PB91-216333

Health and Environmental Effects Document for 4-Aminopyridine

(U.S.) Environmental Protection Agency, Cincinnati, OH

Jan 89

U.S. Department of Commerce
National Technical Information Service
NTIS

TECHNICAL REPORT DATA
(Please read Instructions on the reverse before complet

1. REPORT NO. EPA/600/8-89/050	2.	3. PB91-216333
4. TITLE AND SUBTITLE Health and Environmental Effects Document for 4-Aminopyridine		5. REPORT DATE January 1989
		6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S)		8. PERFORMING ORGANIZATION REPORT NO.
9. PERFORMING ORGANIZATION NAME AND ADDRESS		10. PROGRAM ELEMENT NO.
		11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS Environmental Criteria and Assessment Office Office of Research and Development U.S. Environmental Protection Agency Cincinnati, OH 45268		13. TYPE OF REPORT AND PERIOD COVERED
		14. SPONSORING AGENCY CODE EPA/600/22

15. SUPPLEMENTARY NOTES

16. ABSTRACT

Health and Environmental Effects Documents (HEEDS) are prepared for the Office of Solid Waste and Emergency Response (OSWER). This document series is intended to support listings under the Resource Conservation and Recovery Act (RCRA) as well as to provide health-related limits and goals for emergency and remedial actions under the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency Program Office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Several quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Reference Doses (RfDs) for chronic and subchronic exposures for both the inhalation and oral exposures. In the case of suspected carcinogens, RfDs may not be estimated. Instead, a carcinogenic potency factor, or q_1*, is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively. Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group

18. DISTRIBUTION STATEMENT Public	19. SECURITY CLASS (This Report) Unclassified	21. NO. OF PAGES 72
	20. SECURITY CLASS (This page) Unclassified	22. PRICE

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

PB91-216333

EPA/600/8-89/050
January 1989

HEALTH AND ENVIRONMENTAL EFFECTS DOCUMENT FOR 4-AMINOPYRIDINE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
CINCINNATI, OH 45268

DISCLAIMER

This document has been reviewed in accordance with the U.S. Environmental Protection Agency's peer and administrative review policies and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

PREFACE

Health and Environmental Effects Documents (HEEDs) are prepared for the Office of Solid Waste and Emergency Response (OSWER). This document series is intended to support listings under the Resource Conservation and Recovery Act (RCRA) as well as to provide health-related limits and goals for emergency and remedial actions under the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained for Agency Program Office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched for in this document and the dates searched are included in "Appendix: Literature Searched." Literature search material is current up to 8 months previous to the final draft date listed on the front cover. Final draft document dates (front cover) reflect the date the document is sent to the Program Officer (OSWER).

Several quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Reference doses (RfDs) for chronic and subchronic exposures for both the inhalation and oral exposures. The subchronic or partial lifetime RfD, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval i.e., for an interval that does not constitute a significant portion of the lifespan. This type of exposure estimate has not been extensively used, or rigorously defined as previous risk assessment efforts have focused primarily on lifetime exposure scenarios. Animal data used for subchronic estimates generally reflect exposure durations of 30-90 days. The general methodology for estimating subchronic RfDs is the same as traditionally employed for chronic estimates, except that subchronic data are utilized when available.

In the case of suspected carcinogens, RfDs are not estimated. Instead, a carcinogenic potency factor, or q_1^* (U.S. EPA, 1980a), is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity, and acute mammalian toxicity). Chemical-specific RQs reflect the lowest of these six primary criteria. The methodology for chronic toxicity and cancer based RQs are defined in U.S. EPA, 1984 and 1986b, respectively.

EXECUTIVE SUMMARY

4-Aminopyridine is an odorless, white crystalline compound that is stable to light. It is moderately soluble in water (Farm Chemicals Handbook, 1987). The compound is manufactured by Reilly Tar & Chemical Corporation (Indianapolis, IN) by a synthetic process (SRI, 1987); recent production figures are not available.

4-Aminopyridine, sold under the trade name Avitrol, is used as a registered bird repellent (Farm Chemicals Handbook, 1987; Hadler, 1982). Ingestion of 4-aminopyridine-laden bait by birds results in aberrant behavior that frightens away other flock members (Hadler, 1982; Carlson, 1984). 4-Aminopyridine can also be used as a chemical intermediate (Hawley, 1981).

When released to the atmosphere, 4-aminopyridine can be expected to exist partly in the gas-phase where it will be degraded rapidly by reaction with photochemically-produced hydroxyl radicals. Using the method of Atkinson (1987), the half-life for this reaction in a typical ambient atmosphere can be estimated to be 8 hours. Because 4-aminopyridine has very low volatility from soil (Sims and Sommers, 1985,1986) or water, however, it is not expected to partition significantly to air when released to soil or water. By analogy to aromatic amines as a chemical class (Mill and Mabey, 1985), 4-aminopyridine may undergo significant degradation in sunlit natural water by reaction with photochemically-generated free radicals. Although 4-aminopyridine is soluble in water, significant partitioning from the water column to suspended solids and sediment may occur because of a covalent binding reaction that has been observed in other aromatic amines (Parris, 1980). Hydrolysis, direct photolysis and bioconcentration may not be

important. The degradation of 4-aminopyridine in soil has been studied by several investigators (Naik et al., 1972; Betts et al., 1976; Starr and Cunningham, 1975; Sims and Sommers, 1985, 1986). Although the biodegradation in soil can vary greatly, their results indicate that 4-aminopyridine is generally resistant to biodegradation in soil. Soil half-lives ranging from 3 months to >22 months have been observed (Starr and Cunningham, 1975). Soil column leaching studies have shown that 4-amino-pyridine is not leached significantly in either alkaline or acidic soils, although mobility in alkaline soils is slightly greater (Starr and Cunningham, 1975).

4-Aminopyridine is released directly to the environment (primarily soil) through its use as a bird repellent. Environmental releases from waste streams or fugitive emissions from the manufacture of 4-aminopyridine or its use as a chemical intermediate may be minor in relation to its use as a bird repellent. From a NIOSH survey (NOES) conducted between 1981 and 1983, it has been estimated that annually about 898 U.S. workers are potentially exposed to 4-amino-pyridine (NIOSH, 1985). Pertinent water, food, air or dermal monitoring data were not located in the available literature cited in Appendix A.

Studies assessing the acute toxicity of 4-aminopyridine to fish revealed that toxicity was not dependent on water temperature or hardness. The 96-hour LC_{50}s for channel catfish and bluegill sunfish exposed to 4-amino-pyridine ranged from 2.43-7.56 mg/ℓ (Schafer and Marking, 1975). The toxicity of 4-aminopyridine to aquatic invertebrates was assessed by Marking and Chandler (1981). Juvenile glass shrimp were the most sensitive species tested (96-hour LC_{50}=0.37 mg/ℓ), followed by mayfly nymphs (0.58 mg/ℓ), crayfish (2.2 mg/ℓ), frog larvae (2.4 mg/ℓ), water fleas (3.2

mg/ℓ), caddisfly larvae (15 mg/ℓ), Asiatic clams (45 mg/ℓ) and snails (62 mg/ℓ). The NOEC for larval frogs appears to be ≤1 mg/ℓ (Marking and Chandler, 1981).

The toxicity of 4-aminopyridine to birds was studied extensively by a series of investigators. Oral LD_{50} values ranged from 2.4-35 mg/kg for periods of exposure and observation of varying lengths. There was no evidence that reproduction among the progeny of 4-aminopyridine-treated birds was affected by treatment of the parents (Schafer et al., 1975). There was no evidence of secondary hazard potential among predatory birds from the consumption of 4-aminopyridine-killed birds (Holler and Schafer, 1982).

Pharmacokinetic data in humans indicate that 4-aminopyridine is absorbed readily and nearly completely from the gastrointestinal tract (Uges et al., 1982). 4-Aminopyridine appears to distribute widely throughout the tissues (Rupp et al., 1983), but excretion data (Uges et al., 1982) suggest that bioaccumulation does not occur in humans. Metabolites have not been found in the urine of humans treated with 4-aminopyridine, and biotransformation appears unlikely (Uges et al., 1982). In a study using volunteers (Uges et al., 1982), ~85% of an oral dose and 90% of an intravenous dose of 4-aminopyridine was recovered in the urine, with an elimination half-life of 3.6 hours.

4-Aminopyridine acts on the nervous system to increase the release of acetylcholine. The compound has been used in humans for the reversal of residual neuromuscular blockade from some neuromuscular blocking agents and antibiotics. Experimental uses include treatment of patients with Botulinus intoxication, myoneural disorders and Alzheimer's disease. The clinical use of 4-aminopyridine is limited by its narrow therapeutic index; following a clinical dose of 0.15-0.3 mg/kg (route not specified), the only side effects

noted were a slight increase in systolic blood pressure and heart rate, while doses >0.5 mg/kg were likely to result in restlessness, confusion, nausea, weakness and tonic-clonic seizures (Agoston et al., 1985). A case report of an accidental oral exposure (Spyker et al., 1980) indicated that a single dose of ~0.6 mg/kg results in frank effects in humans.

The only data concerning the subchronic oral toxicity of 4-aminopyridine are two 90-day studies in the OPP CBI files summarized by U.S. EPA (1980b). Kohn (1968) observed hyperirritability in rats at dietary concentrations of 30 and 300 ppm 4-aminopyridine, with no effects noted at 3 ppm. In dogs (Cervenka and Vega, 1968), salivation, muscular weakness and decreased brainweight were observed at a doses of ≥1.0 mg/kg/day.

4-Aminopyridine has tested negative for reverse mutation in Salmonella typhimurium (Ogawa et al., 1986; Wakabayshi et al., 1982). Data concerning the carcinogenicity, reproductive effects and toxicity of 4-aminopyridine following inhalation or chronic oral exposure were not available in the literature cited in Appendix A. No effects on reproduction or fetal development were reported in rats treated with 1-5 mg/kg/day by intraperitoneal injection for 1 or 6 months (Mitsov and Uzunov, 1972).

The only available guideline or standard for 4-aminopyridine is an RQ of 1000 pounds (U.S. EPA, 1985).

Because of the lack of data concerning carcinogenicity in humans and animals, 4-aminopyridine can be classified as a CAG Group D chemical. The derivation of carcinogenic potency factors and a cancer-based RQ is precluded by the lack of carcinogenicity data. Based on the 90-day rat study by Kohn (1968), subchronic and chronic oral RfDs of 0.0002 mg/kg/day (0.01 mg/day) and 0.00002 mg/kg/day (0.001 mg/day) were calculated. These RfDs should be considered tentative because only limited information concerning the CBI studies (Cervenka and Vega, 1968; Kohn, 1968) were available.

Based on low confidence in the study and the data base, confidence in these RfDs is low. Data were insufficient for the development of freshwater and saltwater criteria for 4-aminopyridine. A chronic toxicity RQ for 4-aminopyridine of 100 pounds was calculated from the Kohn (1968) 90-day rat study.

TABLE OF CONTENTS

		Page
1.	INTRODUCTION	1
1.1.	STRUCTURE AND CAS NUMBER	1
1.2.	PHYSICAL AND CHEMICAL PROPERTIES	1
1.3.	PRODUCTION DATA	2
1.4.	USE DATA	2
1.5.	SUMMARY	3
2.	ENVIRONMENTAL FATE AND TRANSPORT	4
2.1.	AIR	4
2.1.1.	Reaction with Hydroxyl Radicals	4
2.1.2.	Physical Removal Processes	4
2.2.	WATER	4
2.2.1.	Hydrolysis	4
2.2.2.	Oxidation	4
2.2.3.	Photolysis	5
2.2.4.	Microbial Degradation	5
2.2.5.	Volatilization	5
2.2.6.	Adsorption	5
2.2.7.	Bioconcentration	6
2.3.	SOIL	6
2.3.1.	Adsorption	6
2.3.2.	Microbial Degradation/Persistence	7
2.3.3.	Volatilization	8
2.4.	SUMMARY	8
3.	EXPOSURE	10
3.1.	WATER	10
3.2.	FOOD	10
3.3.	AIR	10
3.4.	DERMAL	10
3.5.	SUMMARY	10
4.	ENVIRONMENTAL TOXICOLOGY	12
4.1.	AQUATIC TOXICOLOGY	12
4.1.1.	Acute Toxic Effects on Fauna	12
4.1.2.	Chronic Effects on Fauna	13
4.1.3.	Effects on Flora	14
4.1.4.	Effects on Bacteria	14

TABLE OF CONTENTS (cont.)

		Page
4.2.	TERRESTRIAL TOXICOLOGY	14
4.2.1.	Effects on Fauna	14
4.2.2.	Effects on Flora	22
4.3.	FIELD STUDIES	22
4.4.	SUMMARY	22
5.	PHARMACOKINETCS	23
5.1.	ABSORPTION	23
5.2.	DISTRIBUTION	23
5.3.	METABOLISM	24
5.4.	EXCRETION	24
5.5.	SUMMARY	25
6.	EFFECTS	27
6.1.	SYSTEMIC TOXICITY	27
6.1.1.	Inhalation Exposure	27
6.1.2.	Oral Exposure	27
6.1.3.	Other Relevant Information	28
6.2.	CARCINOGENICITY	31
6.3.	MUTAGENICITY	31
6.4.	TERATOGENICITY	31
6.5.	OTHER REPRODUCTIVE EFFECTS	31
6.6.	SUMMARY	31
7.	EXISTING GUIDELINES AND STANDARDS	34
7.1.	HUMAN	34
7.2.	AQUATIC	34
8.	RISK ASSESSMENT	35
8.1.	CARCINOGENICITY	35
8.1.1.	Weight of Evidence	35
8.1.2.	Quantitative Risk Estimates	35
8.2.	SYSTEMIC TOXICITY	35
8.2.1.	Inhalation Exposure	35
8.2.2.	Oral Exposure	35
8.3.	AQUATIC	38

TABLE OF CONTENTS (cont.)

	Page
9. REPORTABLE QUANTITIES	40
9.1. BASED ON SYSTEMIC TOXICITY	40
9.2. BASED ON CARCINOGENICITY	40
10. REFERENCES	45
APPENDIX A: LITERATURE SEARCHED	55
APPENDIX B: SUMMARY TABLE FOR 4-AMINOPYRIDINE	58

LIST OF TABLES

No.	Title	Page
4-1	Acute Toxicity of 4-Aminopyridine to 36 Species of Birds. . .	15
6-1	Acute Toxicity of 4-Aminopyridine to Mammals.	30
6-2	Mutagenic Testing of 4-Aminopyridine.	32
9-1	Oral Toxicity Data for 4-Aminopyridine.	41
9-2	Composite Scores for 4-Aminopyridine Based on Oral Toxicity .	42
9-3	Minimum Effective Dose (MED) and Reportable Quantity (RQ) . .	43

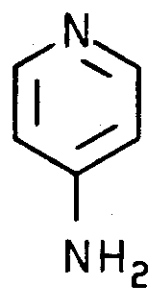
LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
BCF	Bioconcentration factor
CAS	Chemical Abstract Service
CNS	Central nervous system
CS	Composite score
FEL	Frank effect level
GMAV	Genus mean acute value
HCl	Hydrochloride salt
K_{ow}	Octanol/water partition coefficient
LC_{50}	Concentration lethal to 50% of recipients (and all other subscripted dose levels)
LD_{50}	Dose lethal to 50% of recipients
LOAEL	Lowest-observed-adverse-effect level
MED	Minimum effect dose
NOAEL	No-observed-adverse-effect level
NOEC	No-observed-effect concentration
NOEL	No-observed-effect level
NOES	National Occupational Exposure Survey
pKa	Negative $\log_{10}$ of dissociation constant
ppm	Parts per million
RBC	Red blood cell
RfD	Reference dose
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
TLC	Thin layer chromatography
WBC	White blood cell

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

4-Aminopyridine is a common chemical name for the compound currently referenced by CAS as 4-pyridinamine (SANSS, 1988). Other synonyms for 4-aminopyridine include 4-AP, p-aminopyridine, amino-4-pyridine, gamma-pyridylamine and 4-pyridylamine (SANSS, 1988). It is also known by the tradename Avitrol (Farm Chemicals Handbook, 1987). The structure, molecular weight, empirical formula and CAS Registry number for 4-aminopyridine are as follows:



Molecular weight: 94.12

Empirical formula: $C_5H_6N_2$

CAS Registry number: 504-24-5

1.2. PHYSICAL AND CHEMICAL PROPERTIES

4-Aminopyridine is an odorless, white crystalline compound that is stable to light and moderately soluble in water (Farm Chemicals Handbook, 1987). It is soluble in alcohol, ether and benzene (Weast, 1985). Selected physical properties are as follows:

Melting point:	158-9°C	Weast, 1985
Boiling point:	273.5°C	Hawley, 1981
Vapor pressure:		
at 180°C	13 mm Hg	Weast, 1985
at 25°C (estimated)	0.00122 mm Hg	U.S. EPA, 1987
Water solubility:		
at 25°C	76,600-83,000 ppm	U.S. EPA/NIH, 1988

Log K_{ow}:	0.26	Hansch and Leo, 1985
pKa at 25°C	9.11	Weast, 1985
Air conversion factors (25°C):	mg/m^3 = 3.9 ppm ppm = 0.26 mg/m^3	

In general, the aminopyridines react with alkylating agents at the aromatic nitrogen to give derivatives (Goe, 1982). With a pKa of 9.11 at 25°C (Weast, 1985), 4-aminopyridine is a strong base in aqueous solution (U.S. EPA/NIH, 1988).

1.3. PRODUCTION DATA

4-Aminopyridine is manufactured by Reilly Tar & Chemical Corporation (Indianapolis, IN), which produces a wide range of pyridine compounds by synthetic processes (SRI, 1987). 4-Aminopyridine can be produced by the hydrogenation of 4-nitro pyridine-N-oxide in the presence of a Raney-nickel or palladium-carbon catalyst (Goe, 1982).

Recent production figures for 4-aminopyridine were not located. Reilly Tar & Chemical Corporation sells 4-aminopyridine (97% minimum purity) in packages ranging from 1 kg cans to 55 gallon drums (Kuney, 1986). The U.S. EPA TSCA Production File for 1977 (U.S. EPA, 1977) cites Reilly Tar & Chemical Corp. as the only U.S. manufacturer of 4-aminopyridine; however, their 1977 production volume is listed as confidential.

1.4. USE DATA

4-Aminopyridine, sold under the trade name Avitrol, is used as a bird repellent (Farm Chemicals Handbook, 1987; Hadler, 1982). When ingested from bait, 4-aminopyridine acts as a soporific, causing birds to utter distress calls and fly in uncoordinated and spiral patterns. This aberrant behavior frightens other feeding flock members away from the crop area (Hadler, 1982; Carlson, 1984). Some or all applications of Avitrol may be classified by

the U.S. EPA as a registered pesticide. It is used to control crows, pigeons, grackles, starlings, sparrows, cowbirds, gulls and blackbirds in and around structures and agricultures (sunflowers, field corn, sweet corn). It is applied in grain baits that contain 0.5-3.0% 4-aminopyridine or 25-50% powder concentrate (Farm Chemicals Handbook, 1987). 4-Aminopyridine can also be used as an intermediate (Hawley, 1981).

1.5. SUMMARY

4-Aminopyridine is an odorless, white crystalline compound that is stable to light. It is moderately soluble in water (Farm Chemicals Handbook, 1987). The compound is manufactured by Reilly Tar & Chemical Corporation (Indianapolis, IN) by a synthetic process (SRI, 1987); recent production figures are not available.

4-Aminopyridine, sold under the trade name Avitrol, is used as a registered bird repellent (Farm Chemicals Handbook, 1987; Hadler, 1982). Ingestion of 4-aminopyridine-laden bait by birds results in aberrant behavior that frightens away other flock members (Hadler, 1982; Carlson, 1984). 4-Aminopyridine can also be used as an intermediate (Hawley, 1981).

2. ENVIRONMENTAL FATE AND TRANSPORT

2.1. AIR

Organic compounds having vapor pressures >0.0001 mm Hg are expected to exist almost entirely in the vapor phase in the ambient atmosphere (Eisenreich et al., 1981). Based on an estimated vapor pressure of 0.00122 mm Hg at 25°C (U.S. EPA, 1987), 4-aminopyridine can be expected to exist in the vapor phase in ambient air.

2.1.1. **Reaction with Hydroxyl Radicals.** Using the method of Atkinson (1987), the rate constant for the vapor phase reaction of 4-aminopyridine with photochemically produced hydroxyl radicals can be estimated to be 47.9×10^{-12} cm^3/molecule-sec at 25°C. Assuming a typical ambient atmospheric hydroxyl radical concentration of $5 \times 10^{+5}$ molecules/cm^3 (Atkinson, 1985), the half-life for this reaction can be estimated to be ~8 hours. Thus, reaction with hydroxyl radicals is expected to cause rapid loss of 4-aminopyridine in the atmosphere.

2.1.2. **Physical Removal Processes.** 4-Aminopyridine is soluble in water (Weast, 1985); therefore, removal of the free base or its salts from the atmosphere by wet deposition processes (rainfall, etc.) may be possible. If the salts of this compound exist in particulate form in the atmosphere, they may be partly removed by dry deposition.

2.2. WATER

2.2.1. **Hydrolysis.** Aromatic amines are generally resistant to aqueous environmental hydrolysis (Harris, 1982). Therefore, 4-aminopyridine is not expected to hydrolyze significantly in water.

2.2.2. **Oxidation.** As a chemical class, aromatic amines can react relatively rapidly in sunlit natural water by reaction with photochemically-generated free radicals such as hydroxyl radicals and peroxy radicals (Mill

and Mabey, 1985). Typical half-lives for the reaction of aromatic amines with hydroxyl and peroxy radicals on the surface of natural water are ~30 and 19.2 hours, respectively, (Mill and Mabey, 1985). Although photooxidation rate constants specifically for 4-aminopyridine are not available, the data cited above suggest that photooxidation of 4-aminopyridine in natural water may be an important loss process.

2.2.3. Photolysis. 4-Aminopyridine is reported to be stable to light (Farm Chemicals Handbook, 1987); therefore, direct photolysis is not expected to be significant in the environment. As noted above, however, 4-aminopyridine may react relatively rapidly with oxidants formed by sunlight in natural water.

2.2.4. Microbial Degradation. Pertinent data regarding the microbial degradation of 4-aminopyridine in water could not be located in the available literature as cited in Appendix A. Based on the soil degradation data presented in Section 2.3., however, 4-aminopyridine may be resistant or only slowly biodegradable by microbes in water.

2.2.5. Volatilization. Using the chemical bond estimation method of Hine and Mookerjee (1975), the Henry's Law constant for 4-aminopyridine can be estimated to be 2.81×10^{-9} atm-m³/mol at 25°C. This value of Henry's Law constant indicates that volatilization from water is not environmentally important (Thomas, 1982).

2.2.6. Adsorption. Experimental data regarding the adsorption of 4-aminopyridine to suspended solids and sediment in water could not be located in the available literature as cited in Appendix A. Although 4-aminopyridine is soluble in water, the adsorption/leaching data presented in Section 2.3. suggest that some partitioning from the water column to humic materials present in suspended solids and sediment may occur as a result of covalent binding.

2.2.7. **Bioconcentration.** The BCF of an organic chemical may be estimated from the equations (Bysshe, 1982),

$$\log BCF = 0.76 \log K_{ow} - 0.23 \text{ and} \quad (2\text{-}1)$$

$$\log BCF = 2.791 - 0.564 \log \text{water solubility (in ppm)} \quad (2\text{-}2)$$

Based on a log K_{ow} of 0.26 (Hansch and Leo, 1985) and a water solubility of ~80,000 ppm at 25°C (U.S. EPA/NIH, 1988), the BCF for 4-aminopyridine can be estimated from both equations to be ~1. This indicates that bioconcentration in aquatic organisms may not be significant.

2.3. SOIL

2.3.1. **Adsorption.** Starr and Cunningham (1975) measured the leaching of ^{14}C alpha-labeled 4-aminopyridine in three alkaline soils (pH 7.6-7.8) and four acidic soils (pH 4.1-5.8). The leaching tests were conducted using 15 cm long soil columns that received an initial surface application of the 4-aminopyridine. Over a 20-day period, 1-7 inches of simulated rainfall were applied to each column. Sufficient water was applied every 2-3 days to produce an effluent from the bottom of each column. At the end of the 20-day period, only 0.02-0.18% of the applied radioactivity had been recovered in the effluents from the alkaline soils, while <0.01% was recovered in the effluents from the acidic soils. Examination of the soil columns after the 20-day period indicated that 95-99% of the radioactivity applied to the alkaline soils had remained in the upper 1-inch layer of soil and that essentially all of radioactivity applied to the acidic soils was in the upper 1-inch layer. These tests clearly demonstrated that 4-aminopyridine may remain adsorbed strongly onto soil colloids; therefore, significant leaching is not expected to occur in most soils.

Aromatic amines have been observed to undergo rapid and reversible covalent binding with humic materials in aqueous solution (Parris, 1980). The initial fast reaction of the amine group with carbonyl of humate to form imine linkoyd is followed by a slower and much less reversible reaction believed to represent the addition of the amine to quinoidal structures, followed by oxidation of the product to give an amino-substituted quinone. These processes represent pathways by which aromatic amines may be converted to latent forms in the biosphere (Parris, 1980). This covalent binding may account for the strong adsorption observed by Starr and Cunningham (1975) in their soil column leaching studies.

2.3.2. Microbial Degradation/Persistence. The degradation of 4-aminopyridine in soil has been studied by several investigators (Naik et al., 1972; Betts et al., 1976; Starr and Cunningham, 1975; Sims and Sommers, 1985, 1986). Their results indicate that 4-aminopyridine is not rapidly destroyed in soil, and may be relatively persistent.

Naik et al. (1972) examined the degradation of 4-aminopyridine in enrichment cultures using a 1 mM solution of the chemical and a 0.5% aqueous solution of fertile garden soil as the inocula. The disappearance of applied 4-aminopyridine required >170 days under both aerobic and anaerobic conditions. The authors concluded that aminopyridine is resistant to microbial attack.

Betts et al. (1976) examined the degradation of ^{14}C-labelled 4-aminopyridine in three different soils and in pure cultures of five soil microorganisms. In aerobic soil degradation experiments, a lag period of ~20 days was required before a significant rate of $^{14}CO_2$ evolution was observed in any of the soils. At the end of 60 days, 6-24% of the applied radioactivity had been recovered as $^{14}CO_2$. In 60-day flooded soil

tests, 21-24% of applied radioactivity was lost; however, the loss may have been due to binding to the soil in an unextractable form rather than to actual degradation. Pure cultures of five microorganisms isolated from soil were unable to metabolize 4-aminopyridine in 5-6 days of incubation.

Starr and Cunningham (1975) studied the degradation of ^{14}C-labeled 4-aminopyridine in various alkaline and acidic soils under varying conditions. Under anaerobic conditions, metabolization to $^{14}CO_2$ was negligible. Under aerobic conditions, a lag period of at least 1 week was required before significant conversion to $^{14}CO_2$ was observed. Metabolization rates varied significantly with soil type, temperature and moisture content. A 3-month CO_2 evolution rate at 30°C varied from 0.4% in an acidic (pH 4.1) loam soil to >50% in a lighter textured, alkaline (pH 7.8) loamy sand. The metabolization half-life of 4-aminopyridine in the soils tested ranged from ~3 months to >22 months.

Sims and Sommers (1985,1986) found 4-aminopyridine to be generally resistant to degradation in soil decomposition studies using a silt loam soil. Only ~6% degradation at an initial concentration of 2 mmol/kg was observed in 64 days. The authors suggested that this resistance to biodegradation may have been due to toxicity of the 4-aminopyridine to the microorganisms. In the Betts et al. (1976) pure culture study mentioned above, 4-aminopyridine was not toxic to the microorganisms, but also was not metabolized by the microorganisms.

2.3.3. Volatilization. Sims and Sommers (1985, 1986) reported that 4-aminopyridine has very low volatility from soil.

2.4. SUMMARY

When released to the atmosphere, 4-aminopyridine can be expected to exist partly in the gas-phase where it will be degraded rapidly by reaction

with photochemically-produced hydroxyl radicals. Using the method of Atkinson (1987), the half-life for this reaction in a typical ambient atmosphere can be estimated to be 8 hours. Because 4-aminopyridine has very low volatility from soil (Sims and Sommers, 1985,1986) or water, however, it is not expected to partition significantly to air when released to soil or water. By analogy to aromatic amines as a chemical class (Mill and Mabey, 1985), 4-aminopyridine may undergo significant degradation in sunlit natural water by reaction with photochemically-generated free radicals. Although 4-aminopyridine is soluble in water, significant partitioning from the water column to suspended solids and sediment may occur because of a covalent binding reaction that has been observed in other aromatic amines (Parris, 1980). Hydrolysis, direct photolysis and bioconcentration may not be important. The degradation of 4-aminopyridine in soil has been studied by several investigators (Naik et al., 1972; Betts et al., 1976; Starr and Cunningham, 1975; Sims and Sommers, 1985, 1986). Although the biodegradation in soil can vary greatly, their results indicate that 4-aminopyridine is generally resistant to biodegradation in soil. Soil half-lives ranging from 3 months to >22 months have been observed (Starr and Cunningham, 1975). Soil column leaching studies have shown that 4-aminopyridine is not leached significantly in either alkaline or acidic soils, although mobility in alkaline soils is slightly greater (Starr and Cunningham, 1975).

3. EXPOSURE

4-Aminopyridine is released directly to the environment (primarily soil) through its use as a bird repellent. It is applied to crop fields in grain baits containing 0.5-3.0% 4-aminopyridine or as a 25-50% powder concentrate (Farm Chemicals Handbook, 1987). Environmental releases from waste streams or fugitive emissions from the manufacture of 4-aminopyridine or its use as a chemical intermediate may be minor in relation to its use as a bird repellent.

From the preliminary results of the NIOSH survey (NOES) conducted between 1981 and 1983, it has been estimated that 898 U.S. workers per year are potentially exposed to 4-aminopyridine (NIOSH, 1985).

3.1. WATER

Pertinent data regarding the monitoring of 4-aminopyridine in water could not be located in the available literature as cited in Appendix A.

3.2. FOOD

Pertinent data regarding the monitoring of 4-aminopyridine in food could not be located in the available literature as cited in Appendix A.

3.3. AIR

Pertinent data regarding the monitoring of 4-aminopyridine in air could not be located in the available literature as cited in Appendix A.

3.4. DERMAL

Pertinent data regarding dermal monitoring of 4-aminopyridine could not be located in the available literature as cited in Appendix A.

3.5. SUMMARY

4-Aminopyridine is released directly to the environment (primarily soil) through its use as a bird repellent. Environmental releases from waste

streams or fugitive emissions from the manufacture of 4-aminopyridine or itsuse as a chemical intermediate may be minor in relation to its use as a bird repellent. From a NIOSH survey (NOES) conducted between 1981 and 1983, it has been estimated that annually about 898 U.S. workers are potentially exposed to 4-aminopyridine (NIOSH, 1985). Pertinent water, food, air or dermal monitoring data could not be located in the available literature as cited in Appendix A.

4. ENVIRONMENTAL TOXICOLOGY

4.1. AQUATIC TOXICOLOGY

4.1.1. Acute Toxic Effects on Fauna. Schafer and Marking (1975) assessed the acute toxicity of 4-aminopyridine to channel catfish, Ictalurus punctatus, and bluegill sunfish, Lepomis macrochirus, at various temperatures and water hardnesses. Water hardness concentrations ranged from 10-13, 40-48, 160-180 and 280-320 mg/ℓ as $CaCO_3$ for very soft, soft, hard and very hard water, respectively. Toxcity of 4-aminopyridine to catfish varied by <2-fold based on variations in water hardness and temperature. The static acute 3-, 6-, 24- and 96-hour LC_{50}s (and 95% confidence limits) for channel catfish exposed to 4-aminopyridine at 22°C in soft water were 13.8 (12.3-15.5), 13.8 (12.3-15.5), 9.35 (8.3-10.6) and 5.8 mg/ℓ (5.2-6.4), respectively. Values for the 6-, 24- and 96-hour exposure periods for catfish in soft water at 17°C were 16.4 (13.8-19.4), 9.8 (8.6-11.2) and 4.36 mg/ℓ (3.9-4.8), respectively. Toxicity of 4-aminopyridine to catfish at 12°C ranged from 4.36 mg/ℓ (LC_{50}) in very hard water to 8.74 mg/ℓ (LC_{50}) in soft water after 24 hours. The 96-hour LC_{50}s ranged from 2.43 mg/ℓ in very hard water to 4.00 mg/ℓ in hard, soft and very soft water.

The 3-, 6-, 24- and 96-hour LC_{50}s (and 95% confidence limits) for bluegill sunfish exposed to 4-aminopyridine at 22°C in soft water were 18.1 (15.3-21.4), 15.0 (13.0-17.3), 12.3 (10.7-14.1) and 7.56 mg/ℓ (6.3-9.1), respectively. Values in soft water at 17°C were 18.1 (15.3-21.4), 16.2 (14.1-18.6), 11.8 (9.7-14.3) and 5.60 mg/ℓ (4.8-6.5), respectively. The 3-hour LC_{50} for sunfish at 12°C was identical in very soft and soft water (38.1 mg/ℓ). The 6-hour LC_{50}s in very soft, soft and hard water were 26, 23.2 and 38.1 mg/ℓ, respectively. The 24-hour LC_{50} ranged from 8.60

mg/ℓ in very hard water to 12.3 mg/ℓ in hard water. The 96-hour LC_{50} ranged from 2.82 mg/ℓ in hard water to 4.41 mg/ℓ in soft water (Schafer and Marking, 1975).

Marking and Chandler (1981) assessed the acute toxicity of 4-aminopyridine to a variety of aquatic invertebrates in static tests. All studies were conducted in reconstituted water with a hardness of ≤40 mg/ℓ as $CaCO_3$. Tests with mayfly nymphs, Isonychia sp., were conducted at 12°C. Tests with water fleas, Daphnia magna, were conducted at 21°C. All other tests were conducted at 16°C. The 6-, 24- and 96-hour LC_{50}s (and 95% confidence intervals) for D. magna were 24 (19-30), 17 (14-20) and 3.2 mg/ℓ (2.3-4.5), respectively. Values for glass shrimp, Palaemonetes kadiakensis, were 47 (32-70), 3.3 (2.3-4.6) and 0.37 mg/ℓ (0.25-0.56), respectively. Values for crayfish, Procambrus acutus acutus, were >60, 14 (11-18) and 2.2 mg/ℓ (1.7-2.8), respectively. Values for mayflys were 24 (20-28), 5.3 (3.9-7.2) and 0.58 mg/ℓ (0.45-0.74), respectively. Values for caddisfly larvae, Hydropsyche sp., were 99 (78-130), 30 (21-41) and 15 mg/ℓ (9.8-22), respectively. Values for frog larvae, Rana sphenocephala, were >30, 7.2 (6.6-7.8) and 2.4 mg/ℓ (2.0-2.9), respectively. The 24- and 96-hour LC_{50}s (and 95% confidence intervals) for adult Asiatic clams, Corbicula manilensis, were 78 (69-88) and 45 mg/ℓ (40-50), respectively. Values for adult river horn snail, Oxytrema catenaria, were >100 and 62 mg/ℓ (53-73), respectively.

4.1.2. Chronic Effects on Fauna.

4.1.2.1. TOXICITY -- Marking and Chandler (1981) assessed hatching success and larval survival of the leopard frog, Rana sphenocephala, upon exposure to 4-aminopyridine. Eggs were exposed to 4-aminopyridine within 16 hours after deposition at a temperature of 16°C under static conditions.

The exposures were continued until eggs hatched or development ceased. Hatching of control eggs required 9-11 days. The investigators reported a hatching success of <5% among eggs exposed to <10 mg/ℓ. Larval survival was ≥95% at 1 mg/ℓ but <5% at 2 mg/ℓ.

4.1.2.2. BIOACCUMULATION/BIOCONCENTRATION -- No measured steady-state BCF value for 4-aminopyridine was found in the literature. Based on the regression equation, log BCF = 0.76 log K_{ow} - 0.23 (Lyman et al., 1982) and a log K_{ow} value of 0.26 (see Section 1.2.), a BCF value of 0.93 is estimated for this compound. This value suggests that 4-aminopyridine will not bioaccumulate significantly in aquatic organisms.

4.1.3. Effects on Flora.

4.1.3.1. TOXICITY -- Pertinent data regarding the effects of chronic exposure of aquatic flora to 4-aminopyridine could not be located in the available literature as cited in Appendix A.

4.1.3.2. BIOCONCENTRATION -- Pertinent data regarding the bioconcentration of 4-aminopyridine by aquatic flora could not be located in the available literature as cited in Appendix A.

4.1.4. Effects on Bacteria. Pertinent data regarding the effects of exposure of aquatic bacteria to 4-aminopyridine could not be located in the available literature as cited in Appendix A.

4.2. TERRESTRIAL TOXICOLOGY

4.2.1. Effects on Fauna. Schafer et al. (1973a) summarized the existing information regarding the toxicity of 4-aminopyridine to birds (Table 4-1). Oral LD_{50} values ranged from 2.4 mg/kg for several species to 35 mg/kg for the domestic chicken, Gallus gallus. Only one study reported an intramuscular LD_{50}: 2.4 mg/kg for the red-winged blackbird, Agelaius phoeniceus. Dermal LD_{50}s reported for red-billed quelea, Quelea quelea, and sparrows, Passer domesticus, were both >100 mg/kg.

TABLE 4-1

Acute Toxicity of 4-Aminopyridine to 36 Species of Birds*

Species (mixed or unknown sex unless noted)	Route	Carrier	LD_{50}	95% Confidence Limits (mg/kg)
Scaled dove *Scardafella squammata*	per os	grain	>4	NR
Ruddy-breasted seedeater *Sporophila minuta*	per os	grain	<7.2	NR
Brown-throated parakeet *Aratinga pertinax*	per os	grain	~10	NR
Blue-black grassquit *Volatina jacarina*	per os	grain	10	5.6-18
Dickcissel *Spiza americana*	per os	grain	~10	NR
Orange-fronted parakeet *Aratinga canicularis*	per os	grain	~12	NR
Ruddy ground dove *Columbigallina talpacoti*	per os	grain	<25	NR
Shiny cowbird *Molothrus bonariensis*	per os	propylene glycol	<1.0	NR
Black-billed magpie *Pica pica*	per os	propylene glycol	2.4	NR

01240
09/19/88

TABLE 4-1 (cont.)

Species (mixed or unknown sex unless noted)	Route	Carrier	LD_{50}	95% Confidence Limits (mg/kg)
Common crow *Corvus brachyrhynchos*	per os	propylene glycol	2.4	NR
Yellow-billed magpie *Pica nuttalli*	per os	propylene glycol	2.4	NR
Common grackle *Quiscalus quiscula*	per os	propylene glycol	2.4	NR
Bronzed cowbird *Tangavius aeneus*	per os	propylene glycol	3.2	1.8-5.6
Mallard *Anas platyrhynchos*	per os	propylene glycol	4.2	NR
Robin *Turdus migratorius*	per os	propylene glycol	4.2	2.4-7.5
Brown-headed cowbird *Molothrus ater*	per os	propylene glycol	4.2	NR
Tricolored blackbird *Agelaius tricolor*	per os	propylene glycol	4.2	NR
Sparrow hawk *Falco sparverius*	per os	propylene glycol	5.6	4.2-7.5
Budgerigar *Melopsittacus undulatus*	per os	propylene glycol	5.6	NR

TABLE 4-1 (cont.)

Species (mixed or unknown sex unless noted)	Route	Carrier	LD_{50}	95% Confidence Limits (mg/kg)
House finch *Carpodacus mexicanus*	per os	propylene glycol	5.6	NR
Golden-crowned sparrow *Zonotrichia atricapilla*	per os	propylene glycol	5.6	3.2-10
White-crowned sparrow *Zonotrichia leucophrys*	per os	propylene glycol	5.6	3.2-10
Ring-necked pheasant *Phasianus colchicus* (4 weeks)	per os	propylene glycol	7.5	5.7-9.8
(female)	per os	propylene glycol	5.6	3.2-10
Coturnix quail *Coturnix coturnix* (male and female)	per os	propylene glycol	7.65	6.59-8.89
	per os	propylene glycol	8.05	7.01-9.24
Mourning dove *Zenaidura macroura*	per os	propylene glycol	8.1	7.5-10
Green jay *Cyanocorax yncas*	per os	propylene glycol	<10	NR
White-winged dove *Zenaida asiatica*	per os	propylene glycol	13	NR
Ring-billed gull *Larus delawarensis*	per os	water	8 (HCl)	NR
Bobwhite *Colinus virginianus*	per os	water	15 (HCl)	NR

TABLE 4-1 (cont.)

Species (mixed or unknown sex unless noted)	Route	Carrier	LD_{50}	95% Confidence Limits (mg/kg)
Starling *Sturnus vulgaris*	per os	water	14 (HCl)	NR
	per os	pellet	<6	NR
	per os	propylene glycol	4.9	3.6-6.6
Domestic chicken *Gallus gallus* (2-3 weeks)	per os	water	35 (HCl)	NR
	per os	water	15 (HCl)	NR
Red-winged blackbird *Agelaius phoeniceus* (male)	per os	water	8.5	NR
	per os	water	3.2 (HCl)	NR
	per os	propylene glycol	2.4	1.5-3.8
	intramuscular	propylene glycol	2.4	NR
Common pigeon *Columbia livia*	per os	water	20 (HCl)	NR
	per os	propylene glycol	7.5	NR
House sparrow *Passer domesticus*	per os	propylene glycol	7.5	NR
	per os	water	4.0	NR
	per os	water	3.8	NR
	per os	water	3.6	NR
	dermal	acetone	>100	NR
Red-billed quelea *Quelea quelea*	per os	propylene glycol	5.6	3.2-10
	dermal	acetone	>100	NR
Boat-tailed grackle *Cassidix mexicanus*	per os	propylene glycol	3.2	1.8-5.6
	per os	water	1.7-7.1	NR

*Source: Schafer et al., 1973a

NR = Not reported

Schafer et al. (1973b) reported the oral and dermal toxicity of 4-aminopyridine to quelea, Quelea quelea, house sparrows, Passer domesticus, and red-winged blackbirds, Agelaius phoeniceus. Oral toxicity was determined by per os administration of propylene glycol solutions from a microsyringe. Dermal toxicity was determined by applying acetone solutions to a sparsely feathered skin area. The acute oral LD_{50}s were 5.6, 7.5 and 2.4 mg/kg, respectively. The dermal LD_{50}s for quelea and sparrows were both >100 mg/kg. LD_{50}s were based on a 4-day observation period following a single dose of 4-aminopyridine.

Schafer and Marking (1975) assessed the effects of long-term exposure of bobwhite quail, Colinus virginianus, mourning dove, Zenaida macroura, ring-necked pheasant, Phasianus colchicus, quail, Coturnix coturnix, and starling, Sturnus vulgaris, to 4-aminopyridine. Acute oral LD_{50}s for quail, dove and female pheasant offered 3% 4-aminopyridine-contaminated bait (cracked corn) for 7-35 days were 15.0, 8.1 and 7.5 mg/kg, respectively. The acute oral LD_{50}s for quail offered 4-aminopyridine-contaminated feed ($\leq$1,000 ppm) for 28-40 days were 7.65 mg/kg for males and 8.05 mg/kg for females. An LD_{50} for doves offered contaminated feed could not be calculated because of an insufficient level of mortality. Treatment of starlings by gavage daily for 25 days with a propylene glycol solution containing a dose of 1.78 mg/kg 4-aminopyridine resulted in an acute oral LD_{50} of 4.9 mg/kg.

Schafer et al. (1975) assessed the effects of 4-aminopyridine on reproduction and survival in quail, Coturnix coturnix, in three separate studies. In the initial study, male and female birds were gavaged with a propylene glycol solution containing either 0 or 5.62 mg/kg 4-aminopyridine, then paired with untreated mates. All birds treated with 4-aminopyridine

exhibited hyperactivity, tremors and minor motor seizures within 4 hours of treatment, while two males died within 24 hours of treatment. Egg production by treated females was reduced significantly during the 3rd week of the study. Hatchability of eggs was not affected. In a second study, breeding pairs were fed a diet that contained 0-1,000 ppm 4-aminopyridine for 4 weeks. No effects were observed among birds fed ≤31.6 ppm 4-aminopyridine. There were no significant reproductive effects among birds fed 100 and 316 ppm 4-aminopyridine, although growth among males during the 4-week study was depressed and food consumption was reduced for the first 2 weeks in the 316 ppm dose group. All birds dosed with 1,000 ppm 4-aminopyridine died within 3 weeks. The 28-day LC_{50}s for male and female quail in this study were 447 and 562 ppm, respectively. In the third study, the F_1 progeny from the second study were mated when they reached sexual maturity; no effects on reproduction were observed among these birds.

Garrison et al. (1982) assessed the lethal and sublethal effects of 4-aminopyridine to three species of mannikins, Lonchura punctulata, Lonchura leucogaster and Lonchura malacca, and one species of sparrow, Passer montanus. Birds were dosed with various concentrations of 4-aminopyridine in propylene glycol using a 50 mL syringe with 4 cm polyethylene tubing attached to the needle. Four to six birds per treatment (species dependent) received a dose volume of 10 µL/10 g bw. The investigators reported LD_{50} values (and 95% confidence limits) of 7.94 (5.47-11.52), 3.11 (2.62-3.69), 4.45 (3.33-5.97) and 3.54 mg/kg (1.84-6.80) for L. punctulata, L. leucogaster, L. malacca and P. montanus, respectively. Garrison et al. (1982) reported that the average times from dosing with 5.0 mg/kg to the first distress call emitted by dosed birds were 33.8, 21.3, 52.8 and 23.0 minutes, respectively. The investigators also assessed the effects of

4-aminopyridine-treated grain on sparrows. Six birds were force-fed one kernel of rice treated with either 0.5 (4.4 mg/kg) or 1.0% (9.8 mg/kg) 4-aminopyridine. All birds demonstrated effects from the treatments within 30 minutes. The average times to mortality were 90 and 26 minutes, respectively.

Holler and Schafer (1982) assessed the hazards to sharp-shinned hawks, Accipter striatus, and American kestrels, Falco sparveirus, from the consumption of blackbirds killed with 4-aminopyridine. The food source for isolated hawks and kestrels was obtained by feeding caged blackbirds a 1% 4-aminopyridine bait diluted 1:1 or 1:9 or a 3% 4-aminopyridine bait diluted 1:99. Dead blackbirds were frozen at -20°C until needed. Hawks were offered two dead blackbirds/day for 7 days, while kestrels were offered one dead blackbird/day for 7 days. The investigators reported that there was no indication of secondary hazard potential to either of these predatory birds from the consumption of 4-aminopyridine-contaminated blackbirds.

Hudson et al. (1984) reported acute oral LD_{50}s for male mallard ducks, Anas platyrhynchos, offered products containing 95 and 99.9% 4-aminopyridine. The oral LD_{50}s (and 95% confidence limits) for 3- to 4-month-old ducks were 4.36 (3.36-5.66) and 5.19 mg/kg (4.00-6.73), respectively.

Sultana et al. (1986) determined the acute oral LD_{50} of 4-aminopyridine for rock dove, Columba livia, rose-ringed parakeets, Psittacula krameri, house sparrows, Passer domesticus, and white-backed munias, Lonchura striata. Birds were gavaged with propylene glycol solutions of 4-aminopyridine by microsyringe or ball-tipped gavage needle, then segregated one to a cage and monitored for mortality for 48 hours after treatment. The investigators reported LD_{50} values (and 95% confidence limits) of 2.50 (3.73-1.68), 3.02 (3.02-3.02), 4.20 (7.14-4.28) and 2.97 mg/kg (4.26-2.08), respectively.

4.2.2. Effects on Flora. Pertinent data regarding the effects of exposure of terrestrial flora to 4-aminopyridine could not be located in the available literature as cited in Appendix A.

4.3. FIELD STUDIES

Pertinent data regarding the effects of 4-aminopyridine on flora and fauna in the field could not be located in the available literature as cited in Appendix A.

4.4. SUMMARY

Studies assessing the acute toxicity of 4-aminopyridine to fish revealed that toxicity was not dependent on water temperature or hardness. The 96-hour LC_{50}s for channel catfish and bluegill sunfish exposed to 4-aminopyridine ranged from 2.43-7.56 mg/ℓ (Schafer and Marking, 1975). The toxicity of 4-aminopyridine to aquatic invertebrates was assessed by Marking and Chandler (1981). Juvenile glass shrimp were the most sensitive species tested (96-hour LC_{50}=0.37 mg/ℓ), followed by mayfly nymphs (0.58 mg/ℓ), crayfish (2.2 mg/ℓ), frog larvae (2.4 mg/ℓ), water fleas (3.2 mg/ℓ), caddisfly larvae (15 mg/ℓ), Asiatic clams (45 mg/ℓ) and snails (62 mg/ℓ). The NOEC for larval frogs appears to be $\leq$1 mg/ℓ (Marking and Chandler, 1981).

The toxicity of 4-aminopyridine to birds was studied extensively by a series of investigators. Oral LD_{50} values ranged from 2.4-35 mg/kg for periods of exposure and observation of varying lengths. There was no evidence that reproduction among the progeny of 4-aminopyridine-treated birds was affected by treatment of the parents (Schafer et al., 1975). There was no evidence of secondary hazard potential among predatory birds from the consumption of 4-aminopyridine-killed birds (Holler and Schafer, 1982).

5. PHARMACOKINETICS

5.1. ABSORPTION

In a study by Uges et al. (1982), six volunteers (60-81 kg) were treated orally with 20 mg 4-aminopyridine (two 10 mg enteric-coated tablets). Concentrations of 4-aminopyridine in the serum and urine were measured at varying intervals for up to 9 and 36 hours, respectively. 4-Aminopyridine was detected in the serum 128±38 minutes after ingestion of the coated tablets, and a maximum serum concentration of 62±15 µg/ℓ was reached at 193±51 minutes after treatment. Based on urinary excretion data, the investigators estimated that 98±8% of the dose was absorbed. The same subjects and three additional volunteers (one male, two females) were also treated with an intravenous injection of 20 mg 4-aminopyridine (at least 14 days between treatments). By comparing serum 4-aminopyridine concentrations following oral and intravenous dosing, the investigators calculated that bioavailability was 95±29%.

Coated capsules were required for oral treatment with 4-aminopyridine because of the occurrence of gastric cramps in three of four persons treated with uncoated tablets (two 10 mg tablets). Following treatment with uncoated tablets, urine and saliva concentrations of 4-aminopyridine were measured. 4-Aminopyridine was found in the saliva ~6 minutes after ingestion, with salivary concentrations higher than those in serum, and peaking at 25±30 minutes. The investigators stated that the rapid absorption of 4-aminopyridine (beginning within 15 minutes of ingestion) indicates that the compound is absorbed from the stomach.

5.2. DISTRIBUTION

Following oral and intravenous treatment of human volunteers (60-81 kg) with a 20 mg dose of 4-aminopyridine, no difference was found in 4-aminopyridine concentrations in the serum before and after ultrafiltration,

indicating negligible binding to serum proteins (Uges et al., 1982). In a review of the pharmacokinetics and side-effects of 4-aminopyridine, Sohn and Uges (1981) stated that the compound readily crosses the blood-brain barrier. Supporting data were not provided.

Rupp et al. (1983) treated seven fasted anesthetized mongrel dogs with an intravenous injection of 4-aminopyridine (1 mg/kg). The volume of distribution was calculated to be 8.6 times the volume of the serum, suggesting extensive distribution to the tissues.

5.3. METABOLISM

In the study by Uges et al. (1982), urine collected for 24 hours from persons treated with 4-aminopyridine as described above (six oral, nine intravenous) contained ≥85% of the administered dose. When urine was incubated with beta-glucuronidase or hydrochloric acid there was no increase in the amount of detectable free 4-aminopyridine in the urine, suggesting that 4-aminopyridine did not undergo glucuronidation or sulfonation. Using a TLC technique, N-acetyl-4-aminopyridine hydrochloride was not detected in the urine from volunteers treated with 4-aminopyridine, indicating that N-acetylation of 4-aminopyridine had not occurred. The investigators concluded that biotransformation of 4-aminopyridine is unlikely.

5.4. EXCRETION

In a study by Evenhuis et al. (1981), six volunteers anesthetized for 1 hour with a ketamine-diazepam anesthetic were treated with an intravenous injection of 4-aminopyridine (a ketamine-diazepam antagonist) at a dose of 0.3 mg/kg. Blood and urine were sampled and analyzed for 4-aminopyridine for varying periods up to 8 or 48 hours, respectively. In five of the six volunteers, a secondary increase in plasma concentration was observed after the initial decrease. The time of onset of the secondary increase was

highly variable between individuals, occurring 20-90 minutes after the injection. 4-Aminopyridine excreted in the urine accounted for 84.7% of the dose 12-14 hours after the injection and 87.3% of the dose at 48 hours.

In volunteers given an intravenous injection of 4-aminopyridine (20 mg), Uges et al. (1982) reported that the elimination half-life in the serum was 3.6±0.9 hours. About 30 hours after six human volunteers were given an intravenous injection of 4-aminopyridine, 90.6±7.8% of the compound was excreted in the urine. About 30 hours following an oral dose of 4-aminopyridine (20 mg) in enteric-coated tablets, 88.5±4.8% of the unchanged compound was excreted in the urine. Treatment of four volunteers with uncoated tablets of 4-aminopyridine resulted in the recovery of 86.3±6.7% of the dose in the urine in ~30 hours. The investigators concluded that excretion was almost exclusively through the kidney.

During 10 hours after dosing, Rupp et al. (1983) recovered from the urine of seven fasted anesthetized dogs 60±9% of a dose of 4-aminopyridine at 1 mg/kg. During the same period, only 0.01±0.01% of the administered compound was recovered in the bile. An elimination half-life of 125 minutes was calculated. The investigators estimated renal clearance rate ~4-fold greater than glomerular filtration rate and concluded that renal excretion involved tubular secretion.

5.5. SUMMARY

Pharmacokinetic data in humans indicate that 4-aminopyridine is absorbed readily and nearly completely from the gastrointestinal tract (Uges et al., 1982). 4-Aminopyridine appears to distribute widely throughout the tissues (Rupp et al., 1983), but excretion data (Uges et al., 1982) suggest that bioaccumulation does not occur in humans. Metabolites have not been found in the urine of humans treated with 4-aminopyridine, and biotransformation

appears unlikely (Uges et al., 1982). In a study using human volunteers (Uges et al., 1982), ~85% of an oral dose and 90% of an intravenous dose of 4-aminopyridine was recovered in the urine, with an elimination half-life of 3.6 hours.

6. EFFECTS

6.1. SYSTEMIC TOXICITY

6.1.1. Inhalation Exposures. Pertinent data regarding the toxicity of 4-aminopyridine following subchronic or chronic inhalation exposure could not be located in the available literature as cited in Appendix A.

6.1.2. Oral Exposure.

6.1.2.1. SUBCHRONIC -- The only data regarding the subchronic oral toxicity of 4-aminopyridine are two studies in the OPP CBI files summarized by U.S. EPA (1980b). Kohn (1968) fed rats (number not provided) 4-aminopyridine hydrochloride in the diet at concentrations of 3, 30 or 300 ppm for 90 days. Information regarding controls was not provided. At 300 ppm, all surviving rats (specific survival data not provided) were hyperirritable to noise and touch. Brain weights of female rats and liver weights of male rats treated at 300 ppm were significantly ($p<0.05$) elevated. No changes in blood and urinalyses were noted. Gross and histopathologic examinations also did not reveal any significant changes. Additional data in the CBI version of the study indicate that sporadic hyperirritability also occurred at 30 ppm, and that the 3 ppm dose was a NOEL (U.S. EPA, 1986a).

In a study by Cervenka and Vega (1968), beagle dogs (number unspecified) were fed diets containing 4-aminopyridine hydrochloride at concentrations that provided doses of 0.1, 1.0 or 2.0-3.25 mg 4-aminopyridine/kg/day for 90 days. Information regarding controls was not provided. At >2.0 mg/kg/day, dogs exhibited salivation and muscular weakness; no histopathological lesions were observed. According to the summary, no dose-related trends in mean organ weights were observed, although at the two highest doses brain weights were slightly decreased. The review from which these data were taken (U.S. EPA, 1980b) stated that "examination of the brain revealed no

abnormalities," but the extent and protocol of that examination were not described. No changes in blood and urinalyses were noted.

6.1.2.2. CHRONIC -- Pertinent data regarding the toxicity of 4-aminopyridine following chronic oral exposure could not be located in the available literature as cited in Appendix A.

6.1.3. Other Relevant Information. 4-Aminopyridine acts at the motor nerve terminal to decrease membrane potassium conductance, which prolongs the action potential, causing an influx of calcium and an increase in the release of acetylcholine (Agoston et al., 1985). Because of this activity, 4-aminopyridine has been used in humans to reverse residual neuromuscular blockade resulting from nondepolarizing neuromuscular blocking agents and certain antibiotics. Experimental uses of 4-aminopyridine include treatment of patients with Botulinus intoxication, myoneural disorders (e.g., myasthenia gravis, Eaton-Lambert syndrome) and Alzheimer's disease. The clinical use of 4-aminopyridine is limited by its narrow therapeutic index. Agoston et al. (1985) reported that following a clinical dose of 0.15-0.3 mg/kg (route not specified), the only side effects noted were a slight increase in systolic blood pressure and heart rate, while doses >0.5 mg/kg were likely to result in restlessness, confusion, nausea, weakness and tonic-clonic seizures.

Lundh et al. (1979) treated six myasthenia gravis patients with intravenous injections of 4-aminopyridine at a dose of 10 mg injected over a 10-minute period (body weights of patients were not provided). The treatment alleviated muscular weakness. Side effects reported included paraesthesia periorally, a sensation of unsteadiness during walking, restlessness and pain in the arm of the injection. Wesseling et al. (1984) found some improvement in the mental capacity of 14 Alzheimer's patients treated with 4-aminopyridine (10 mg twice a day) compared with treatment with placebos.

Spyker et al. (1980) reported that two men (100 kg) who accidentally ingested a pinch (estimated to be ~60 mg) of 4-aminopyridine were admitted to the hospital and survived the poisoning. The symptoms observed in these men included nausea, weakness, dizziness, profuse perspiration, altered mental status and hypertension. One man also experienced three tonic-clonic seizures.

Schafer et al. (1973a) summarized the acute toxicity of 4-aminopyridine in birds and mammals; LD_{50} values for mammals are presented in Table 6-1. Dogs were the most sensitive mammal studied, with an oral LD_{50} of 3.7 mg/kg.

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

In a study by Mitsov and Uzunov (1972), white rats of both sexes were treated with 4-aminopyridine by intraperitoneal injection for 1 or 6 months. In the 1-month study, groups of 10 rats/sex were treated with 4-aminopyridine at doses of 1 or 5 mg/kg/day, while in the 6-month study, similar groups of rats were treated at doses of 1 or 4 mg/kg/day. Control groups for both studies were injected with physiologic saline. Histopathologic examination was limited to heart, liver, brain, lung, kidney and spleen. No effects on body weight, hemoglobin concentration and RBC or WBC counts were noted in either study. 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 addition to the effects observed in the 1-month study, dose-related parenchymatous degeneration and fatty degeneration of the liver were observed in the 6-month study.

TABLE 6-1

Acute Toxicity of 4-Aminopyridine to Mammals

Species	Route	Vehicle	LD_{50} (mg/kg)	Reference
Rat	oral	water	20	Schafer et al., 1973a
Rat	intraperitoneal	water	6.5	Schafer et al., 1973a
Mouse	intraperitoneal	water	14.7	Humphreys, 1962
Mouse	intraperitoneal	water	10	Vohra et al., 1965
Mouse	intraperitoneal	water	9	Fastier and McDowall, 1958
Mouse	subcutaneous	water	5	Lemeignan and Lechat, 1967
Mouse	intravenous	water	7	Fastier and McDowall, 1958
Dog	oral	capsule	4	Deichman and Gerarde, 1969
Dog	oral	water	3.7	Schafer et al., 1973a
Rabbit	dermal	water	327	Deichman and Gerarde, 1969

6.2. CARCINOGENICITY

Pertinent data regarding the carcinogenicity of 4-aminopyridine could not be located in the available literature as cited in Appendix A.

6.3. MUTAGENICITY

4-Aminopyridine has tested negative for reverse mutation in Salmonella typhimurium (Ogawa et al., 1986; Wakabayshi et al., 1982). Details of these studies are summarized in Table 6-2. Additional data concerning the mutagenicity of 4-aminopyridine were not located.

6.4. TERATOGENICITY

Mitsov and Uzunov (1972) did not observe any malformations in offspring born to rats during 1- and 6-month intraperitoneal injection studies (see Section 6.1.3.). This study was limited; only 12 offspring from treated rats and 7 offspring from control rats were born from an unspecified number of pregnancies that "evolved normally." Additional data regarding the teratogenicity of 4-aminopyridine were not located.

6.5. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding reproductive effects of 4-aminopyridine could not be located in the available literature as cited in Appendix A.

6.6. SUMMARY

4-Aminopyridine acts on the nervous system to increase the release of acetylcholine. The compound has been used in humans for the reversal of residual neuromuscular blockade from some neuromuscular blocking agents and antibiotics. Experimental uses include treatment of patients with Botulinus intoxication, myoneural disorders and Alzheimer's disease. The clinical use of 4-aminopyridine is limited by its narrow therapeutic index; following a clinical dose of 0.15-0.3 mg/kg (route not specified), the only side effects noted were a slight increase in systolic blood pressure and heart rate,

TABLE 6-2

Mutagenicity Testing of 4-Aminopyridine

Assay	Indicator/ Organism	Purity	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Reverse mutation	Salmonella typhimurium TA1537, TA2637, TA98, TA100	NR	preincubation plate incorporation	NR	none	-	Also - when tested with cobalt (II) chloride, which enhanced the mutagenicity of other heteroatomic compounds (9-aminoacridine, 4-aminoquinoline and harman)	Ogawa et al., 1986
Reverse mutation	S. typhimurium TA98, TA100	>98%	preincubation	up to 2 mg/plate	±S-9	+	Also - when tested with norharman, caused 3-aminopyridine and 2-amino-3-methylpyridine to become mutagenic in the presence of S-9	Wakabayashi et al., 1982

NR = Not reported

0124d

09/19/88

while doses >0.5 mg/kg were likely to result in restlessness, confusion, nausea, weakness and tonic-clonic seizures (Agoston et al., 1985). A case report of an accidental oral exposure (Spyker et al., 1980) indicated that a single dose of ~0.6 mg/kg results in frank effects in humans.

The only data concerning the subchronic oral toxicity of 4-aminopyridine are two 90-day studies in the OPP CBI files summarized by U.S. EPA (1980b). In a rat study (Kohn, 1968), hyperirritability was observed at dietary concentrations of 30 and 300 ppm 4-aminopyridine, with no effects noted at 3 ppm. In dogs (Cervenka and Vega, 1968), salivation, muscular weakness and decreased brain weight were observed at doses of ≥1.0 mg/kg/day.

4-Aminopyridine has tested negative for reverse mutation in Salmonella typhimurium (Ogawa et al., 1986; Wakabayshi et al., 1982). Data concerning the carcinogenicity, reproductive effects and toxicity of 4-aminopyridine following inhalation or chronic oral exposure were not available in the literature cited in Appendix A. No effects on reproduction or fetal development were reported in rats treated with 1-5 mg/kg/day by intraperitoneal injection for 1 or 6 months (Mitsov and Uzunov, 1972).

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

The RQ for 4-aminopyridine is 1000 pounds (U.S. EPA, 1985). Additional guidelines and standards, including EPA ambient water and air quality criteria, drinking water standards, FAO/WHO ADIs, EPA or FDA tolerances for raw agricultural commodities or foods, and ACGIH, NIOSH or OSHA occupational exposure limits could not be located in the available literature as cited in Appendix A.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic life from exposure to 4-aminopyridine could not be located in the available literature as cited in Appendix A.

8. RISK ASSESSMENT

8.1. CARCINOGENICITY

Pertinent data regarding the carcinogenicity of 4-aminopyridine could not be located in the available literature as cited in Appendix A. 4-Aminopyridine has tested negative for reverse mutation in Salmonella typhimurium (Ogawa et al., 1986; Wakabayshi et al., 1982).

8.1.1. Weight of Evidence. As a result of a lack of data concerning carcinogenicity in humans and animals, 4-aminopyridine can be classified as an EPA Group D chemical (U.S. EPA, 1986b), not classifiable as to human carcinogenicity.

8.1.2. Quantitative Risk Estimates. The derivation of carcinogenic potency factors for 4-aminopyridine is precluded by the lack of carcinogenicity data.

8.2. SYSTEMIC TOXICITY

8.2.1. Inhalation Exposure. The derivation of inhalation risk assessment values for 4-aminopyridine is precluded by the lack of inhalation data.

8.2.2. Oral Exposures.

8.2.2.1. LESS THAN LIFETIME EXPOSURES (SUBCHRONIC) -- 4-Aminopyridine has been used in humans to reverse neuromuscular blockade resulting from nondepolarizing neuromuscular blocking agents and certain antibiotics, and as an experimental treatment for Botulinus intoxication, myoneural disorders and Alzheimer's disease (Agoston et al., 1985). Human experience indicates that the compound has a very narrow therapeutic index, with a dose of 0.15-3 mg/kg resulting in a slight increase in systolic blood pressure and heart rate, and a dose >0.5 mg/kg resulting in restlessness, confusion, nausea, weakness and tonic-clonic seizures (Agoston et al., 1985). The report by Spyker et al. (1980), in which two 100 kg men who accidentally ingested ~60

mg of 4-aminopyridine developed nausea, weakness, dizziness, altered mental status, and in one case tonic-clonic seizures, indicates that a dose of ~0.6 mg/kg is a FEL in humans. The available acute human data are not sufficient for risk assessment, but indicate that a subchronic RfD for 4-aminopyridine should be <0.15 mg/kg/day.

In a study by Cervenka and Vega (1968), dogs were fed diets containing 4-aminopyridine at concentrations that provided doses of 0.1, 1.0 or 2.0-3.25 mg/kg/day for 90 days. At ≥2.0 mg/kg/day, dogs exhibited salivation and muscular weakness; no compound-related histopathologic lesions were observed. No dose-related trends in mean organ weights were observed, although brain weights were decreased at the two highest dosages. This study indicates that ≥2.0 mg/kg/day is an adverse effect level, but from the information available, it is not clear whether the slight and nondose-related decrease in brain weight at 1.0 mg/kg/day should be considered an adverse effect.

In a 90-day study (Kohn, 1968), rats fed 4-aminopyridine in the diet at 300 ppm were hyperirritable to noise and touch; males had increased liver weights and females had increased brain weights. Additional information in the CBI files indicates that sporadic hyperirritability also occurred at 30 ppm. No effects were observed in rats fed 4-aminopyridine in the diet at 3 ppm. Assuming rats consume food equivalent to 5% of their body weight/day (U.S. EPA, 1986c), the dietary concentrations of 4-aminopyridine of 3, 30 and 300 ppm correspond to dosages of 0.15, 1.5 and 15 mg/kg/day, respectively.

Although the information concerning the Kohn (1968) study is also very limited, it is the only data available from which a subchronic RfD can be estimated. Application of an uncertainty factor of 1000 [10 for species-to-species extrapolation, 10 to protect sensitive individuals and 10 to reflect

deficiencies in the data base (U.S. EPA, 1988)] to the rat NOAEL of 0.15 mg/kg/day yields a subchronic oral RfD of 0.0002 mg/kg/day or 0.01 mg/day for a 70 kg human. This subchronic RfD is well below the acute human effect level of 0.5 mg/kg/day.

Confidence in the RfD is low, based on low confidence in the study and data base. Few details were available concerning the CBI study. The validity of the study (Kohn, 1968) completed at Industrial BioTest Laboratories is unknown. The supporting data are limited to a subchronic study in dogs (Cervenka and Vega, 1968), for which few details were available. This RfD should be considered preliminary and should be reviewed when additional data are available. The RfD is currently under review by the Agency's RfD Work Group (U.S. EPA, 1989).

8.2.2.2. CHRONIC EXPOSURE -- Chronic oral studies of 4-aminopyridine were not available. As mentioned in Section 8.2.2.1., an oral RfD for 4-aminopyridine is under review by the Reference Dose Work Group (U.S. EPA, 1989).

A tentative RfD of 0.00002 mg/kg/day or 0.001 mg/day for a 70 kg human can be derived by dividing the subchronic oral RfD [derived from the Kohn (1968) rat study] by an additional uncertainty factor of 10 to extrapolate from chronic to subchronic data. Confidence in this RfD is low, based on low confidence in the study and data base. Because the basis of this RfD is not defensible, verification of an RfD for 4-aminopyridine should be deferred until the details of the Cervenka and Vega (1968) and Kohn (1968) studies are available or until additional studies are completed.

8.3. AQUATIC

Insufficient data prevented the development of a criterion for the protection of freshwater life exposed to 4-aminopyridine (Figure 8-1). The data base lacked an acute LC_{50} with a representative species from the

Family	TEST TYPE		
	Acute[a,b]	Chronic[a]	BCF[a]
#1 Chordate (Salmonid-fish)	NA	NA	NA
#2 Chordate (warmwater fish)	3.973[c]	NA	NA
#3 Chordate (fish or amphibian)	4.230[d]	NA	NA
#4 Crustacean (planktonic)	0.37[e]	NA	NA
#5 Crustacean (benthic)	2.2[f]	NA	NA
#6 Insectan	0.58[g]	NA	NA
#7 non-Arthropod/-Chordate	45.0[h]	NA	NA
#8 New Insectan or phylum representative	15.0[i]	NA	NA
#9 algae	NA	NA	NA
#10 Vascular plant	NA	NA	NA

[a]NA = Not available

[b]All values represent 96-hour LC_{50}s

[c]Channel catfish, Ictalurus punctatus

[d]Bluegill sunfish, Lepomis macrochirus

[e]Glass shrimp, Palaemonetes kadiakensis

[f]Crayfish, Procambrus acutus acutus

[g]Mayfly, Isonychia sp.

[h]Asiatic clam, Corbicula manilensis

[i]Caddisfly, Hydropsyche sp.

FIGURE 8-1

Organization chart for listing GMAVs required to derive numerical water quality criteria by the method of EPA/OWRS (1986) for the protection of freshwater aquatic life exposed to 4-aminopyridine

Salmonid family and the results of chronic tests either with freshwater algae or vascular plants. The data base also lacked acceptable chronic tests with fish or invertebrates and results from studies assessing the bioaccumulation or bioconcentration of 4-aminopyridine in aquatic organisms.

No data were available regarding the effects of exposure of marine fauna and flora to 4-aminopyridine, preventing the development of a saltwater criterion.

9. REPORTABLE QUANTITIES

9.1. BASED ON SYSTEMIC TOXICITY

The toxicity of 4-aminopyridine was discussed in Chapter 6. The only data suitable for the derivation of an RQ are the 90-day dog studies (Cervenka and Vega, 1968) rat study (Kohn, 1968). Table 9-1 summarizes these studies and Table 9-2 presents the derivation of CSs and RQs. In the study by Cervenka and Vega (1968), muscular weakness, salivation and a decrease in brain weight was observed in dogs treated at $\geq$2.0 mg/kg/day and a slight decrease in brain weight was observed at 1 mg/kg/day. From the limited information available, it is not clear if the 1.0 mg/kg/day dose was a NOAEL or LOAEL; therefore, only the $\geq$2.0 mg/kg/day dose, corresponding to an RV_d of 4.2, will be considered for CS derivation. Kohn (1968) reported sporadic hyperirritability to noise and touch in rats treated orally with 4-aminopyridine in the diet at a dose of ~1.5 mg/kg/day, or an RV_d of 5.1. Effects in both dogs and rats correspond to an RV_e of 7. Multiplying the larger RV_d of 5.1 from the rat study by the RV_e of 7, a CS of 35.7 is calculated.

The CS of 35.7 calculated from the rat study (Kohn, 1968), corresponding to an RQ of 100 pounds, is selected to represent the toxicity of 4-aminopyridine and is presented in Table 9-3.

9.2. BASED ON CARCINOGENICITY

No data were available concerning the carcinogenicity of 4-aminopyridine. 4-Aminopyridine has tested negative for reverse mutation in Salmonella typhimurium (Ogawa et al., 1986; Wakabayshi et al., 1982) (see Section 6.3.). The lack of data concerning the carcinogenicity of 4-aminopyridine in either humans or animals indicates that the compound should be

TABLE 9-1

Oral Toxicity Data for 4-Aminopyridine[a]

Species/ Strain[b]	Sex	Average Body Weight[c] (kg)	Vehicle/ Physical State	Exposure	Animal Dosage (mg/kg/day)	Equivalent Human Dosage[d] (mg/kg/day)	Effect	Reference
Dog/NR	NR	12	diet	2 mg/kg/day in the diet for 90 days	2[e]	0.1	Salivation, muscular weakness	Cervenka and Vega, 1968
Rat/NR	M&F	0.35	diet	300 ppm in the diet for 90 days	1.5[f]	0.026	Sporadic hyper-irritability to noise and touch	Kohn, 1968

[a]Purity not reported

[b]Number of animals/group not reported

[c]Reference dog body weight (12 kg), reference rat body weight (0.35 kg) (U.S. EPA, 1986c)

[d]Animal dose multiplied by the cube root of the ratio of the animal to reference human body weight (70 kg) and by 70 kg to express human MED in mg/day, and divided by an uncertainty factor of 10 to expand from subchronic to chronic exposure

[e]Estimated by investigators

[f]Reference food factor for rats = 0.05 (U.S. EPA, 1980b)

NR = Not reported

02/08/89 01240

TABLE 9-2

Composite Scores for 4-Aminopyridine Based on Oral Toxicity

Species	Animal Dose (mg/kg/day)	Chronic Human MED[a] (mg/day)	RV_d	Effect	RV_e	CS[b]	RQ	Reference
Dog	2	7.0	4.2	CNS effect	7	29.4	100	Cervenka and Vega, 1968
Rat	1.5	1.8	5.1	CNS effect	7	35.7	100	Kohn, 1968

[a]Equivalent human dosage (mg/kg/day) multiplied by 70 kg

[b]RV_d multiplied by RV_e

0124d

09/19/88

TABLE 9-3

4-Aminopyridine
Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	oral
Dose*:	1.8 mg/kg
Effect:	CNS effects
Reference:	Kohn, 1968
RV_d:	5.1
RV_e:	7
CS:	35.7
RQ:	100 pounds

*Equivalent human dose

classified as an EPA Group D chemical (U.S. EPA, 1986b), not classifiable as to human carcinogenicity. Hazard ranking based on carcinogenicity is not possible for EPA Group D compounds.

10. REFERENCES

Agoston, S., D. Langreher and D.E. Newton. 1985. Pharmacology and possible clinical applications of 4-aminopyridine. Semin. Anesth. 4(1): 81-86.

Atkinson, R. 1985. Kinetics and mechanisms of the gas-phase reactions of the hydroxyl radical with organic compounds under atmospheric conditions. Chem. Rev. 85: 69-201.

Atkinson, R. 1987. A structure-activity relationship for the estimation of the rate constants for the gas-phase reactions of OH radicals with organic compounds. Int. J. Chem. Kinet. 19: 799-828.

Betts, P.M., C.W. Giddings, and J.R. Fleeker. 1976. Degradation of 4-amino-pyridine in soil. J. Agric. Food Chem. 24: 571-574.

Bysshe, S.E. 1982. Bioconcentration factor in aquatic organisms. In: Handbook of Chemical Property Estimation Methods, W.J. Lyman, W.F. Reehl and D.H. Rosenbatt, Ed. McGraw-Hill Book Co., NY. p. 5-4, 5-10.

Carlson, D.A. 1984. Repellents. In: Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed., M. Grayson and D. Eckroth, Ed. John Wiley and Sons, Inc., NY. Vol. Supplement. p. 798.

Cervenka, H. and S.M. Vega. 1968. Ninety-day subacute oral toxicity of compound 1861 (4-aminopyridine) -- Beagle dogs. Project Number 777 (unpublished study). Prepared by Lifestream Laboratories, Inc. under IF 1013. Submitted by Phillips Petroleum Co., Bartelsville, OK. CDL:091756-G. (Cited in U.S. EPA, 1980b)

Deichman, W.B. and H.W. Gerarde. 1969. Toxicology of Drugs and Chemicals. Academic Press, New York. p. 93. (Cited in Schafer et al., 1973a)

Eisenreich, S.J., B.B. Looney and D.J. Thornton. 1981. Airborne organic contaminants in the Great Lakes ecosystem. Environ. Sci. Technol. 15: 30-38.

EPA/OWRS. (Environmental Protection Agency/Office of Water Regulations and Standards). 1986. Guidelines for Deriving Numerical National Water Quality Criteria for the Protection of Aquatic Organisms and their uses. EPA/OWRS Washington, DC. 106 p.

Evenhuis, J., S. Agoston, P.J. Salt, A.R. DeLange, W. Wouthuyzen and W. Erdmann. 1981. Pharmacokinetics of 4-aminopyridine in human volunteers. Br. J. Anaest. 53: 567-570.

Farm Chemicals Handbook. 1987. Farm Chemicals Handbook 87. Meister Publishing Co., Willougby, OH. p. C26.

Fastier, F.N. and M.A. McDowall. 1958. A comparison of the pharmacological properties of three isomeric aminopyridines. Aust. J. Exp. Biol. Med. Sci. 36: 365-372. (Cited in Schafer et al., 1973a)

Garrison, M.V., A. Ammayao and J.L. Libay. 1982. Evaluation of 4-aminopyridine as a bird control agent in the Philippines. Philipp. Agric. 65(1): 53-58.

Goe, G.L. 1982. Pyridine and pyridine derivatives. In: Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed., M. Grayson and D. Eckroth, Ed. John Wiley and Sons, Inc., NY. 19: 454-483.

Hadler, M.R. 1982. Poisons, economic. In: Kirk-Othmer Encyclopedia of Chemical Technology, 3rd. ed., M. Grayson and D. Eckroth, Ed. John Wiley and Sons, Inc., New York. 18: 317-318.

Hansch, C. and A.J. Leo. 1985. Medchem Project. Issue No. 26. Pomona College, Claremont, CA.

Harris, J.C. 1982. Rate of hydrolysis. In: Handbook of Chemical Property Estimation Methods, W.J., Lyman, W.F. Reehl and D.H. Rosenblatt, Ed. McGraw-Hill Book Co., NY. p. 7-4.

Hawley, G.G. 1981. The Condensed Chemical Dictionary, 10 ed. Van Nostrand Reinhold Co., New York. p. 55.

Hine, J. and P.K. Mookerjee. 1975. The intrinsic hydrophilic character of organic compounds. Correlations in terms of structural contributions. J. Org. Chem. 40: 292-298.

Holler, N.R. and E.W. Schafer, Jr. 1982. Potential secondary hazards of Avitrol baits to sharp-shinned hawks and American kestrels. J. Wildl. Manage. 46(2): 457-4462.

Houston, T. and B.J. Pleuvry. 1984. Comparison of some pharmacological properties of 4-aminopyridine and 3,4-diaminopyridine in vivo. Br. J. Anaes. 56(10): 1139-1142.

Hudson, R.H., R.K. Tucher and M.A. Haegele. 1984. Handbook of toxicity of pesticides to wildlife. U.S. Dept. of the Interior, Fish and Wildlife Service. Resource Publ. No. 153. Washington, DC. p. 12.

Humphreys, S.R.. 1962. Toxicity and antileukemic effectiveness of pyridine derivatives and 1,2,4-thiadiazol derivatives in mice -- Relation to nicotinamide antagonism. Cancer Res. Suppl. 22(2):483-550. (Cited in Schafer et al., 1973a)

Kohn, F.E. 1968. Four-week subacute oral toxicity of compound 1861 Hydrochloride -- Albino rats. (Unpublished study). Prepared by Industrial Biotest Laboratories, Inc. under 224-12. Submitted by Phillips Petroleum Co., Bartlesville, OK. CDL: 229844-E. (Cited in U.S. EPA, 1980b)

Kuney, J.H., Ed. 1986. Chemcyclopedia 1987. Volume 5. American Chemical Society, Washington, DC. p. 51.

Lemeignan, M and P. Lechat. 1967. Anticurare action of aminopyridines. C.R. Acad. Sci. Ser. D. 264: 169-172. (Cited in Schafer et al., 1973a)

Lundh, H., O Nilsson and I. Rosen. 1979. Effects of 4-aminopyridine in myasthenia gravis. J. Neurol. Neurosurg. Psychiat. 42(2): 171-175.

Lyman, W.J., W.F. Reehl and D.H. Rosenblatt. 1982. Handbook of Chemical Property Estimation Methods. Environmental Behavior of Organic Compounds. McGraw-Hill Book Co., New York, NY. 5-5.

Marking, L.L. and J.H. Chandler. 1981. Toxicity of six bird control chemicals to aquatic organisms. Bull. Environ. Contam. Toxicol. 26(6): 705-716.

Mill, T. and W. Mabey. 1985. Photochemical transformations. In: Environmental Exposure From Chemicals, Volume I, W.B. Neely and G.E. Blau, Ed. CRC Press, Inc., Boca Raton, FL. p. 206-210.

Mitzov, V. and P. Uzunov. 1972. Toxicity of the compound VMI-10-3. EK. sp. Med. No. ful. 11(3): 162-165. (Bulgarian with English translation)

Naik, M.N., R.B. Jackson, J. Stokes and R.J. Swaby. 1972. Microbial degradation and phytotoxicity of picloram and other substituted pyridines. Soil Biol. Biochem. 4: 313-323.

NIOSH (National Institute for Occupational Safety and Health). 1985. National Occupational Exposure Survey (NOES). Computer printout of survey as of 9/20/85.

Ogawa, H.I., K. Sakata, T. Inouye, et al. 1986. Combined mutagenicity of cobalt(II) salt and heteroaromatic compounds in Salmonella typhimurium. Mutat. Res. 172(2): 97-104.

Parris, G.E. 1980. Covalent binding of aromatic amines to humates. 1. Reactions with carbonyls and quinones. Environ. Sci. Technol. 14: 1099-1106.

Rupp, S.M., Y. Shinohara, D.M. Fisher, R.D. Miller and N.J. Castagnoli. 1983. Pharmacokinetics and pharmacodynamics of 4-aminopyridine in anesthetized dogs. J. Pharmacol. Exp. Ther. 225(2): 351-354.

SANSS. (Structure and Nomenclature Search System). 1988. Chemical Information System (CIS) computer data base.

Schafer, E.W., Jr. and L.L. Marking. 1975. Long-term effects of 4-aminopyridine exposure to birds and fish. J. Wildl. Manage. 39(4): 807-811.

Schafer, E.W., Jr., R.B. Brunton and D.J. Cunningham. 1973a. A summary of the acute toxicity of 4-aminopyridine to birds and mammals. Toxicol. Appl. Pharmacol. 26(4): 532-538.

Schafer, E.W., Jr., R.B. Bunton, N.W. Lockyer and J.F. DeGrazio. 1973b. Comparative toxicity of seventeen pesticides to the quelea, house sparrow and red-winged blackbird. Toxicol. Appl. Pharmacol. 26(1): 154-157.

Schafer, E.W., Jr., R.B. Brunton and N.F. Lockyer. 1975. The effects of subacute and chronic exposure to 4-aminopyridine on reproduction in coturnix quail. Bull. Environ. Contam. Toxicol. 13(6): 758-764.

Sims, G.K. and L.E. Sommers. 1985. Degradation of pyridine derivatives in soil. J. Environ. Qual. 14: 580-584.

Sims, G.K. and L.E. Sommers. 1986. Biodegradation of pyridine derivatives in soil suspensions. Environ. Toxicol. Chem. 5: 503-509.

Sohn, Y.J. and D.R.A. Uges. 1981. Pharmacokinetics and side-effects of 4-aminopyridine. Int. Congr. Ser. - Excerpta Med. 538: 224-228.

Spyker, D.A., C. Lynch, J. Shabanowitz and J.A. Sinn. 1980. Poisoning with 4-aminopyridine: Report of three cases. Clin. Toxicol. 16(4): 487-497.

SRI (Stanford Research Institute International). 1987. 1987 Directory of Chemical Producers. United States of America. SRI International, Menlo Park, CA. p. 325, 459.

Starr, R.I. and D.J. Cunningham. 1975. Leaching and degradation of carbon-14 labeled 4-aminopyridine in several soil systems. Arch. Environ. Contam. Toxicol. 3: 72-83.

Sultana, P., J.E. Brooke and R.L. Bruggers. 1986. Repellency and toxicity of bird control chemicals to pest birds in Bangladesh. Trop. Pest. Manage. 32(3): 246-248.

Thomas, R.G. 1982. Volatilization from water. In: Handbook of Chemical Property Estimation Methods, W.J. Lyman, W.F. Reehl and D.H. Rosenblatt, Ed. McGraw-Hill Book Co., NY. p. 15-15, 15-16.

Uges, D.R.A., Y.J. Sohn, B. Greijdanus, A.H.J. Scaf and S. Agoston. 1982. 4-Aminopyridine kinetics. Clin. Pharmacol. 31: 587-593.

U.S. EPA. 1977. Computer print-out of non-confidential production data from the TSCA Production File for 1977. U.S. EPA, Washington, DC.

U.S. EPA. 1980a. Guidelines and Methodology used in the Preparation of Health Effects Assessment Chapters of the Consent Decree Water Criteria Documents. Federal Register. 45(231): 79347-79357.

U.S. EPA. 1980b. 4-Aminopyridine. Avitrol Pesticide Registration Standard. OPTS, U.S. EPA, Washington, DC. NTIS PB84-209907.

U.S. EPA. 1984. Methodology and Guidelines for Ranking Chemicals Based on Chronic Toxicity Data. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1985. Notification Requirements; reportable quantity adjustments; final rule and proposed rule. Federal Register. 50(65): 13456-13522.

U.S. EPA. 1986a. CBI Appendix for Review and Evaluation of ADI for: P008 4-Aminopyridine. Prepared by SRC under Contract No. 68-03-3228 for Environmental Criteria and Assessment Office, Cincinnati, OH.

U.S. EPA. 1986b. Guidelines for Carcinogen Risk Assessment. Federal Register. 51(185): 33992-34003.

U.S. EPA. 1986c. Reference Values for Risk Assessment. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste, Washington, DC.

U.S. EPA. 1987. Graphical Exposure Modeling System (GEMS). PCCHEM. Version April 1987.

U.S. EPA. 1988. Reference Dose (RfD): Description and Use in Health Risk Assessments. Integrated Risk Information System (IRIS). Online. Intra-Agency Reference Dose (RfD) Work Group, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH, February.

U.S. EPA. 1989. Integrated Risk Information System (IRIS). Online. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

U.S. EPA/NIH (Environmental Protection Agency/National Institute of Health). 1988. OHM-TADS (Oil and Hazardous Materials-Technical Assistance Data System). Online: May, 1988.

Vohra, M.M., S.N. Pradhan, P.C. Jain, S.K. Chatterlee and N. Anand. 1965. Synthesis and structure-activity relations of some aminopyridine - Imidazo pyridines and triazole pyridines. J. Med. Chem. 8: 296-304. (Cited in Schafer et al., 1973a)

Wakabayashi, K., T. Yahagi, M. Nagao and T. Sugimura. 1982. Comutagenic effect of norharman with aminopyridine derivatives. Mutat. Res. 105(4): 205-210.

Weast, R.C., Ed. 1985. CRC Handbook of Chemistry and Physics, 66th ed. CRC Press, Inc., Boca Raton, FL. p. C-462, D-160.

Wesseling, H., S. Agoston, G.B.P. van Dam, et al. 1984. Effects of 4-aminopyridine in elderly patients with Alzhemiers disease. N. Engl. J. Med. 310: 988-989.

APPENDIX A

LITERATURE SEARCHED

This HEED is based on data identified by computerized literature searches of the following:

CHEMLINE
TSCATS
CASR online (U.S. EPA Chemical Activities Status Report)
TOXLINE
TOXLIT
TOXLIT 65
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP
NTIS
Federal Register
CAS ONLINE (Chemistry and Aquatic)
HSDB

These searches were conducted in May 1988, and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1986. Documentation of the Threshold Limit Values and Biological Exposure Indices, 5th ed. Cincinnati, OH.

ACGIH (American Conference of Governmental Industrial Hygienists). 1987. TLVs: Threshold Limit Values for Chemical Substances in the Work Environment adopted by ACGIH with Intended Changes for 1987-1988. Cincinnati, OH. 114 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2A. John Wiley and Sons, NY. 2878 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2B. John Wiley and Sons, NY. p. 2879-3816.

Clayton, G.D. and F.E. Clayton, Ed. 1982. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2C. John Wiley and Sons, NY. p. 3817-5112.

Grayson, M. and D. Eckroth, Ed. 1978-1984. Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. John Wiley and Sons, NY. 23 Volumes.

Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed. Publishing Sciences Group, Inc., Littleton, MA. 575 p.

IARC (International Agency for Research on Cancer). IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. IARC, WHO, Lyons, France.

Jaber, H.M., W.R. Mabey, A.T. Lieu, T.W. Chou and H.L. Johnson. 1984. Data acquisition for environmental transport and fate screening for compounds of interest to the Office of Solid Waste. EPA 600/6-84-010. NTIS PB84-243906. SRI International, Menlo Park, CA.

NTP (National Toxicology Program). 1987. Toxicology Research and Testing Program. Chemicals on Standard Protocol. Management Status.

Ouellette, R.P. and J.A. King. 1977. Chemical Week Pesticide Register. McGraw-Hill Book Co., NY.

Sax, I.N. 1984. Dangerous Properties of Industrial Materials, 6th ed. Van Nostrand Reinhold Co., NY.

SRI (Stanford Research Institute). 1987. Directory of Chemical Producers. Menlo Park, CA.

U.S. EPA. 1986. Report on Status Report in the Special Review Program, Registration Standards Program and the Data Call in Programs. Registration Standards and the Data Call in Programs. Office of Pesticide Programs, Washington, DC.

USITC (U.S. International Trade Commission). 1986. Synthetic Organic Chemicals. U.S. Production and Sales, 1985, USITC Publ. 1892, Washington, DC.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY.

Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

Windholz, M., Ed. 1983. The Merck Index, 10th ed. Merck and Co., Inc., Rahway, NJ.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Volume 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under Contract No. 68-01-0007. Washington, DC.

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. U.S. Dept. Interior, Fish and Wildlife Serv. Res. Publ. 137, Washington, DC.

McKee, J.E. and H.W. Wolf. 1963. Water Quality Criteria, 2nd ed. Prepared for the Resources Agency of California, State Water Quality Control Board. Publ. No. 3-A.

Pimental, D. 1971. Ecological Effects of Pesticides on Non-Target Species. Prepared for the U.S. EPA, Washington, DC. PB-269605.

Schneider, B.A. 1979. Toxicology Handbook. Mammalian and Aquatic Data. Book 1: Toxicology Data. Office of Pesticide Programs, U.S. EPA, Washington, DC. EPA 540/9-79-003. NTIS PB 80-196876.

APPENDIX B

Summary Table for 4-Aminopyridine

	Species	Exposure	Effect	RfD or q_1*	Reference
Inhalation Exposure					
Subchronic				ID	
Chronic				ID	
Carcinogenicity				ID	
Oral Exposure					
Subchronic	rat	0.15 mg/kg/day	NOAEL for CNS effects	0.0002 mg/kg/day or 0.01 mg/day for a 70 kg human†	Kohn, 1968
Chronic	rat	0.15 mg/kg/day	NOAEL for CNS effects	0.00002 mg/kg/day or 0.001 mg/day for a 70 kg human†	Kohn, 1968
Carcinogenicity				ID	
REPORTABLE QUANTITIES					
Based on chronic toxicity	100				Kohn, 1968
Based on carcinogenicity	ID				

†These RfDs should be considered tentative and should be reviewed when additional data are available.

ID = Insufficient data