Literature searches were conducted from 1986 thru December 2002 for studies relevant to the derivation of provisional toxicity values for nicotinonitrile. Databases searched included: TOXLINE, MEDLINE, CANCERLIT, BIOSIS, TSCATS, RTECS, CCRIS, DART/ETICBACK, EMIC/EMICBACK, HSDB and GENETOX. Additional literature searches from December 2002 through September 2004 were conducted by NCEA-Cincinnati using MEDLINE, TOXLINE, Chemical and Biological Abstracts databases.

REVIEW OF PERTINENT DATA

Human Studies

No studies were located regarding the subchronic or chronic toxicity or carcinogenicity of nicotinonitrile in humans.

Animal Studies

No studies were located regarding the subchronic or chronic toxicity or carcinogenicity of nicotinonitrile in animals.

Other Studies

Nicotinonitrile was negative for induction of mutation in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 when tested with or without S9 metabolic activation (Florin et al., 1980).

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR NICOTINONITRILE

Provisional subchronic or chronic oral RfD values for nicotinonitrile cannot be derived because human and animal toxicity data following subchronic or chronic oral exposure to nicotinonitrile are lacking.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfC VALUES FOR NICOTINONITRILE

Provisional subchronic or chronic inhalation RfC values for nicotinonitrile cannot be derived because human and animal toxicity data following subchronic or chronic inhalation exposure to nicotinonitrile are lacking.

DERIVATION OF A PROVISIONAL CARCINOGENICITY ASSESSMENT FOR NICOTINONITRILE

No data were located regarding the carcinogenicity of nicotinonitrile in humans or animals. Nicotinonitrile did not induce mutations in bacteria (Florin et al., 1980). Under the proposed U.S. EPA (1999) cancer guidelines, the data are inadequate for an assessment of human carcinogenic potential.

Derivation of quantitative estimates of cancer risk for nicotinonitrile is precluded by the absence of pertinent carcinogenicity data.

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