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Provisional Peer Reviewed Toxicity Values for

Malononitrile
(CASRN 109-77-3)

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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

4-5-2007

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR MALONONITRILE (CASRN 109-77-3)

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

The HEAST (U.S. EPA, 1997) lists both subchronic and chronic RfD values for malononitrile: 2E-4 and 2E-5 mg/kg-day, respectively. The source document for this assessment was a Health and Environmental Effects Profile (HEEP) for Malononitrile (U.S. EPA, 1986a) wherein a LOAEL of 0.21 mg/kg-day was established for adverse effects in the liver and spleen of rats receiving malononitrile by gavage for 120 days (Panov et al., 1972). The RfD was reviewed by the RfD/RfC Work Group, but was not verified due to deficiencies in the critical study (Panov et al., 1972) and inadequate documentation (U.S. EPA, 1986b). A toxicity assessment for malononitrile is not available on IRIS (U.S. EPA, 2007) or in the Drinking Water Standards and Health Advisories list (U.S. EPA, 2000). The CARA list (U.S. EPA, 1991, 1994) includes no documents for malononitrile other than the aforementioned HEEP (U.S. EPA,

1986a). Although it is not listed in the HEAST, the HEEP also contains a carcinogenicity assessment that placed malononitrile in cancer weight-of-evidence group D, not classifiable as to human carcinogenicity, due to lack of relevant data. NTP (2002a,b) has not conducted a cancer bioassay for malononitrile, but has tested malononitrile for genotoxicity. A toxicological review of malononitrile is not available from ATSDR (2002), IARC (2002) or WHO (2002). Malononitrile has not been evaluated by ACGIH (2001) or OSHA (2002), but NIOSH (2002) lists a REL of 8 mg/m^3 (3 ppm) for this chemical. This exposure limit is based on analogy to acetonitrile and isobutyronitrile, due to lack of adequate toxicity data for malononitrile. A recent toxicity review paper of cyanides and nitriles by Cohrssen (2001) was consulted for relevant information. Literature searches were conducted from 1985 through November 2001 for studies relevant to the derivation of provisional toxicity values for malononitrile. Databases searched included: TOXLINE, MEDLINE, CANCERLIT, TSCATS, RTECS, CCRIS, DART, EMIC/ EMICBACK, HSDB and GENETOX. Using the same databases, additional literature searches were conducted for the period for 2002 through January 2007. This document has passed the STSC quality review and peer review evaluation indicating that the quality is consistent with the SOPs and standards of the STSC and is suitable for use by registered users of the PPRTV system.

REVIEW OF PERTINENT DATA

Human Studies

Limited data are available regarding the toxicity of malononitrile to humans. In the late 1940s, malononitrile was used experimentally by Hyden and Hartelius in the treatment of schizophrenia and depression (Cohrssen, 2001). Patients were given an intravenous infusion of 5% malononitrile for 10-69 minutes. The total dose during each treatment ranged from 1 to 6 mg/kg. Treatments were given 2-3 times/week, with intervals of at least 1 day between doses. Ten to 20 min after the beginning of the infusion, all patients experienced tachycardia. In addition, patients experienced, with varying frequency, local redness, nausea, vomiting, headaches, shivering, muscle spasms and numbness. Two patients experienced convulsions, and one case of cardiac collapse was noted (Cohrssen, 2001). The treatments provided little or no therapeutic benefit, and were discontinued (U.S. EPA, 1986a).

Chronic occupational exposure to other similar nitrile compounds (*e.g.*, acetonitrile) has resulted in interference of iodine uptake by the thyroid and some cases of goiter, presumably by interference of thiocyanate produced during normal cyanide detoxification by the endogenous rhodanese enzyme. Whether this occurs with malononitrile exposure is unknown (Cohrssen, 2001). No other toxicity studies involving human oral or inhalation exposure to malononitrile were located.

Animal Studies

Early studies reported that oral administration of malononitrile to mice at doses near the LD_{50} (19 mg/kg in mice) caused gastric mucosal injury and a general hyperthermia of all organs (Cohrssen, 2001). A study described by Cohrssen (2001) found pathologic changes in the spinal ganglia in rats given a single dose (route unknown) of 6 to 8 mg/kg malononitrile (approximately 10% of rat LD_{50}). Cohrssen (2001) also cites another study wherein lesions of the corpus striatum were reported. No other details are available.

Panov et al. (1972, as cited by U.S. EPA, 1986a,b) administered 0, 0.25, or 0.5 mg/kg-day of malononitrile in water by gastric intubation to male Wistar rats 6 days/week for 120 days. A vehicle control group of 8 rats was used, whereas there were 7 rats in each of the malononitrile dose groups. Rats were sacrificed for histopathological examination 2 months after the final treatment. Administration of malononitrile did not result in mortality. Edema and inflammation were noted in the gastrointestinal tracts of all treated rats, as well as alterations (generally increasing, although fluctuating greatly) in histamine, histaminase, cholinesterase, coproporphyrins and 5-hydroxyindoleacetic acid. Dose-related increases in the severity of lesions in the liver and spleen were reported. In the liver, congestion was observed in both dose groups (more marked at 0.5 mg/kg-day), and liver degeneration and necrosis were observed at 0.5 mg/kg-day. In the spleen, hemosiderosis and reticulocytosis were observed at 0.25 mg/kg-day, with diminished hematopoiesis at 0.5 mg/kg-day. Control data were not reported. This study identified a LOAEL of 0.25 mg/kg-day for histopathological changes in the liver and spleen of rats exposed to malononitrile by gavage for 120 days, but was limited by small group sizes, the two month gap between end of exposure and sacrifice for histopathology, and inadequate reporting of control data.

Lonza (1989) evaluated the subchronic toxicity of malononitrile in Crl:CD(SD)BR rats (10/sex/dose group) in a GLP study conducted for TSCA §4 compliance. Malononitrile (99.7% pure) was administered by gavage in distilled water at 0, 0.4, 2 and 10 mg/kg-day for 90 days. An additional group of rats (5/sex) was administered 0 or 10 mg/kg-day malononitrile for 90 days and retained without treatment for 28 days. The animals were examined weekly for clinical signs, food consumption, and body weight. An ophthalmoscopic examination was conducted on high-dose and control rats at study initiation and termination. Hematology (hemoglobin, cell volume, total and differential white cell count, and platelet count), clinical chemistry (17 parameters), and urinalysis were examined at study termination. A complete necropsy with organ weight (adrenals, brain, gonads, heart, kidneys, liver, lungs, and spleen) and histopathologic examination of 40 tissues was conducted at study termination. Aside from occasional salivation observed among several high-dose rats prior to dosing, no significant clinical signs were reported during treatment, and there was no malononitrile-related mortality (the death of one female control rat was attributed to intubation injury). Group mean body weight of high-dose males was 6% lower than that of controls at 13 weeks. This difference

began after 2 weeks of dosing, was fairly steady from week 7 to 13, and persisted throughout the 28-day recovery period. The authors reported that body weights were analyzed parametrically, but there was no indication that the observed decrease in body weight was statistically significant. Food consumption was not affected by treatment; food conversion efficiency was lower in high-dose males compared to controls. Ophthalmology findings were unremarkable.

Statistically significant changes in several hematology and clinical chemistry parameters were noted at 2 and 10 mg/kg-day (Lonza, 1989). The mean alkaline phosphatase level of high-dose females was greater than controls at week 13 ($p<0.001$). A decrease in mean total serum cholesterol was reported for intermediate- and high-dose females ($p<0.001$ and $p<0.01$, respectively). Increased mean plasma urea levels were noted at week 13 in high dose males and intermediate and high dose females ($p<0.01$ as compared to controls for high dose males and intermediate dose females). At week 13, a dose-dependent increase in platelet counts of the intermediate- (trend) and high-dose ($p<0.01$ as compared to controls) males and high-dose (trend) females was reported. These changes in hematology and clinical chemistry parameters were not observed after the 28-day recovery period. Absolute and relative liver weights were significantly increased in high-dose groups of both sexes ($p<0.001$ for both males and females), and relative liver weight was increased in males at 2 mg/kg-day ($p<0.05$). This effect on liver weight was partially reversed by the recovery period. There were no macroscopic findings that suggested gross target organ toxicity related to malononitrile administration. Hepatocellular hypertrophy (accompanied by vacuolization of the cytoplasm of the hepatocytes) was observed in intermediate- and high-dose males and among high-dose females. This effect was not present after the recovery period. Administration of malononitrile at 0.4 mg/kg-day for 90 days did not result in any toxicologically significant adverse effects. This study established a NOAEL of 0.4 mg/kg-day and a LOAEL of 2 mg/kg-day for hepatic effects (increased relative liver weight and hepatocellular hypertrophy and vacuolization) in male CD rats and changes in clinical pathology profiles for both sexes.

Only one study of the inhalation toxicity of malononitrile is available. Panov (1970, as cited by U.S. EPA, 1986a) exposed groups of 10 white rats (strain and sex were not reported) to malononitrile vapors at concentrations of 0 or 36 mg/m^3, 2 hours per day, for 35 days. The rats exposed to malononitrile exhibited signs of irritation during exposure, a nonsignificant tendency toward reticulocytosis, significantly decreased hemoglobin concentrations on days 22 and 35, and significantly increased lung weight post mortem. No treatment-related increase in mortality was reported. There were no effects on body weight, red or white blood cell counts, oxygen consumption, or weights of brain, liver, or kidneys. The utility of this study for risk assessment is limited by the brief (2 hours) daily exposures, the short (35-day) treatment period, use of only a single exposure level, the limited number of endpoints studied, the marginal nature of the findings, and incomplete reporting of methods and results.

No studies of the possible reproductive or developmental hazards of malononitrile were located, nor were any chronic toxicity studies of malononitrile available. The available data show that malononitrile did not induce reverse mutations in *Salmonella typhimurium* (U.S. EPA, 1986a; NTP, 2002b).

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR MALONONITRILE

Limited information on the oral toxicity of malononitrile in humans and animals exists. At the time of the 1986 HEEP (U.S. EPA, 1986a), information available for derivation of an oral p-RfD was limited to the study by Panov et al. (1972), which identified a LOAEL of 0.21 mg/kg-day for adverse effects in the liver and spleen of rats receiving malononitrile by gavage for 120 days. Subsequent to that assessment, Lonza (1989) published a high quality subchronic study that identified a NOAEL of 0.4 mg/kg-day and a LOAEL of 2 mg/kg-day for hepatic effects (increased relative liver weight and hepatocellular hypertrophy and vacuolization) in male CD rats and changes in clinical pathology profiles for both sexes. The Panov et al. (1972) study was limited by small group sizes, a two month gap between end of exposure and sacrifice for histopathology, and inadequate reporting of control data. Therefore, the Lonza (1989) study is more appropriate as the principal study for derivation of provisional subchronic and chronic oral RfD values.

To the rat NOAEL of 0.4 mg/kg-day established by Lonza (1989), a combined uncertainty factor of 300 (10 for interspecies extrapolation, 10 for human variability, and 3 for database deficiencies, including lack of reproductive and developmental toxicity tests) was applied. No modifying factor was used (*i.e.*, the modifying factor = 1). A provisional **subchronic oral RfD of 1E-3 mg/kg-day** was calculated as follows:

subchronic p-RfD = NOAEL / UF
= 0.4 mg/kg-day / 300
= 0.001 mg/kg-day or 1E-3 mg/kg-day

A provisional chronic oral RfD can also be derived by dividing the NOAEL of 0.4 mg/kg-day established by Lonza (1989) by a combined uncertainty factor of 3000 (10 to account for extrapolation from a subchronic study, 10 for interspecies extrapolation, 10 for human variability, and 3 for database deficiencies). No modifying factor was used (*i.e.*, the modifying factor = 1). A provisional **chronic oral RfD of 1E-4 mg/kg-day** was calculated as follows:

p-RfD = NOAEL / UF
= 0.4 mg/kg-day / 3000
= 0.0001 mg/kg-day or 1E-4 mg/kg-day

These provisional subchronic and chronic RfD values are both five times higher than the corresponding values derived in the HEEP (U.S. EPA, 1986a) and listed in the HEAST (U.S. EPA, 1997). The difference is due to the recent availability of higher quality data that better define critical effect levels for this chemical.

Confidence in the principal study is high; it is a well-designed GLP study that examined a number of relevant endpoints and identified both a LOAEL and a NOAEL. Confidence in the database is low; supporting data for the critical study are available only from one other subchronic study of uncertain reliability, no chronic study is available, and no information is available on the potential of ingested malononitrile to induce developmental, reproductive, or neurological effects (a potential target organ suggested by early acute studies). Confidence in the provisional RfD is low.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfC VALUES FOR MALONONITRILE

No data regarding the inhalation toxicity of malononitrile in humans were found in the available review documents (U.S. EPA, 1986a; Cohrssen, 2001) or the literature search. The HEEP (U.S. EPA, 1986a) included one study involving repeated inhalation exposure of rats to malononitrile; however, the study limitations preclude its use for quantitative risk assessment. No other information was located regarding repeated inhalation exposure of animals to malononitrile in the available review documents or the literature search. Derivation of a p-RfC for malononitrile is precluded by the absence of relevant inhalation data.

DERIVATION OF A PROVISIONAL CARCINOGENICITY ASSESSMENT FOR MALONONITRILE

The existing review documents (Cohrssen, 2001; U.S. EPA, 1986a) and update literature search did not identify relevant studies regarding the carcinogenicity of malononitrile in humans or animals following oral or inhalation exposure. Available genotoxicity data report that malononitrile did not induce reverse mutations in *Salmonella typhimurium* (US. EPA, 1986a; NTP, 2002b). In accordance with the cancer guidelines (U.S. EPA, 2005), the available data are inadequate for an assessment of human carcinogenic potential.

Derivation of quantitative estimates (provisional oral slope factor or a provisional inhalation unit risk) of cancer risk for malononitrile is precluded by the absence of carcinogenicity data.

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