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Provisional Peer Reviewed Toxicity Values for

4-Aminopyridine

(CASRN 504-24-5)

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

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PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR 4-AMINOPYRIDINE (CASRN 504-24-5)

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

4-Aminopyridine (CASRN 504-24-5) is an odorless white crystalline compound that acts as a potassium channel blocker in excitable membranes of the nervous system. 4-Aminopyridine is marketed under the trade name Avitrol as a registered bird repellent (U.S. EPA, 1980) and has been formulated for medical use under the pharmaceutical name Fampridine (Acorda Therapeutics, 2003). 4-Aminopyridine increases nerve transduction in demyelinated nerve fibers and has been proposed as a symptomatic treatment for people with disorders of neuromuscular transmission, multiple sclerosis (MS), and spinal cord injury (SCI).

The 1997 HEAST (U.S. EPA, 1997) lists subchronic and chronic oral RfD values of 2E-04 and 2E-05 mg/kg-day, respectively, for 4-aminopyridine. The source document for these derivations is a Health and Environmental Effects Document (HEED) for 4-Aminopyridine (U.S.

EPA, 1989). The RfD values are based on sporadic hyperirritability and organ weight changes in rats fed 4-aminopyridine in the diet for 90 days (Kohn, 1968). The NOAEL and LOAEL for this study were 3 ppm and 30 ppm, respectively. Assuming that the rats consumed an amount of food equivalent to 5% of their body weight per day, the NOAEL and LOAEL dietary concentrations correspond to approximately 0.15 and 1.5 mg/kg-day. An uncertainty factor (UF) of 1000 (including factors of 10 for interspecies extrapolation, 10 for protection of human subpopulations, and 10 for deficiencies in the database) was applied to the NOAEL of 0.15 mg/kg-day to derive a subchronic RfD of 0.0002 mg/kg-day. An uncertainty factor of 10,000 (including an extra factor of 10 for use of a subchronic NOAEL) was applied to derive a chronic RfD of 0.00002 mg/kg-day. U.S. EPA (1989) concluded that confidence in the RfD values was low, based on low confidence in the principal study (an unpublished proprietary study with few experimental details available) and limited supporting data (an unpublished, proprietary subchronic study in dogs with few details available) and indicated that the RfD values were not defensible and should be regarded as preliminary until additional data were available. The Office of Pesticide Programs has reported an ADI (U.S. EPA, 1980) of 0.0002 mg/kg-day based on hyperirritability observed in the subchronic feeding study in rats (Kohn, 1968) and an uncertainty factor of 1000. An RfD for 4-aminopyridine is not available on IRIS (U.S. EPA, 2006).

The HEAST and source HEED do not include RfC or cancer assessments for 4-aminopyridine due to lack of data. No RfC or quantitative cancer assessment for 4-aminopyridine is available on IRIS (U.S. EPA, 2006). IRIS (U.S. EPA, 2006) and the Office of Pesticide Programs tracking report list a cancer weight-of-evidence classification of D, not classifiable as to human carcinogenicity.

Additional sources of information were reviewed for toxicity reference values or cancer assessments for 4-aminopyridine. 4-Aminopyridine is not included in 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). The California Environmental Protection Agency does not list toxicity reference or cancer potency values. ATSDR (2003) has not produced a Toxicological Profile for 4-aminopyridine and an Environmental Health Criteria Document is not available (WHO, 2003). The carcinogenicity of 4-aminopyridine has not been assessed by IARC (2003) or studied by NTP (2003). Occupational exposure limits have not been established by ACGIH (2003), OSHA (2003), or NIOSH (2003).

Literature searches were conducted from 1988 thru August, 2003 for studies relevant to the derivation of provisional toxicity values for 4-aminopyridine. Databases searched included: TOXLINE (including NTIS and BIOSIS updates), MEDLINE, CANCERLIT, TSCATS, RTECS, CCRIS, DART/ETICBACK, EMIC/EMICBACK, HSDB, and GENETOX. Additional literature searches from August 2003 through September 2004 were conducted by NCEA-Cincinnati using MEDLINE, TOXLINE, Chemical and Biological Abstracts databases and no additional information was found.

REVIEW OF PERTINENT DATA

Human Studies

4-Aminopyridine blocks fast, voltage-gated (A current) K^+ channels in demyelinated internodes of central axons (Potter et al., 1998). This blockade prolongs the duration of the action potential and results in increased Ca^{2+} at dendritic terminals, resulting in increased neurotransmitter release in a wide range of neuronal subtypes (including GABA-ergic, cholinergic, and adrenergic neurons). These properties have resulted in a long history of clinical use in humans. Therapeutic applications have included use as an antagonist for neuromuscular blockade from various anesthetics, enhancement of neural or neuromuscular transmission in patients with Alzheimer's disease, botulinum toxicity, myasthenia gravis, or Eaton-Lambert Syndrome, and as a means of overcoming conduction deficits in patients with MS or SCI (Potter et al., 1998).

Human toxicity data for 4-aminopyridine are available from case reports of accidental ingestion by non-health-compromised individuals, case reports of accidental overdose by individuals medicated with 4-aminopyridine for health conditions, and from clinical trials or studies conducted in individuals with MS or SCI. The clinical trials and studies have focused on the therapeutic benefits of treatment in health-compromised individuals, and data on the health effects of 4-aminopyridine in healthy individuals are limited.

Accidental ingestion of a capsule or tablet (description varied with publication) containing 4-aminopyridine (dose not reported) by an 8-month old child resulted in tachycardia, tachypnea, low diastolic blood pressure, opisthotonic posturing (spasm of the back muscles causing the head and limbs to bend backwards and the trunk to arch forward) without evidence of seizure activity, vermiform tongue fasciculations (worm-like muscle twitching), and other neurological symptoms (Velez et al., 2000, 2003). A one-year old child was observed to be drooling and lethargic after ingestion of an unknown number of 10 mg capsules of 4-aminopyridine and subsequently developed tonic-clonic seizures (prolonged muscle contraction and/or a series of alternating contractions with partial relaxations) (Lowry et al., 2002). After treatment for the seizure and admission to intensive care, the child was observed to have elevated pulse and respiration, lateral nystagmus (rapid involuntary oscillations of the eyeball), intermittent fasciculations, and myoclonic movements (irregular muscle contractions) of all extremities. An electrocardiogram showed sinus tachycardia with no QRS or QTc abnormalities. The measured level of 4-aminopyridine in the serum was 266 ng/mL (therapeutic level 30-59 ng/mL); pharmacokinetic analysis suggested that as little as 10 mg (0.85 mg/kg) may have been ingested. A 14-year-old male who intentionally ingested between 100 and 150 mg experienced rapid pulse and respiration, diaphoresis (excessive sweating), neuromuscular excitability (including fasciculations and increased muscle tone), and one generalized seizure (Traub et al., 2002). An electrocardiogram showed sinus tachycardia with normal QRS and Qtc intervals. A

peak serum level of 256 ng/mL was reported for the patient. No lasting effects were observed after treatment. Spyker et al. (1980) reported that two men (100 kg) accidentally ingested a pinch (estimated to be approximately 60 mg) of 4-aminopyridine, were admitted to the hospital and survived the poisoning. The men had symptoms of nausea, weakness, dizziness, profuse perspiration, altered mental status and hypertension. One of these men experienced three tonic-clonic seizures.

An estimated 10,000 to 20,000 MS and SCI patients in the United States and Canada are taking 4-aminopyridine (immediate release formulation) for symptomatic treatment (Hayes et al., 2003). Typical therapeutic doses appear to be in the range of 2-35 mg/day. There are a number of case reports of adverse effects in adults taking immediate release formulations of 4-aminopyridine in unregulated situations. In one such case, a 34-year-old woman with a 2-year history of MS ingested 28-36 mg of 4-aminopyridine in two doses roughly 4 hours apart (Pickett and Enns, 1996). Approximately 2 hours after the second dose, the patient experienced shaking and tremulous dystonic and choreoathetoid-type (purposeless and uncontrolled) writhing of the extremities which were not tonic-clonic in nature. The patient was delirious and disoriented, had a fixed stare without roving eye movements, a facial grimace, tachypnea, slurred speech, and was confabulating (filling in gaps in memory by fabrication). The serum level of 4-aminopyridine measured after admission to the hospital was 233.6 ng/mL. Following treatment and observation, the patient was released. Two days after the episode the only symptom reported by the patient was mild muscle fatigue in her extremities. The clinical use of 4-aminopyridine is limited by its narrow therapeutic index; following a clinical dose of 0.15-0.3 mg/kg, the only side effects noted were slight decreases in systolic blood pressure and heart rates, while doses >0.05 mg/kg resulted in restlessness, confusion, nausea, weakness and tonic-clonic seizures (Agoston et al., 1985).

Stork and Hoffman (1994) reported 3 cases of 4-aminopyridine overdose in MS patients that resulted in seizure activity. In the best characterized case, a 28-year-old woman with a history of MS had been maintained on 2 mg/day for 2 years. Three weeks prior to admission she discontinued use of 4-aminopyridine for unknown reasons. On the day of admission, she consumed a "catch up" dose of 6 mg of 4-aminopyridine. Approximately 4-5 hours after ingestion she had a generalized tonic-clonic seizure that spontaneously resolved. Another seizure occurred on admission and was accompanied by mental dullness, left-side weakness, and rapid pulse. Subsequent ECG, electrolytes, and arterial blood gas determinations were normal. The serum level of 4-aminopyridine at the time of the second seizure was 136.3 ng/mL. In the remaining cases, one patient experienced two grand mal seizures and the second patient experienced 40 minutes of status epilepticus following ingestion of unknown amounts of 4-aminopyridine.

Solari et al. (2003) reviewed clinical trials on the use of 4-aminopyridine for symptomatic treatment in MS. A total of 26 potentially relevant studies were identified for 4-aminopyridine

and/or the structurally related compound diaminopyridine. Information on safety (i.e., the occurrence of side effects) was summarized for five single institution, double blind, crossover randomized controlled trials on 4-aminopyridine. Two instances of major side effects were reported among 198 treated patients participating in the reviewed clinical trials. These major effects included one case of acute encephalopathy and one case of epileptic seizure in patients receiving oral doses of 4-aminopyridine. The authors noted the low power of their systematic review to reliably detect major adverse events and further noted that trials excluded people with a history of seizures, unexplained loss of consciousness, or epileptiform activity on EEG (i.e., those who might be more susceptible to certain side effects).

Symptoms of nausea, dizziness, paresthesias or dysthesias, insomnia, restlessness and anxiety, gastric upsets, agitation, hepatitis, and/or gait instability have also been reported in MS patients treated with 4-aminopyridine (e.g., Stefoski et al., 1991; van Diemen et al., 1992, 1993; Bever et al., 1994; Polman et al., 1994; Schwid et al., 1997; Potter et al., 1998; Segal et al., 2000). Some information on occurrence of side effects in relation to dose has been reported. Stefoski et al. (1991) reported that 15/17 MS patients given 4-aminopyridine (7.5 to 20 mg in 1 to 3 daily doses) experienced mild to moderate side effects that seldom lasted more than 60 to 90 minutes. In the opinion of the authors, the type of side effect observed did not appear to be dose-related when the subjects were evaluated as a group, although a pattern was often evident in individual patients. Perioral and acroparathesias (numbness or tingling in extremities upon awakening) occurred with lower doses, while some patients reported dizziness and light-headedness at higher doses (no quantitative information provided). Further dose increments produced occasional sensations of vigor or nervousness.

Several other publications have reported dose- or serum level-related patterns for occurrence of side effects. A review of 4-aminopyridine in overdose (Stork and Hoffman, 1994) noted that side effects in therapeutic use showed a dose-related trend. The duration of treatment was not specified. Side effects were uncommon at doses of 0.2-0.5 mg/kg. Doses of 0.5-1.0 mg/kg routinely produced hyperexcitability, and doses greater than 1.0 mg/kg could produce seizure activity. Only a minority of patients (incidence not reported) reported side effects at doses up to 10 mg, whereas most patients experienced side effects at doses of 12.5 mg. At higher doses, most affected patients reported side effects within 30-45 minutes after dosing and the effects generally resolved within 2 to 5 hours. Van Diemen et al. (1993) observed side effects (dizziness, light-headedness, paresthesia) in subjects receiving total daily doses ranging from 5 to 50 mg (administered as single doses of 5 to 20 mg) for 12 weeks. However, 14 subjects in the same study who consumed total daily doses of 25 to 30 mg (0.38-0.55 mg/kg) did not experience side effects, indicating that adverse response to 4-aminopyridine was variable among the study population. Bever et al. (1994) noted dose-related trends in the incidence of dizziness, paresthesia, nausea, and nervousness or anxiety following one day of treatment with 4-aminopyridine (placebo, 5-10 mg, or 7.5-12.5 mg) and reported that these side effects correlated with the time of peak serum levels in most patients. Polman et al. (1994) reported

drug-related occurrence of one case of hepatitis after 6 months of treatment and one case of epileptic seizure after 18 months of treatment among 31 patients exposed to doses of up to 0.5 mg/kg-day for 6 to 32 months.

4-Aminopyridine has been clinically tested for treatment of SCI. There is no comprehensive review of the literature on this therapeutic use, but a review of information in a recent publication (Hayes et al., 2003) indicates that there is published information on oral dosing with immediate-release (at least 6 studies) and sustained-release (at least 2 studies) formulations. The most common side effects in SCI patients appear to be light-headedness and paresthesia. Hayes et al. (2003) characterized the side effects following controlled doses of 4-aminopyridine as predictable, mild, and transient. Side effects were reported to be temporally associated with peak plasma levels (but oftentimes lagging) following doses of 10-25 mg.

Study data on the adverse effects of 4-aminopyridine in healthy individuals are limited. Hayes et al. (2003) examined the pharmacokinetics and side effects of an immediate release oral formulation of 4-aminopyridine in normal subjects and subjects with SCI. Eight healthy young male subjects (age 20-26 years) provided informed consent to participate in a double-blind, randomized, placebo-controlled trial of an immediate release formulation of 4-aminopyridine. Six subjects were randomly assigned to receive immediate release 4-aminopyridine at escalating doses of 10, 15, 20, and 25 mg (gelatin capsules; triturated with lactose) with a one-week wash-out interval between each dose. Two subjects received a placebo capsule formulated without 4-aminopyridine. Based on a reported mean body weight of 81.2 kg for the subjects receiving 4-aminopyridine, the administered doses correspond to 0.12, 0.18, 0.25, and 0.31 mg/kg. The most commonly reported adverse effects included light-headedness (placebo: 2/2 subjects, dosed: 6/6 subjects), dysesthesias (0/2, 5/6), and dizziness (0/2, 3/6). Other effects noted in the dosed normal subjects but not in those receiving the placebo included abdominal discomfort (1/6), nausea (1/6), paresthesias (1/6), rash (1/6), and stomach discomfort (1/6). The specific doses at which these effects occurred were not reported. All adverse events were reported to be mild or moderate in severity (criteria not provided), were transient, and resolved spontaneously. There were no deaths, serious adverse events, or notable changes in ECGs, clinical laboratory tests, or vital signs. The period of observation was not reported.

No studies were located in which humans were exposed to 4-aminopyridine by inhalation.

Animal Studies

Mitsov and Uzunov (1972) treated male and female rats (10 rats/sex) with 4-aminopyridine by IP (interperitoneal) injection for 1-6 months. The only histopathologic changes noted in the 1-month study were a dose-related “plethora of the capillaries” in the myocardial interstitium and cerebral edema. In the 6-month study, dose-related parenchymatous degeneration and fatty degeneration of the liver were observed.

In an unpublished, proprietary oral exposure study reported by Cervenka and Vega (1968) and summarized by U.S. EPA (1980, 1989), unspecified numbers of male and female beagle dogs were fed diets containing 4-aminopyridine at concentrations of 0, 200, 2000, or 4000-6500 ppm for 90 days. These concentrations provided doses of 0.1, 1.0, or ≥2-3.25 mg/kg-day (U.S. EPA, 1980). At the highest dose, the dogs exhibited salivation and muscular weakness, but did not develop compound-related histopathological lesions. No dose-related trends occurred in mean organ weights, although male and female dogs given the intermediate or high doses had decreased brain weights. Blood and urine parameters were reported to be comparable in treated and control animals. The results of this study indicate that ≥2mg/kg-day is an adverse effect level, but it is unclear from the limited information available whether the slight and non-dose-related decrease in brain weight at 1.0 mg/kg-day should be regarded as an adverse effect.

Houston and Pleuvry (1984) reported gross ataxia in >40% of mice given an IP injection of 4-aminopyridine at 1.6 mg/kg. Convulsions were also reported in an unspecified number of mice.

In an unpublished, proprietary oral exposure study reported by Kohn (1968) and summarized by U.S. EPA (1980, 1989), male and female rats were fed 4-aminopyridine in the diet at concentrations of 3, 30, or 300 ppm for 90 days. No control data were reported for this study. Assuming that rats consumed an amount of food equivalent to 5% of their body weight per day, these dietary concentrations correspond to doses of 0.15, 1.5, and 15 mg/kg-day. Rats consuming the 300 ppm diet were hyperirritable to noise and touch. Males had increased liver weights and females had increased brain weights. Gross and histopathologic examinations did not reveal significant changes. No changes in blood and urinalysis were reported. Additional information in Confidential Business Information (CBI) files for the study indicates that sporadic hyperirritability occurred at 30 ppm. No effects were noted in rats fed the 3 ppm diet. The NOAEL and LOAEL for this study are 3 ppm (0.15 mg/kg-day) and 30 ppm (1.5 mg/kg-day), respectively. This study was completed by Industrial Biotest Laboratories prior to implementation of GLP (Good Laboratory Practices) regulation. This contractor was subsequently determined to have fraudulently reported test results.

No studies were located in which animals were exposed to 4-aminopyridine by inhalation.

No data are available on the reproductive or developmental toxicity of 4-aminopyridine by the oral or inhalation routes. Mitsov and Uzunov (1972) did not observe malformations in offspring born to rats treated by intraperitoneal injection with 1 or 5 mg/kg-day for 1 month or with 1 or 4 mg/kg-day for 6 months. However, only 12 offspring from treated rats and 7 offspring from control rats were born from an unspecified number of pregnancies.

Other Studies

The mutagenicity of 4-aminopyridine has been tested in reverse mutation assays in *Salmonella typhimurium*. Ogawa et al. (1986) obtained negative results for mutagenicity of 4-aminopyridine in *S. typhimurium* strains TA98, TA100, TA1537, and TA2637 when tested alone or in the presence of cobalt (II) chloride (cobalt chloride was tested because it was found to enhance the mutagenicity of other heteroaromatic compounds). Wakabayashi et al. (1982) obtained negative results in strains TA98 and TA100 at 4-aminopyridine concentrations up to 2 mg per plate when tested in the presence or absence of S9 hepatic homogenates or in the presence of tryptophan pyrolysate.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR 4-AMINOPYRIDINE

No human data appropriate for derivation of provisional subchronic or chronic RfDs for 4-aminopyridine are available. Human data are available from clinical trials in informed, health-compromised individuals, but were not considered appropriate for derivation of provisional RfDs, because the responses in health-compromised individuals may not be representative of the general population. For example, absorption rates in SCI patients appear to be injury-level dependent and enterohepatic recirculation may be prolonged (Segal et al., 2000). Clinical trial data from healthy individuals are limited and no data were identified that would be adequate for derivation of provisional subchronic or chronic RfDs.

Animal toxicity data on 4-aminopyridine are also limited. No published subchronic or chronic data are available. Limited data are available from two unpublished proprietary studies of subchronic duration (Kohn, 1968; Cervenka and Vega, 1968) based on descriptions in secondary sources (U.S. EPA, 1980, 1989). The original study reports summarizing these studies are not available for review. The previously developed RfD from the source HEED (U.S. EPA, 1989) concluded that confidence in the RfD was low and not defensible based on the limited details available, including lack of control data and limited experimental details and data in the unpublished proprietary studies, and should be regarded as preliminary until additional data are available. Previously developed indefensible RfDs in the HEED are not being used. Therefore, the available data on 4-aminopyridine are regarded as too limited for derivation of provisional RfD values.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfC VALUES FOR 4-AMINOPYRIDINE

There are no human or animal inhalation data available for 4-aminopyridine. Derivation of provisional subchronic or chronic inhalation RfC values is precluded by lack of data.

DERIVATION OF A PROVISIONAL CARCINOGENICITY ASSESSMENT FOR 4-AMINOPYRIDINE

There are no human or animal carcinogenicity data for 4-aminopyridine. Genotoxicity data indicate that this chemical is not mutagenic in bacteria, with or without metabolic activation or in the presence of cobalt. Under the U.S. EPA (2005) cancer guidelines, the available data on 4-aminopyridine are inadequate for an assessment of human carcinogenic potential.

Derivation of quantitative estimates of cancer risk for 4-aminopyridine is precluded by the absence of carcinogenicity data for this chemical.

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