TOXICOLOGICAL PROFILE FOR PYRIDINE

Agency for Toxic Substances and Disease Registry
U.S. Public Health Service

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FOREWORD

The Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) extended and amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare toxicological profiles for hazardous substances which are most commonly found at facilities on the CERCLA National Priorities List and which pose the most significant potential threat to human health, as determined by ATSDR and the Environmental Protection Agency (EPA). The lists of the 250 most significant hazardous substances were published in the Federal Register on April 17, 1987; on October 20, 1988; on October 26, 1989; and on October 17, 1990. A revised list of 275 substances was published on October 17, 1991.

Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the lists. Each profile must include the following content:

> (A) An examination, summary, and interpretation of available toxicological information and epidemiological evaluations on the hazardous substance in order to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects.
>
> (B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure which present a significant risk to human health of acute, subacute, and chronic health effects.
>
> (C) Where appropriate, an identification of toxicological testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and EPA. The original guidelines were published in the Federal Register on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile is intended to characterize succinctly the toxicological and adverse health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature (that has been peer-reviewed) that describes a hazardous substance's toxicological properties. Other pertinent literature is also presented but described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

Foreword

Each toxicological profile begins with a public health statement, which describes in nontechnical language a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health will be identified by ATSDR, the National Toxicology Program (NTP) of the Public Health Service, and EPA. The focus of the profiles is on health and toxicological information; therefore, we have included this information in the beginning of the document.

The principal audiences for the toxicological profiles are health professionals at the federal, state, and local levels, interested private sector organizations and groups, and members of the public.

This profile reflects our assessment of all relevant toxicological testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, the Centers for Disease Control, the NTP, and other federal agencies. It has also been reviewed by a panel of nongovernment peer reviewers. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

William L. Roper

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CONTENTS

LIST OF FIGURES

LIST OF TABLES

1. PUBLIC HEALTH STATEMENT

This Statement was prepared to give you information about pyridine and to emphasize the human health effects that may result from exposure to it. The Environmental Protection Agency (EPA) has identified 1,177 sites on its National Priorities List (NPL). Pyridine has been found at 4 of these sites. However, we do not know how many of the 1,177 NPL sites have been evaluated for pyridine. As EPA evaluates more sites, the number of sites at which pyridine is found may change. This information is important for you to know because pyridine may cause harmful health effects and because these sites are potential or actual sources of human exposure to pyridine.

When a chemical is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment as a chemical emission. This emission, which is also called a release, does not always lead to exposure. You can be exposed to a chemical only when you come into contact with the chemical. You may be exposed to it in the environment by breathing, eating, or drinking substances containing the chemical or from skin contact with it.

If you are exposed to a hazardous chemical such as pyridine, several factors will determine whether harmful health effects will occur and what the type and severity of those health effects will be. These factors include the dose (how much), the duration (how long), the route or pathway by which you are exposed (breathing, eating, drinking, or skin contact), the other chemicals to which you are exposed, and your individual characteristics such as age, sex, nutritional status, family traits, life style, and state of health.

1.1 WHAT IS PYRIDINE?

Pyridine is a flammable colorless liquid with an unpleasant smell. It can be made from crude coal tar or from other chemicals. Pyridine is used as a solvent and to make many different products such as medicines, vitamins, food flavorings, pesticides, paints, dyes, rubber products, adhesives, and waterproofing for fabrics. Pyridine can also be formed from the breakdown of many natural materials in the environment. Many of the foods that you eat have flavors that are the result of complex compounds that contain pyridine.

Liquid pyridine evaporates into the air very easily. If pyridine is released to the air, it may take several months to years until it breaks down into other compounds. Pyridine also mixes very easily with water. If it is released to water or soil, it may break down in a few days to few months.

You may find information on the properties and uses of pyridine and how it behaves in the environment in Chapters 3, 4, and 5.

1.2 HOW MIGHT I BE EXPOSED TO PYRIDINE?

Pyridine and pyridine-containing compounds are present throughout the environment at very low levels. Pyridine has been found in the air inside and

around factories that produce it or use it to make other products. You could be exposed to pyridine if you work in one of these factories or if you live or work near a hazardous waste site that releases it to the surrounding air. Pyridine is also released into the air from burning cigarettes and from hot coffee.

Pyridine is not usually found in rivers or other natural waters. It has been found in wells in an industrial area in Wyoming. The levels of pyridine in the well water were as high as 53 parts of pyridine in 1 billion parts of water (53 ppb). Pyridine is not usually found in the soil near hazardous waste sites or in industrial areas. Pyridine has been found in drinking water samples taken around hazardous waste sites and industrial areas. However, we do not know the levels. It is also found in certain foods such as fried chicken, cheese, and fried bacon. Although the levels in these foods are not known, they are probably very low and are not expected to result in any health effects. The level of pyridine in some frozen mango (a tropical fruit) was reported to be 1 part of pyridine per million parts of mango (1 ppm). You could be exposed to small amounts of pyridine if you eat these foods or drink water containing pyridine.

You can find more information on how you might be exposed to pyridine in Chapter 5.

1.3 HOW CAN PYRIDINE ENTER AND LEAVE MY BODY?

Pyridine can enter your body when you breathe in air, drink water, or eat food that contains this chemical, or by skin contact with the chemical. When it enters your body by mouth, more than half of it is absorbed. Within 1 day, most of what was absorbed leaves your body in urine as pyridine itself or its breakdown products. We do not know what happens to the rest of it. There is also no information about what happens to pyridine that is breathed in or gets on your skin.

You can find more information on how pyridine enters and leaves the body in Chapter 2.

1.4 HOW CAN PYRIDINE AFFECT MY HEALTH?

Very few studies have been conducted to determine the possible effects of pyridine exposure on human health. From case reports on humans and studies in animals, we think the most important health concern for humans exposed to pyridine will be damage to the liver. Other health concerns for humans may be neurological effects, renal effects, and irritation of the skin and eye. We do not know whether pyridine can cause cancer, birth defects, or problems with reproduction.

You can find more information on health effects of pyridine in humans and animals in Chapter 2.

1.5 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO PYRIDINE?

Tests can be used to find out whether you have been recently exposed to pyridine. These tests measure levels of pyridine in urine and blood. They use special equipment and are done in special laboratories, so they are not usually available in a doctor's office. The levels of pyridine in urine or blood cannot be used, however, to find out how much pyridine you were exposed to or whether specific harmful effects will occur.

You will find more information on how pyridine can be measured in exposed humans in Chapters 2 and 6.

1.6 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government has set certain regulations and guidelines to help protect people from the possible health effects of pyridine in the environment. The EPA has not set limits on the amount of pyridine that may be present in drinking water. The Occupational Safety and Health Administration (OSHA) has set an average air exposure level of 5 ppm for an g-hour day, 40-hour work week. The National Institute for Occupational Safety and Health (NIOSH) has set 3,600 ppm in air as the level that is immediately dangerous to life and health (IDLH). The American Conference of Governmental Industrial Hygienists (ACGIH), which is a special nongovernment group set up to protect workers, also recommends 5 ppm for an g-hour day.

You will find more information on governmental rules for pyridine in Chapter 7.

1.7 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns not covered here, please contact your state health or environmental department or:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road, E-29
Atlanta, Georgia 30333

This agency can also provide you with information on the location of the nearest occupational and environmental health clinic. Such clinics specialize in recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of pyridine and a depiction of significant exposure levels associated with various adverse health effects. It contains descriptions and evaluations of studies and presents levels of significant exposure for pyridine based on toxicological studies and epidemiological investigations.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure--inhalation, oral, and dermal--and then by health effect--death, systemic, immunological, neurological, developmental, reproductive, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods--acute (less than 15 days), intermediate (15-364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing noobserved-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects, These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear. They should also help to determine whether or not the effects vary with dose and/or duration, and place into perspective the possible
significance of these effects to human health.

The significance of the exposure levels shown in the tables and figures may differ depending on the user's perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons may be interested in levels of exposure associated with "serious" effects. Public health officials and project managers concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAEL) have been observed.

Estimates of levels posing minimal risk to humans (Minimal Risk Levels, MRLs) may be of interest to health professionals and citizens alike. Estimates of exposure levels posing minimal risk to humans (MRLs) have been made, where data were believed reliable, for the most sensitive noncancer effect for each exposure duration. MRLs include adjustments to reflect human variability from laboratory animal data to humans.

Although methods have been established to derive these levels (Barnes et al. 1988; EPA 1989a), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

2.2.1 Inhalation Exposure

2.2.1.1 Death

No studies were located regarding death in humans after inhalation exposure to pyridine.

A l-hour LC_{50} for pyridine of 9,010 ppm for male rats and of 9,020 ppm for female rats was reported by Vernot et al. (1977).

These l-hour LC_{50} levels for rats are recorded in Table 2-l and plotted in Figure 2-l.

2.2.1.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, or dermal/ocular effects in humans or animals after inhalation exposure to pyridine.

Renal Effects. No useful studies were located regarding renal effects in humans after inhalation exposure to pyridine.

Rats exposed to pyridine vapors at 5-10 mg/L for a single exposure period of about 40 minutes showed a decrease in glutamine level in the kidneys accompanied by an increase in ammonia excretion in the urine (Bolonova 1972, as cited in EPA 1978).

2.2.1.3 Immunological Effects

No studies were located regarding immunological effects in humans or animals after inhalation exposure to pyridine.

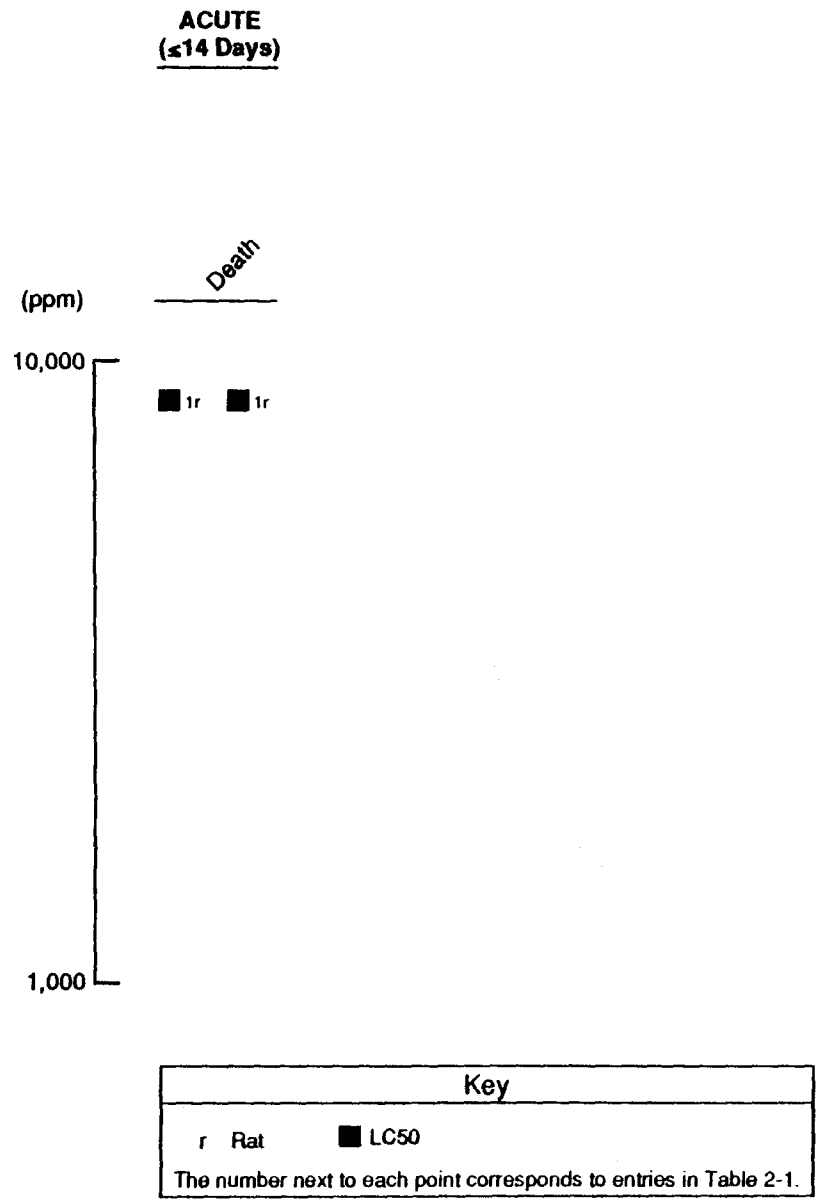
TABLE 2-1. Levels of Significant Exposure to Pyridine - Inhalation

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
ACUTE EXPOSURE							
Death							
1	Rat	1 hr				9010 (LC50 - males) 9020 (LC50 - females)	Vernot et al. 1977

[a]The number corresponds to entries in Figure 2-1.

hr = hour(s); LC50 = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

FIGURE 2-1. Levels of Significant Exposure to Pyridine – Inhalation



2.2.1.4 Neurological Effects

There are limited studies regarding neurological effects in humans after inhalation exposure to pyridine. In a case report on healthy adults, symptoms that developed following exposure to undetermined levels of pyridine vapors included headaches, giddiness, a desire to sleep, and quickening of pulse and respiration (Neff 1886). The study did not describe the concentration of pyridine or other exposure conditions such as duration of exposure.

No studies were located regarding neurological effects in animals after inhalation exposure to pyridine.

No studies were located regarding the following health effects in humans or animals after inhalation exposure to pyridine:

2.2.1.5 Developmental Effects

2.2.1.6 Reproductive Effects

2.2.1.7 Genotoxic Effects

In vitro genotoxicity studies are discussed in Section 2.4.

2.2.1.8 Cancer

No studies were located regarding cancer effects in humans or animals after inhalation exposure to pyridine.

2.2.2 Oral Exposure

2.2.2.1 Death

No useful studies were located regarding death in humans after oral exposure to pyridine.

The death of a 32-year-old man who had been receiving pyridine as an intermittent medication for the treatment of epilepsy has been reported (Pollock et al. 1943). Because other medications such as magnesium sulfate, sodium bromide, phenobarbital, and/or sodium dilantin were stated to be previous and continuing medications for this patient and because the physical condition of this man at the start of pyridine treatment was not described, it is not possible to attribute this death specifically to pyridine exposure.

Another case study reported the incident of a 29-year-old man who died within 2 days of ingesting approximately a half cup (about 125 mL) of pyridine during a syphoning accident (Helme 1893). Upon admission to a hospital he was treated by the administration of demulcents (not otherwise described), milk, and brandy, application of mustard and linseed poultices to his throat and

chest, and a brandy enema which he was reported to have retained. It is not clear whether this medical intervention was of benefit to this man or possibly exacerbated an already serious situation.

An LD_{50} of 1,580 mg/kg was reported in rats within 14 days following a single oral administration of pyridine (Smyth et al. 1951). No compound related deaths were reported in rats that received pyridine by gavage for 90 days at dosage levels up to 50 mg/kg/day (Anderson 1987).

The LD_{50} value for rats in the acute-duration category and a NOAEL and LOAEL for death in rats in the intermediate-duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.2 Systemic Effects

The NOAEL values and all reliable LOAEL values for each systemic effect in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

Respiratory Effects. No studies were located regarding respiratory effects in humans after oral exposure to pyridine.

No compound-related gross or histopathological effects were observed in the lungs of rats that received pyridine by gavage for 90 days at dosage levels up to 50 mg/kg/day (Anderson 1987).

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans after oral exposure to pyridine.

No compound-related gross or histopathological effects were observed in the hearts of rats that received pyridine by gavage for 90 days at dosage levels up to 50 mg/kg/day (Anderson 1987).

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after oral exposure to pyridine.

No compound-related gross or histopathological effects were observed in the gastrointestinal organs of rats that received pyridine by gavage for 90 days at levels up to 50 mg/kg/day (Anderson 1987).

Hematological Effects. No studies were located regarding hematological effects in humans after oral exposure to pyridine.

No adverse effects on hematological parameters were noted in rats that received pyridine by gavage for 90 days at levels up to 50 mg/kg/day (Anderson 1987).

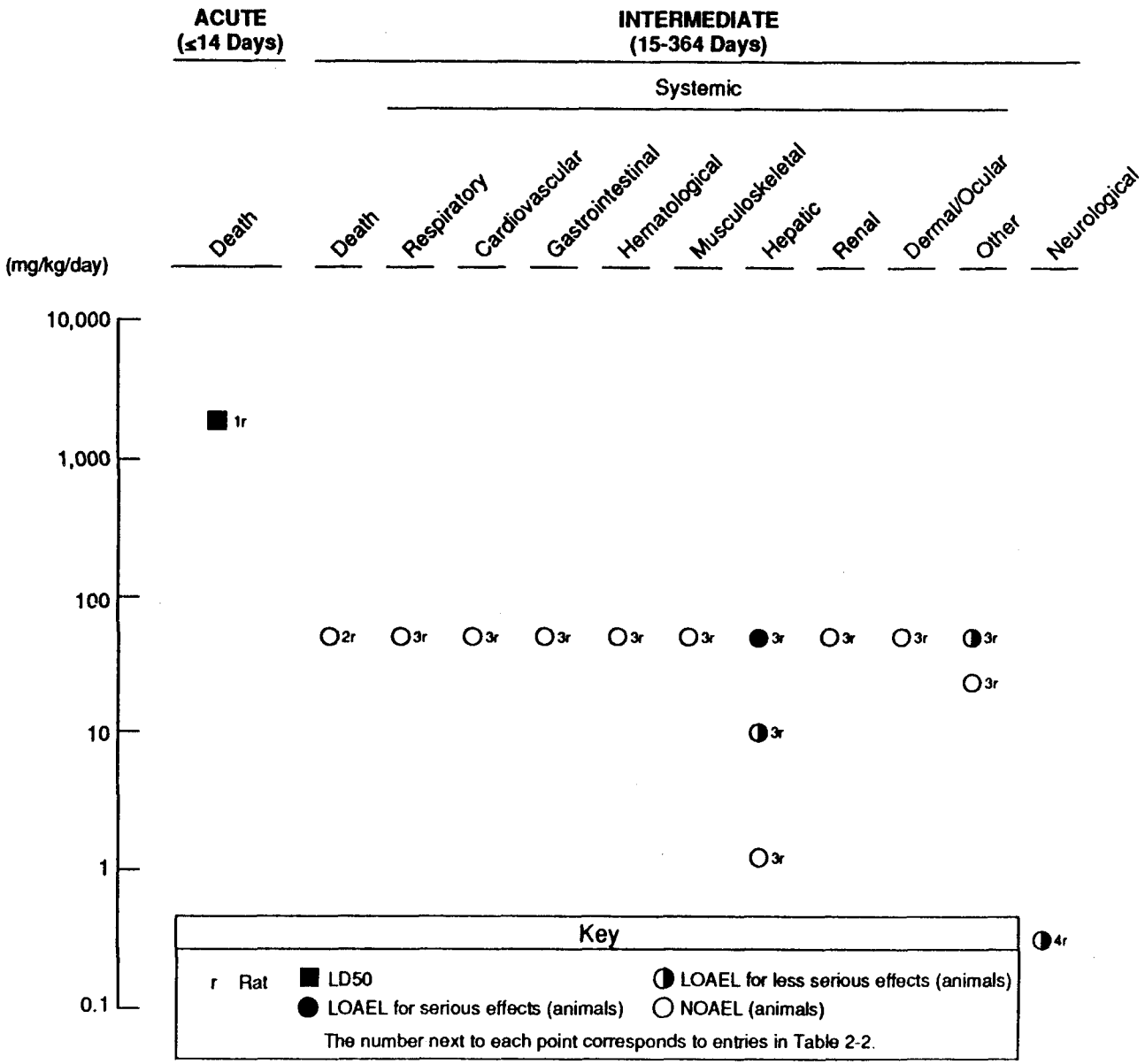
TABLE 2-2. Levels of Significant Exposure to Pyridine - Oral

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
ACUTE EXPOSURE								
Death								
1	Rat		1 d 1x/d				1580 (LD50)	Smyth et al. 1951
INTERMEDIATE EXPOSURE								
Death								
2	Rat	(GW)	90 d 1x/d		50			Anderson 1987
Systemic								
3	Rat	(GW)	90 d 1x/d	Resp	50			Anderson 1987
				Cardio	50			
				Gastro	50			
				Hemato	50			
				Musc/skel	50			
				Hepatic	1	10 (increased liver weight)	50 (inflammatory lesions)	
				Renal	50			
				Derm/oc	50			
				Other	25	50 (decreased weight gain)		
Neurological								
4	Rat	(GW)	90 d 1x/d			25 (restlessness)		Anderson 1987

[a]The number corresponds to entries in Figure 2-2.

Cardio = cardiovascular; d = day(s); Derm/oc = dermal/ocular; Gastro = gastrointestinal; (GW) = gavage in water; Hemato = hematological; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; X = time

FIGURE 2-2. Levels of Significant Exposure to Pyridine – Oral



Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after oral exposure to pyridine.

No compound-related gross or histopathological effects were observed in the muscles or bones of rats that received pyridine by gavage for 90 days at levels up to 50 mg/kg/day (Anderson 1987).

Hepatic Effects. No reliable studies were located regarding hepatic effects in humans after oral exposure to pyridine. Case studies have been reported in which two patients with epilepsy developed hepatic effects when treated with pyridine (Pollock et al. 1943). Co-administration of other medications including magnesium sulfate, sodium bromide, phenobarbital, and/or sodium dilantin to these patients before and during pyridine administration and the lack of information on their hepatic status previous to pyridine administration preclude a clear understanding of the role of pyridine in the observed effects.

Pyridine exposure has been associated with hepatic effects in rats. In a 90-day study, female rats that received pyridine by gavage at dosage levels of 10 mg/kg/day and higher had significantly increased liver weights (Anderson 1987). Inflammatory hepatic lesions were found in 70% of male rats that received 50 mg/kg/day. Lesions included bile ductule proliferation, mixed peribiliary infiltrate, and enlarged vacuolated hepatocytes. These lesions were reported in 20% of females at 50 mg/kg/day. The NOAEL for liver effects in this study was 1 mg/kg/day. In a 3-month drinking water study, mice that received pyridine at dosage levels up to 380 mg/kg/day did not have significantly increased levels of malondialdehyde (a measure of lipid peroxidation) in their livers (Pinsky and Bose 1988). Hepatic effects, including liver enlargeness, vacuolization, and necrosis were also reported in early studies in which pyridine citrate in diets was administered to male rats for up to 4 months in a complex series of dietary experiments (Baxter 1948; Coulson and Brazela 1948; Baxter and Mason 1947). However, due to extreme variations in the dietary sources of vital nutrients and the failure to describe in detail the effects of the diets alone (without pyridine) on the liver of these rats, it is difficult to clearly attribute the observed effects to pyridine exposure.

Renal Effects. No reliable studies were located regarding renal effects in humans after oral exposure to pyridine. Renal effects have been reported in case studies in which patients with convulsive disorders were given pyridine in conjunction with other medications such as magnesium sulfate, sodium bromide, phenobarbital, and/or sodium dilantin (Pollock et al. 1943). Because of the coadministration of other substances and because the renal status of these patients before pyridine administration was not described, it is not possible to attribute the observed renal effects to pyridine.

No compound-related gross or histopathological effects were observed in the kidneys of rats that received pyridine by gavage for 90 days at dosage levels up to 50 mg/kg/day (Anderson 1987). Renal degeneration has been reported in studies in which pyridine citrate was administered in the diets of male rats for up to 4 months (Baxter 1948; Baxter and Mason 1947). However, despite variations in the composition of the diets and a lack of detailed information on the effects of those diets on the renal status of the test animals, it is possible to draw conclusions on the renal effects of pyridine administration from these studies.

Dermal/Ocular Effects. No studies were located regarding dermal/ocular effects in humans after oral exposure to pyridine. However, congestion of the epiglottis, trachea, bronchi, lungs, esophagus, and stomach was reported in a case of accidental swallowing of half a cupful of pyridine which resulted in death (Helme 1893). This common finding of congestion would indicate that pyridine is irritating to mucous membranes of the gastrointestinal and respiratory systems.

No compound-related dermal or ocular effects were observed in rats that received pyridine by gavage for 90 days at dosage levels up to 50 mg/kg/day (Anderson 1987).

Other Systemic Effects. No studies were located regarding other systemic effects in humans after oral exposure to pyridine.

In a go-day study, total body weight gain for male rats that received pyridine by gavage at 50 mg/kg/day was significantly decreased from that of controls during weeks 8-12 of the study (Anderson 1987). Significantly decreased weight gain was not found in any other dosage group. The NOAEL for this effect was 25 mg/kg/day.

2.2.2.3 Immunological Effects

No studies were located regarding immunological effects in humans or animals after oral exposure to pyridine.

2.2.2.4 Neurological Effects

No useful studies were located regarding neurological effects in humans after oral exposure to pyridine. A case study was reported in which a patient with epilepsy was reported to develop further neurological roblems, including a stuporous condition, slow and slurred speech, and slow reflexes during a 4-month oral treatment with pyridine as an anticonvulsive (Pollock et al. 1943). Co-administration of other medications, including magnesium sulfate, sodium bromide, phenobarbital and/or sodium dilantin to this patient before and during pyridine administration, compounded by the existing neurological disease state, preclude a clear understanding of the role of pyridine in the observed effects.

No compound-related effects were observed in the brains of rats that received pyridine by gavage for 90 days at dosage levels up to 50 mg/kg/day (Anderson 1987). However, restlessness was observed in male rats following oral exposure at all dosage levels.

In a 3-month drinking water study, mice that received pyridine at a dosage level of 380 mg/kg/day had significantly increased levels of malondialdehyde (a measure of lipid peroxidation) in the cerebellum and striatum of their brains (Pinsky and Bose 1988). A marked but nonsignificant increase was measured in the cortex. The NOAEL for these effects was 38 mg/kg/day.

The NOAEL value for neurological effects in the rat in the intermediate-duration category is recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.5 Developmental Effects

No studies were located regarding developmental effects in humans or animals after oral exposure to pyridine.

2.2.2.6 Reproductive Effects

No studies were located regarding reproductive effects in humans or animals after oral exposure to pyridine.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans after oral exposure to pyridine.

No chromosomal damage was observed in a micronucleus test in which mice were administered a single dose of pyridine by gavage at doses up to 1,000 mg/kg (Harper et al. 1984). Other genotoxicity studies are discussed in Section 2.4.

2.2.2.8 Cancer

No studies were located regarding cancer effects in humans or animals after oral exposure to pyridine.

2.2.3 Dermal Exposure

2.2.3.1 Death

No studies were located regarding death in humans or animals after dermal exposure to pyridine.

2.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, or other systemic effects in humans or animals after dermal exposure to pyridine.

Dermal/ocular Effects. In primary skin irritation studies in rabbits, application of pure pyridine has resulted in mild dermal irritation (scored 3 out of a possible 10) and moderate ocular irritation (scored 7 out of a possible 10) (Smyth et al. 1951).

No studies were located regarding the following health effects in humans or animals after dermal exposure to pyridine:

2.2.3.3 Immunological Effects

2.2.3.4 Neurological Effects

2.2.3.5 Developmental Effects

2.2.3.6 Reproductive Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.4.

2.2.3.8 Cancer

No studies were located regarding carcinogenic effects in humans or animals after dermal exposure to pyridine.

2.2.4 Other Routes of Exposure

Because the available data on the toxicity of pyridine via inhalation, oral, and dermal exposure are extremely limited, studies conducted via intraperitoneal and subcutaneous exposures have also been considered. These studies are also limited in number and scope, and serve only to provide additional evidence that decreased weight gain is associated with exposure to this chemical.

2.2.4.1 Death

Acute LD_{50} values for subcutaneously administered pyridine in rats have been reported as 1,000 mg/kg (Brazda and Coulson 1946) and 866 mg/kg (Mason et al. 1971). An LD_{50} of 1,200 mg/kg was reported for mice that received pyridine via intraperitoneal injection (Baxter and Mason 1947).

Mortality rates for rats that received subcutaneous injections of pyridine twice weekly for a year at levels up to 100 mg/kg/day were comparable to mortality rates of controls (Mason et al. 1971).

2.2.4.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, or dermal/ocular effects in humans or animals after intraperitoneal or subcutaneous exposure to pyridine.

Other Systemic Effects. No studies were located regarding other systemic effects in humans after intraperitoneal or subcutaneous exposure to pyridine.

In rats that received subcutaneous injections of pyridine at 100 mg/kg/day twice weekly for a year, body weight was decreased 5%-16% below that of controls at the end of treatment. By 6 months after the termination of treatment, weights were comparable to control weights (Mason et al. 1971).

2.2.4.3 Immunological Effects

No studies were located regarding immunological effects in humans or animals after intraperitoneal or subcutaneous exposure to pyridine.

2.2.4.4 Neurological Effects

No studies were located regarding neurological effects in humans or animals after intraperitoneal or subcutaneous exposure to pyridine.

2.2.4.5 Developmental Effects

Abnormal chick development resulted from the injection of pyridine into eggs at very high levels (10 mg/egg or 20 mg/egg). Muscular hypoplasia occurred in 15% of chicks at the low dose and 67% at the high dose. In addition, at the high dose, 4.9% of the chicks had defective beaks and 1.1% had short or twisted necks (Landauer and Salam 1974).

2.2.4.6 Reproductive Effects

No studies were located regarding reproductive effects in humans or animals after intraperitoneal or subcutaneous exposure to pyridine.

2.2.4.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.4.

2.2.4.8 Cancer

No studies were located regarding cancer effects in humans after intraperitoneal or subcutaneous exposure to pyridine.

There was no evidence of carcinogenicity due to pyridine administration in rats that received subcutaneous iniections at levels up to 100 mg/kg/day twice weekly for a year (Mason et al. 1971).

2.3 TOXICOKINETICS

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

No studies were located regarding absorpt inhalation exposure to pyridine. ion in humans or anima1s after inhalation exposure to pyridine.

2.3.1.2 Oral Exposure

The available information indicates that orally administered pyridine is well absorbed by humans and animals.

By 24 hours after ingestion of a single dose of ^{14}C-pyridine at 0.05 mg/kg (administered in orange juice) by humans, approximately 67% of the administered ^{14}C-label was recovered in the urine (D'Souza et al. 1980), indicating that at least 67% had been absorbed within that time period. In that same study, rats and guinea pigs that received ^{14}C-pyridine at 7 mg/kg excreted 58% and 76%, respectively of the ^{14}C-label in urine by 24 hours after administration, indicating absorption of at least those percentages of the administered dose. Rats administered ^{14}C-pyridine at 7, 68, and 357 mg/kg excreted 58%, 13%, and 20%, respectively, of the ^{14}C-label in their urine within 24 hours. The lower rate of excretion at higher doses suggests that the uptake of pyridine may involve nonlinear saturation kinetics.

2.3.1.3 Dermal Exposure

No studies were located regarding absorption in humans or animals after dermal exposure to pyridine.

2.3.2 Distribution

No quantitative studies were located regarding distribution in humans or animals after exposure to pyridine by the following routes:

2.3.2.1 Inhalation Exposure

2.3.2.2 Oral Exposure

2.3.2.3 Dermal Exposure

2.3.3 Metabolism

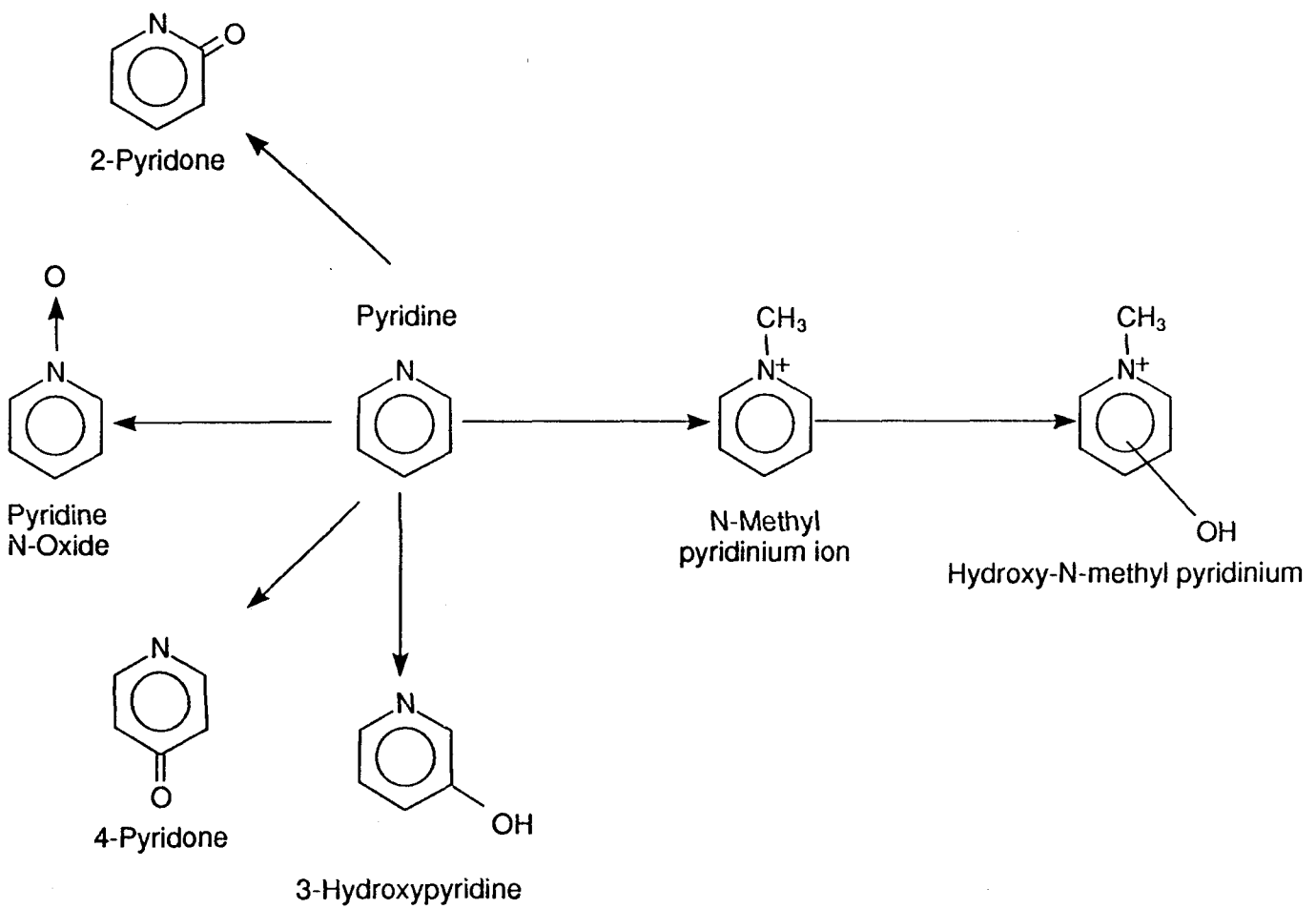
Some information on the metabolism of pyridine is derived from a study in which the N-methylpyridinium ion was identified as a urinary metabolite of ^{14}C-pyridine administered orally to humans, rats, and guinea pigs and via intraperitoneal administration to rats, guinea pigs, gerbils, hamsters, rabbits, and cats (D'Souza et al. 1980). In the 24-hour urine collection in humans, this metabolite was present at 9% of the administered dose, and in other species, levels of N-methylpyridinium varied widely with species, dose level, route of administration, and period of urine collection. Rats had a relatively low ability to methylate pyridine administered at 7 mg/kg either orally or via intraperitoneal injection, with 3.1% and 5.0%, respectively, of the administered dose recovered as the N-methylpyridinium ion in their urine in 24 hours. In guinea pigs, for comparison, these values were 31% and 31%, respectively, for oral and intraperitoneal administration. N-methylpyridinium appears to be more toxic to rats and mice than pyridine itself (Brazda and Coulson 1946). No attempts were made to identify other metabolites of pyridine in this study. However, a subsequent study identified pyridine-Noxide as a urinary metabolite of all species tested in that study except rabbits and as accounting for nearly one-third of the total radioactivity (32% of the administered dose) in the 24-hour urine from the human volunteers in that study (Damani et al. 1982). Other pyridine metabolites determined in these test animals included 2-pyridone, 3-hydroxypyridine, and 4-pyridone (human urine was not analyzed for these metabolites). Pyridine-N-oxide was also identified in the urine of hamsters, mice, rats, rabbits, ferrets, and guinea pigs after intraperitoneal administration of pyridine (Gorrod and Damani 1980). In an analysis of the data on urinary metabolites of pyridine reported in the early literature, EPA (1978) and Santodonato et al. (1985) have proposed the metabolic pathway by which N-methylation followed by ring hydroxylation or, alternatively, ring hydroxylation in the meta position would account for the observed metabolites. The presence of the N-methylpyridinium ion has been reported in the urine of humans, rats, guinea pigs, gerbils, mice, hamsters, and cats (D'Souza et al. 1980). However, this pathway does not take into account the identification of pyridine-N-oxide and other metabolites in the urine of several species (humans, hamsters, rats, rabbits, mice, ferrets, and guinea pigs) after oral or intraperitoneal administration of pyridine (Damani et al. 1982; Gorrod and Damani 1980). A proposed metabolic pathway incorporating all above metabolites for pyridine is shown in Figure 2-3.

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

No studies were located regarding excretion in humans or animals after inhalation exposure to pyridine.

FIGURE 2-3. Proposed Metabolic Pathway for Pyridine*



*Source: D'Sonza, et al. 1980; Damani, et al. 1982; EPA 1978; Santodonato et al. 1985

2.3.4.2 Oral Exposure

The only available information on excretion of orally administered pyridine is a study by D'Souza et al. (1980). In two humans who received ^{14}C-pyridine at 0.05 mg/kg (administered in orange juice), approximately 67% of the administered ^{14}C-label was recovered in the urine in a 24-hour period. In rats and guinea pigs administered 7 mg/kg, recovery was approximately 58% and 76%, respectively. These data indicate that urine is the major route of pyridine excretion in these species at these dose levels. No other information was provided.

2.3.4.3 Dermal Exposure

No studies were located regarding excretion in humans or animals after dermal exposure to pyridine.

2.3.4.4 Other Routes of Exposure

No data are available on the excretion of pyridine administered to humans via other routes of exposure. Several animal species were given intraperitoneal injections of ^{14}C-pyridine in a study by D'Souza et al. (1980). In rats, guinea pigs, gerbils, mice, hamsters, rabbits, and cats that received doses of 7 mg/kg, levels of ^{14}C-label recovered in urine (48-hour collection in cats, 72 hours in rabbits, 24 hours in all other species) ranged from 75% of the administered dose in cats to 48% in rats.

Comparisons of ^{14}C-label excretion in the urine of rats and guinea pigs that received the same dose (7 mg/kg) of ^{14}C-pyridine via oral or intraperitoneal administration indicated that values within each species were similar for both routes of administration; in rats, these values were 58% and 48%, respectively, of the administered dose, and in guinea pigs, these values were 31% and 31%, respectively, of the administered dose for both routes.

2.4 RELEVANCE TO PUBLIC HEALTH

As discussed in Section 2.2, the health effects resulting from exposure to pyridine have not been well studied. Other than LC_{50} data, there are no quantitative studies in humans or animals on the effects from inhalation exposure to pyridine, so no inhalation MRLs can be derived. By the oral route, there is limited evidence from case studies in humans (Pollock et al. 1943) that the liver is a target tissue for pyridine, and this is supported by a recent study in rats (Anderson 1987). However, it is not certain that hepatotoxicity is the most sensitive end point, since pyridine may cause neurobehavioral effects at lower exposure levels (Anderson 1987). Because of the lack of confidence in the most sensitive end point and the sparsity of

quantitative data on the NOAEL for hepatotoxic and neurotoxic effects, no oral MRLs can be derived at present. Similarly, no dermal MRLs can be calculated, due both to a lack of quantitative dermal dose-response data, and the lack of an appropriate methodology for development of dermal MRLs.

Death. No deaths that are clearly attributable to pyridine have been reported in humans. The available information in animals does not suggest that lethality is a public health concern for exposure to pyridine via inhalation or the oral route.

The death of a 32-year-old man who had been receiving pyridine as an oral medication for a convulsive disorder (epilepsy) has been reported (Pollock et al. 1943). Because other medications such as magnesium sulfate, sodium bromide, phenobarbital, and/or sodium dilantin were stated to be previous and continuing medications for this patient and because the physical condition of this man at the start of pyridine treatment was not described, it is not possible to attribute this death specifically to pyridine exposure.

In another case study, a 29-year-old man died within 2 days of swallowing an estimated half-cup of pyridine during a syphoning accident (Helme 1893). Medical intervention was immediate and rigorous and included the administration of demulcents (not otherwise described), milk, and brandy, application of mustard and linseed poultices to his throat and chest, and a brandy enema which he retained. It is not possible to assess the potential contribution of this treatment regimen to his rapid death.

The levels of pyridine necessary to cause death in animals are very high. Reported l-hour validation LC_{50} values for rats were approximately 9,000 ppm (Vernot et al. 1977), and the acute oral LD_{50} value in rats was 1,580 mg/kg (Smyth et al. 1951). No compound-related deaths were reported in rats that received pyridine by gavage for 90 days at levels up to 50 mg/kg/day (Anderson 1987). Therefore, it appears to be unlikely that inhalation or ingestion of the low levels of pyridine that may be present in air, water, or food would present a concern for lethality in humans. A possible exception may be laboratory or industrial settings where accidental exposure to high levels of pyridine can occur.

Systemic Effects.

Hepatic Effects. Hepatic effects are the major potential health concern associated with exposure to pyridine. There is no clear evidence of hepatic effects associated with human exposure to pyridine. In a go-day gavage study in Sprague-Dawley rats, however, increased liver weight and inflammatory hepatic lesions, including bile duct proliferation, mixed peribiliary infiltrate, and enlarged vacuolated hepatocytes were found (Anderson 1987). These observations suggest that human exposure to pyridine via the oral route may pose a concern for adverse liver effects. It is important to note that this concern is based on the results of a single study. However, preliminary

evidence of hepatic effects from pyridine exposure has been previously reported in studies conducted more than 40 years ago. Pyridine citrate was administered to male rats (also Sprague-Dawley) for up to 4 months in a complex series of dietary experiments that included variations in fat and carbohydrate sources and the levels of essential dietary nutrients such as certain amino acids (Baxter 1948; Baxter and Mason 1947; Coulson and Brazda 1948). The authors reported that the addition of pyridine to these diets resulted in hepatic enlargement, vacuolization, and necrosis. However, because of the other variations in the diet and lack of detail in reporting study results, it is difficult to interpret the findings of these experiments or to clearly attribute the observed effects to pyridine exposure. These studies do serve, however, to confirm the general conclusion of the Anderson (1987) study, which is that hepatic effects are of potential concern with oral exposure to pyridine and to suggest that exposed humans may also be at risk for hepatic effects.

Renal Effects. There is no information on renal effects associated with human exposure to pyridine. Observations of degeneration of the renal tubular epithelium were reported in studies in which pyridine citrate was administered to male rats for up to 4 months (Baxter 1948). The numbers of rats used per group and duration of exposure were not clearly reported. However, variations in dietary composition (i.e., source and percentage of vital nutrients) did not contribute to the appearance of the observed lesions.

The currently available data suggest that exposure to pyridine may be associated with potential renal effects in humans.

Other Systemic Effects. There is no clear evidence of other systemic effects in association with human exposure to pyridine. However, decreased weight gain in developing rats during a go-day gavage study (Anderson 1987) suggests that this may be an area of concern associated with exposure to pyridine. During weeks 8-12 of this study, male rats consistently weighed 12%-14% less than controls, a difference that was statistically as well as clinically significant. Food consumption was not decreased in treated animals of either sex. This observation is supported by the results of a l-year study in which the body weights of rats that were administered pyridine at doses up to 100 mg/kg/day via subcutaneous injection were decreased 5%-16% below control values (Mason et al. 1971). Although these observations suggest that effects on body weight might also pose a potential health concern for humans exposed to pyridine, it is important to note that they are based on limited evidence.

Immunological Effects. There are no studies of immunological effects in humans or animals exposed to pyridine via any route of exposure.

Neurological Effects. There are few studies of neurological effects in humans exposed to pyridine via any route of exposure. Pyridine is a central nervous system depressant. Neurological effects in man (nonpatients) have been noted by Pollock et al. (1943) and Neff (1886). Slow and slurred speech, slow reflexes, and a stuporous condition were reported to occur in an epilepsy patient who had been receiving other drugs in addition to pyridine (Pollock et al. 1943). Because of the existing disease state and the co-administration of other drugs, this information can only be viewed as suggestive evidence that exposure to pyridine can result in neurological effects in humans. Healthy adults, exposed to undetermined amounts of pyridine vapors, developed symptomatology which included some neurological effects. Included were slight temporal headaches, sensations approaching giddiness, a desire to sleep, and quickening of pulse and respiration (Neff 1886).

No morphological effects were noted in the brains of rats that received pyridine by gavage for 90 days at dosage levels up to 50 mg/kg/day (Anderson 1987). However, restlessness was noted in the male rats of all groups which received pyridine. This neurological effect was not observed in controls or female test rats. Lipid peroxidation was observed in selected areas of the brain of mice that received pyridine in their drinking water for 3 months at a dosage level of 380 mg/kg/day (Pinsky and Bose 1988). The authors suggest that lipid peroxidation could lead to regionally selective neurotoxicity. The significance of this observation in relation to neurological function and/or morphology is not entirely clear. However, there is some evidence that neurological effects resulting from pyridine exposure via the inhalation and oral routes of exposure may be health concerns.

Developmental Effects. There are no studies of developmental effects in humans or animals exposed to pyridine via the inhalation, oral, or dermal routes. However, abnormal chick development resulted from injection of pyridine into eggs at very high levels (l0-20 mg/egg). Muscular hypoplasia occurred in 15% of chicks at the low dose and 67% at the high dose. In addition, at the high dose, 4.9% of the chicks had defective beaks and 1.1% had short or twisted necks (Landauer and Salam 1974).

Because of the test system and extremely high doses of pyridine used, the relevance of these findings to the potential effects of pyridine on human development is not clear. However, this study constitutes the only investigation of the effects of pyridine on prenatal development; therefore, these findings warrant some consideration.

Reproductive Effects. No studies were located on reproductive effects of pyridine in humans or animals after any route of exposure.

Genotoxic Effects. No studies were located concerning genotoxic effects of pyridine in humans after any route of exposure. The only available in vivo study in animals provides no evidence that exposure to pyridine is potentially

genotoxic. Negative results were reported in a micronucleus test in which single doses of pyridine were administered to mice by gavage at levels up to 1,000 mg/kg (Harper et al. 1984).

In vitro genotoxicity data for pyridine, presented in Table 2-3, also indicate that pyridine does not show genotoxic potential. The results of tests for chromosomal aberrations using Chinese hamster ovary cells were negative (Ishidate and Odashima 1977) and sister chromatid exchange assays were weakly positive (Abe and Sasaki 1977). Results of assays using several strains of Salmonella typhimurium have all been negative (Aeschbacher et al. 1989; Commoner 1976; Riebe et al. 2982; Seixas et al. 1982), as well as the pol A^+/pol A^- assay in Escherichia coli (Riebe et al. 1982).

Cancer. No studies were located of carcinogenic effects of pyridine exposure in humans or animals by any route of exposure.

2.5 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time biologic samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to pyridine are discussed in Section 2.5.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well physiologic

TABLE 2-3. Genotoxicity of Pyridine In Vitro

Species (test system)		End point	Results: With activation	Results: Without activation	Reference
Prokaryotic organisms:					
Salmonella typhimurium	TA98, TA100, TA102, TA109	Gene mutation	-	-	Aesbacher et al. 1989
S. typhimurium	TA1537, TM677		-	-	Seixas et al. 1982
S. typhimurium	TA98, TA100, TA1537		-	-	Riebe et al. 1982
S. typhimurium	TA100, TM1535, TM1537, TM1538, TM1536		-	-	Commoner 1976
Escherichia coli	343/113 pol A⁻	DNA damage	-	-	Riebe et al. 1982
E. coli	KMBL 1787/pol A⁻				
Mammalian systems:					
Chinese hamster ovary cells		Chromosomal aberrations	No data	-	Ishidate and Odashima 1977
Chinese hamster ovary cells		Chromosomal aberrations	No data	-	Abe and Sasaki 1977
Chinese hamster ovary cells		Sister chromatid exchange	No data	(+)	Abe and Sasaki 1977

(+) = weakly positive result; - = negative result

signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are often not substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by pyridine are discussed in Section 2.5.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, biologically effective dose, or target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, "POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE."

2.5.1 Biomarkers Used to Identify and/or Quantify Exposure to Pyridine

There is currently no biomarker that is used to identify or quantify exposure to pyridine. Pyridine can be measured in blood and urine in humans and animals by gas chromatography (Audunsson 1988; Dubowski 1975). Also the rate of urinary excretion levels of ^{14}C-labelled pyridine (Shaker et al. 1982) and its metabolite, the N-methylpyridinuim ion, have been measured (D'Souza et al. 1980). However, these methods cannot be used to measure pyridine exposure in humans. Pyridine-N-oxide can also be identified in the urine of several species, including mice, rats, rabbits, hamsters, guinea pigs and ferrets after intraperitoneal exposure to pyridine (Gorrod and Damani 1980). However, based on the currently available information, the levels of these substances in biological media cannot be used to calculate or estimate corresponding levels of exposure to pyridine.

2.5.2 Biomarkers Used to Characterize Effect Caused by Pyridine

There are currently no subtle or sensitive biomarkers of effects associated with pyridine. Because of the limited amount of data available on this chemical, even the broad categories of toxicity have not yet been adequately characterized.

2.6 INTERACTIONS WITH OTHER CHEMICALS

There is currently no information on the interactions of pyridine with other chemicals.

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

No populations have been identified that are unusually susceptible to pyridine. However, persons with existing liver and kidney disease may be at increased risk of further liver and kidney damage, based on the results of studies in animals.

2.8 MITIGATION OF EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to pyridine. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to pyridine. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

Central nervous system depression and hepatic and renal damage are the major effects observed following exposure to pyridine. Human exposure to pyridine may occur by inhalation, ingestion or by dermal contact. However, inhalation is the predominant route for acute exposures. General recommendations for reducing absorption of pyridine following exposure have included removing the exposed individual from the contaminated area and removing contaminated clothing, followed by washing the skin thoroughly with soap and water. If the eyes are exposed they are rinsed with water. Gastric lavage or administration of activated charcoal and a cathartic are common treatments following oral exposure (Spoerke 1991). Emetics are not recommended due to the hazard of aspirating gastric contents (Bronstein and Currance 1988).

Information is limited regarding the retention of pyridine by the body, and so the need for methods for enhancing elimination is not clear. Excretion studies suggest that the compound is rapidly eliminated from the body (D'Souza et al. 1980). However, no information was located on the biological halflives of pyridine or its metabolites. No methods have been established for reducing the body burden following exposure to pyridine.

The toxicity of pyridine has been attributed to its metabolites. If this is true, it could be possible to reduce toxicity by pharmacologically limiting metabolism, or shunting metabolism to routes that are less toxic than others. However, current knowledge of the metabolism of pyridine does not allow a full assessment of the net effect of interfering with that metabolism. Available studies suggest that methylation of pyridine may cause hepatic and renal injury by draining the labile methyl groups of choline and methionine thus producing an "intrinsic" deficiency of these substances (Baxter 1949; Baxter and Mason 1947). However, based on the metabolites found in urine in more recent excretion studies, methylation may not be a major metabolic route (D'Souza et al. 1980). Therefore, it's role in the overall toxicity of pyridine may be suspect. Urinary excretion of methylated pyridine accounted for only 5-12% of the administered dose in humans (D'Souza et al. 1980). On the other hand, urinary excretion of pyridine-N-oxide accounts for 32% of the administered dose, which is approximately half of the total radioactivity in the 24-hr urine from the human volunteers (Damani et al. 1982). The potential role of N-oxidation in the toxicity of pyridine has not been evaluated. Specific methods for reducing toxic effects cannot be established because of the limited information regarding the mechanisms of toxicity of pyridine.

2.9 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of pyridine is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of pyridine.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

2.9.1 Existing Information on Health Effects of Pyridine

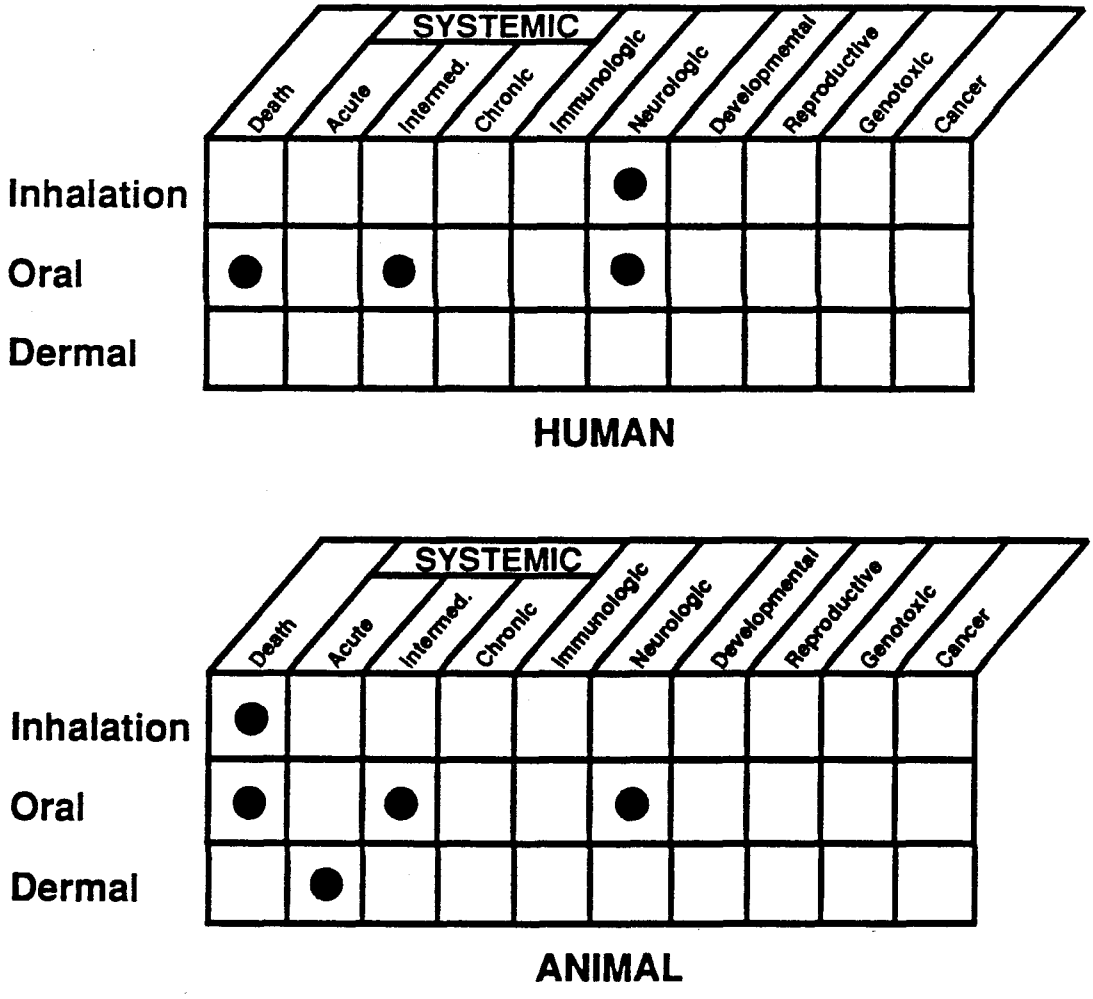
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to pyridine are summarized in Figure 2-4. The purpose of this figure is to illustrate the existing information concerning the health effects of pyridine. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs" information (i.e., data gaps that must necessarily be filled).

As shown in Figure 2-4, studies of human exposure to pyridine are limited to case reports in which systemic effects, neurological effects, and death were associated with oral exposure. Existing animal studies are limited to lethality determinations via the inhalation and oral routes, dermal and ocular irritation data, and information on systemic and neurological effects from an intermediate-duration study via the oral route.

2.9.2 Data Needs

Acute-Duration Exposure. There are currently no useful data available on humans exposed to pyridine for this duration period for any route of exposure. The only information available for animals are inhalation LC_{50} and oral LD_{50} values in rats (Smyth et al. 1951; Vernot et al. 1977) and primary dermal and ocular irritation data in rabbits (Smyth et al. 1951). Data were

FIGURE 2-4. Existing Information on Health Effects of Pyridine



● Existing Studies

not considered sufficient to derive an MRL for any route. Acute-duration studies conducted via the oral route would probably be most useful since persons living or working in the vicinity of hazardous waste sites are likely to be exposed via this route because pyridine has been found in the drinking water in these areas. Also, contamination of food and drinking water is possible in laboratories and industries where pyridine is being used. Inhalation data would also be useful for these populations and exposed workers. Toxicokinetic data are very limited for this chemical. A study using dermal exposure would be relevant to the safety of workers if absorption via this route were first demonstrated in other studies.

Intermediate-Duration Exposure. There are currently no reliable data on humans exposed to pyridine for this duration period via any route of exposure. Data in animals are limited to a 90-day gavage study in rats in which the major adverse effects were hepatic lesions, neurological effects, and effects on weight gain were also seen (Anderson 1987). However, because there were no reliable supporting or confirmatory studies for this duration, the available data are not considered sufficient to derive an MRL for the oral or any other route. Toxicokinetic data are also extremely limited. An intermediateduration (90-day) study via the oral route would be useful since this is an important route of exposure for persons exposed via drinking water as a result of living or working in the vicinity of hazardous waste sites. The National Toxicology Program (NTP) is currently conducting a 14-week drinking water study in rodents (2 strains of rats and 1 strain of mice) which may provide valuable data to compare with information from the Anderson (1987) study which now serves as virtually the entire useful database for this duration period. A study conducted via dermal exposure would be especially useful if dermal absorption could first be demonstrated by other studies.

Chronic-Duration Exposure and Cancer. There are no chronic-duration data available for humans or animals, and there are no toxicokinetic data for this exposure duration. Therefore, it is not possible to derive an MRL for any route for this duration. Chronic studies using the oral route would be useful, since chronic low-level exposure to pyridine via drinking water may occur in the vicinity of hazardous waste sites. Chronic inhalation studies are also necessary to characterize potential effects from breathing low levels of pyridine near these sites.

There is also no information on the carcinogenic potential of pyridine in humans or animals. Chronic-duration studies conducted via any route of exposure should assess this potential effect. As stated previously, exposure via the oral route is probably the most relevant to persons living or working in the vicinity of hazardous waste sites. Inhalation exposure to pyridine in contaminated air is also a route of concern for persons living and working near these sites.

Genotoxicity. The currently available in vivo and in vitro studies do not indicate that pyridine is potentially genotoxic (Abe and Sasaki 1977; Aeschbacher et al. 1989; Commoner 1976; Harper

et al. 1984; Ishidate and Odashima 1977; Riebe et al. 1982; Seixas et al. 1982). Further studies in this area do not appear to be warranted unless metabolic studies indicate the generation of a potentially genotoxic metabolite, an alkylating agent, and/or
a compound that might be capable of DNA binding.

Reproductive Toxicity. There is currently no information on the effects of pyridine on reproductive parameters in humans or animals via any route of exposure. In any further studies conducted for any duration period and via any route of exposure, it would be useful to investigate the potential doseresponse relationship of exposure to pyridine on a number of end points, including sperm count, sperm morphology, and reproductive organ pathology. If the reproductive system were identified as a target, studies to assess reproductive function would be useful. This information would be valuable in helping to assess the impact of pyridine on the reproductive capacity of exposed workers and persons living and working in the vicinity of hazardous waste sites.

Developmental Toxicity. There are currently no available studies on the developmental effects of pyridine via inhalation, oral, or dermal exposure in humans or animals. The relevance of effects observed on the development of chick embryos when extremely high levels of pyridine were injected into eggs (Landauer and Salam 1974) is unknown; these observations suggest that this may be an area in which further study is warranted. Studies to assess the potential developmental effects of exposure to pyridine would therefore, be useful. Chronic studies using the oral and inhalation routes would probably be the most helpful in assessing the potential risks to the offspring of persons exposed in the vicinity of hazardous waste sites.

Immunotoxicity. There are currently no data in humans or animals on the effects of pyridine on the immune system via any route of exposure. Immunological assessments, including analysis of peripheral blood components and effects on lymphoid tissue, would be a valuable component of any intermediate- or chronic-duration studies conducted in the future via any route of exposure. This would be helpful in developing a dose-response relationship and assessing the potential risks of persons exposed in the workplace and in the vicinity of hazardous waste sites.

Neurotoxicity. There are currently few data on the effects of pyridine on the nervous system of humans via any route of exposure. However, pyridine is a central nervous depressant and has been used to treat epileptic patients (Pollock et al. 1943). The only information in animals is a 90-day gavage study in rats (Pinsky and Bose 1988) in which no morphological effects were noted in brain tissue and a 3-month drinking water study in mice which resulted in increased levels of lipid peroxidation in brain tissue, Restlessness in male rats was observed in the 90 day gavage study (Anderson 1987). In any further studies conducted via any route of exposure for any duration period, it would be useful to collect data on any demonstrated

neurological effects, including histopathological changes as well as clinical manifestations in order to assess the potential neurotoxic effects of exposure to pyridine in the workplace or in the vicinity of hazardous waste sites. A study currently being conducted by the firm of Arthur D. Little to assess the neurological effects of short-term oral exposure to pyridine in mice should provide useful information.

Epidemiological and Human Dosimetry Studies. No epidemiological studies have been identified for populations exposed to pyridine. These studies would be useful in assessing potential adverse effects in humans. In any such studies, points of greatest interest based on *the results of previous studies* in animals appear to be effects *on liver and body weight and any developmental* abnormalities in the offspring of exposed persons. Neurological, dermal/ocular, and renal observations would also be of interest. Similarly, human dosimetry studies of these populations would be useful in associating pyridine levels with the reported effects.

Biomarkers of Exposure and Effect. Measurement of pyridine or its metabolites, N-methylpyridinium, or pyridine-N-oxide, in blood or urine may provide an adequate qualitative indication of recent exposure to pyridine (Audunsson 1988; Dubowski 1975; Gorrod and Damani 1980). However, very little information is currently available on these measurements in humans or animals, especially for N-methylpyridinium. The development of methods that could be used to calculate or estimate levels of exposure to pyridine from the levels of these substances in biological fluids would be extremely useful.

There are currently no subtle or sensitive biomarkers of effects known for pyridine. After pyridine toxicity has been more fully studied, further research to identify biomarkers of pyridine effects would be helpful in assessing possible health impacts of pyridine around hazardous waste sites.

Absorption, Distribution, Metabolism, and Excretion. There is currently very little information on the toxicokinetics of pyridine. A study in humans, rats, and guinea pigs indicates that it can be absorbed by these species via the oral route (D'Souza et al. 1980). Estimates of the extent of absorption via the inhalation and dermal routes and calculations of the rates of absorption via all three routes would be useful in helping to compare relative potential risks due to the presence of pyridine in various environmental media. In addition, information on potential determinants of absorption (dose level, nutritional status, etc.) would also be helpful in assessing potential absorption by exposed humans and the consequent relevance of conducting further toxicity tests in animals by the inhalation or dermal routes.

There are no distribution data available for pyridine in humans or animals. The use of multiple species and a comparison of tissue levels of pyridine associated with multiple dose levels via each route of exposure would be useful in helping to assess the likelihood that pyridine would reach potential target organs in exposed humans.

It would be useful to fully elucidate the metabolic pathway for orally administered pyridine in mammalian species. Further studies via the oral route may provide data on potentially toxic intermediates, including evidence for the generation of alkylating agents. It would also be useful to collect data on urinary metabolites identified during inhalation or dermal administration of pyridine.

Available data indicate that in humans, rats, and guinea pigs, orally administered pyridine and/or its metabolites are excreted mainly in the urine (D'Souza et al. 1980). However, complete balance studies to account for all of the pyridine administered are not available. Data on fecal and breath excretion associated with the oral route and with all routes of excretion after inhalation and dermal administration would be useful.

Comparative Toxicokinetics. The toxicokinetic studies available in both humans and animals are limited and it is not possible to determine if there are any major differences in the kinetics of this compound across species. It would be useful to investigate patterns of distribution to identify target organs and to measure rates of excretion in several species and to identify blood metabolites in humans and animals in order to confirm these assumed relationships. Studies in this area would also be helpful in putting the results of all available toxicity studies into perspective in terms of their relevance to the potential human health effects of pyridine under similar conditions of exposure.

Mitigation of Effects. Recommended methods for the mitigation of acute effects of pyridine include administration of oxygen if exposure is by inhalation, flushing with water if exposure is to skin or eyes, and gastric lavage or administration of activated charcoal if exposure is oral (Bronstein and Currance 1988; Spoerke 1991). No information was located concerning mitigation of effects from lower-level or longer-term exposure to pyridine. Further information on techniques to mitigate such effects would be useful in determining the safety and effectiveness of possible methods for treating pyridine-exposed populations surrounding hazardous waste sites.

2.9.3 On-going Studies

A research project is now in progress investigating the neurological effects of short-term exposure to pyridine via gavage in the rat (CCTTE 1988). These tests are being conducted by the firm of Arthur D. Little and are sponsored by EPA's Office of Solid Waste. No other details are currently available for this study.

In addition, NTP is completing the prechronic phase of studies of pyridine (includes 14- and 90-day studies). The objective of these studies is to determine doses for the chronic toxicity and carcinogenicity bioassay of pyridine in a 2-year drinking water study. Dr. June Dunnick is the NTP

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

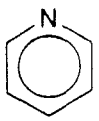
Table 3-1 lists common synonyms, trade names, and other pertinent identification information for pyridine.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Table 3-2 lists important physical and chemical properties of pyridine.

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-1. Chemical Identity of Pyridine

Characteristic	Information	Reference
Chemical name	Pyridine	Weast 1985
Synonyms	Azabenzene; azine	Sax and Lewis 1987
Trade names	No data	
Chemical formula	C_5H_5N	Weast 1985
Chemical structure		
Identification numbers:		
CAS registry	110-86-1	Sax and Lewis 1987
NIOSH RTECS	UR 8400000	Sax 1984
EPA hazardous waste	F005	HSDB 1989
	U196	HSDB 1989
OHM/TADS	7216879	HSDB 1989
DOT/UN/NA/IMCO shipping	UN1282	HSDB 1989
	IMCO 3.0	HSDB 1989
	IMCO 6.1	HSDB 1989
HSDB	0118	HSDB 1989
NCI	C55301	NLM 1989

CAS = Chemical Abstracts Service; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-2. Physical and Chemical Properties of Pyridine

Property	Information	Reference
Molecular weight	79.10	Weast 1985
Color	Slightly yellow to colorless	Sax and Lewis 1987
Physical state	Liquid	Sax and Lewis 1987
Melting point	-42°C	Weast 1985
Boiling point	115.5°C	Weast 1985
Density at 20°C	0.9819	Weast 1985
Odor	Nauseating	Sax and Lewis 1987
Odor threshold:		
Water	0.95 mg/L	Amoore and Hautala 1983
Air	0.17 ppm	Amoore and Hautala 1983
Solubility:		
Water at 20°C	Very soluble	Sax and Lewis 1987
Organic solvents	Soluble in alcohol, ether, benzene	Sax and Lewis 1987
Partition coefficients:		
Log K_{ow}	0.64/1.04	Verschueren 1983
Log K_{oc}	0.84	Roy and Griffin 1985
Vapor pressure at 13.2°C	10 mmHg	Sax 1984
at 20°C	14 mmHg	Verschueren 1983
at 25.5°C	20.6 mmHg	Chao et al. 1983
at 30°C	26 mmHg	Verschueren 1983
Henry's law constant:	1.1×10^{-5} atm-m^3-$mole^{-1}$ (25°C)	Hawthorne et al. 1985
Autoignition temperature	900°F (482°C)	Sax and Lewis 1987
Flashpoint	68°F (20°C) (closed cup)	Sax and Lewis 1987
Flammability limits	Lower 1.8, upper 12.4	*HSDB* 1989
Conversion factors	1 mg/m^3 = 0.30 ppm	Verschueren 1983
	1 ppm = 3.29 mg/m^3	Verschueren 1983
Explosive limits	1.8-12.4%	Sax and Lewis 1987
pKa	5.19	Reinhardt and Brittelli 1981

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.1 PRODUCTION

Pyridine is produced either by isolation from natural sources such as coal, or through chemical synthesis (HSDB 1989). Pyridine is produced by the fractional distillation of coal-tar residues (HSDB 1989; NSC 1978; Santodonato et al. 1985) in which 1 ton of coal produces 0.07-0.21 pounds of pyridine bases of which 57% is pyridine (Santodonato et al, 1985). Synthetically produced pyridine is currently the more important source of pyridine for commercial uses (Santodonato et al. 1985). Small amounts of pyridine are synthesized from acetaldehyde, formaldehyde, and ammonia with a fluidized silica-alumina catalyst, followed by fractionation to isolate the pyridine (Harper et al. 1985; HSDB 1989; NSC 1978).

Pyridine is produced from natural sources by Crowley Tar Products of Stow, Ohio, and Oklahoma City, Oklahoma (Harper et al. 1985; HSDB 1989; SRI 1986, 1987, 1988). Pyridine is synthetically produced by two companies, the Nepera Chemical Co. of Harriman, New York and the Reilly Tar and Chemical Corporation of Indianapolis, Indiana (Harper et al. 1985; SRI 1986, 1987, 1988).

Current volumes of pyridine produced in the United States were not located (HSDB 1989). Production volumes steadily increased from 1945 (844 metric tons) through 1968 (3,366 metric tons), and the estimated 1985 production volume of pyridine was 6,800 metric tons (Santodonato et a1. 1985). Production is expected to continue at a steady annual increase of l-28 depending upon economic conditions (Santodonato et al. 1985). The U.S. production capacity for synthetic pyridines (pyridine and pyridine derivatives) is estimated to be 27,216 metric tons (Santodonato et al. 1985). Harper et al. (1985) estimated the 1982 consumption of pyridine in the United States at 5,400-7,500 metric tons. Facilities that manufacture or process pyridine are shown in Table 4-l.

4.2 IMPORT/EXPORT

No information was located regarding the current import volume of pyridine. The 1973 import volume was 4.5 metric tons (HSDB 1989). The United States exports 50% of the pyridines it produces (Harper et al. 1985). It is not clear whether this includes pyridine derivatives in addition to pyridine. In 1975, exports of pyridine were 341 metric tons (HSDB 1989). No data were located regarding current export volumes.

4.3 USE

Pyridine is used directly in the denaturation of alcohol (ACGIH 1986; HSDB 1989; NSC 1978) and as a solvent in paint and rubber preparation (ACGIH 1986; HSDB 1989; NSC 1978) and in research laboratories for functions such as extracting plant hormones (Santodonato et al. 1985). Half of the pyridine

TABLE 4-1. Facilities that Manufacture or Process Pyridine[a]

Facility	Location	Maximum Amount on site (lbs)	Use
Arkansas Eastman Company	Batesville, AR	10,000-99,999	As a processing aid
Pfizer Inc. Groton Site	Groton, CT	10,000-99,999	As a processing aid
Eli Lilly And Company Clinton Laboratories	Clinton, IN	100,000-999,999	As a processing aid
Reilly Tar & Chemical Corporation	Indianapolis, IN	1,000,000-9,999,999	Produce; for on-site use/processing; for sale/distribution; as a reactant; as a processing aid
Air Products & Chemicals, Inc.	Wichita, KS	100,000-999,999	As a reactant
Union Carbide Corporation Industrial Chemicals	Hahnville, LA	1,000-9,999	As a reactant
Olin Corporation Lake Charles Plant	Lake Charles, LA	100,000-999,999	As a processing aid
Dow Chemical Louisiana Division	Plaquemine, LA	100-999	Produce; as an impurity
The Upjohn Company Portage Site	Portage, MI	10,000-99,999	As a processing aid
Burroughs Wellcome Co.	Greenville, NC	100,000-999,999	As a processing aid
Kollsman	Merrimack, NH	0-99	In ancillary or other uses
Hoffmann-La Roche Inc.	Nutley, NJ	10,000-99,999	As a processing aid
Nepera, Inc.	Harriman, NY	1,000,000-9,999,999	Produce; for sale/distribution
Eastman Kodak Company Kodak Park	Rochester, NY	100,000-999,999	As a reactant; in re-packaging; as a processing aid
Olin Corporation	Rochester, NY	100,000-999,999	As a reactant
The Wool Bureau, Inc.	Woodbury, NY	0-99	As a formulation component
Du Pont Circleville Plant	Circleville, OH	100,000-999,999	As a processing aid
Orsynex	Columbus, OH	1,000-9,999	As a processing aid
Bp Chemicals America, Inc.	Lima, OH	1,000-9,999	As a byproduct
American Cyanamid Company	Marietta, OH	10,000-99,999	As a reactant; as a processing aid
New Boston Coke Corporation	New Boston, OH	1,000-9,999	Produce; as a byproduct
The Upjohn Company	Barceloneta, PR	10,000-99,999	As a reactant; as a processing aid
Schering Industrial Development Corporation	Manati, PR	10,000-99,999	As a processing aid
Tennessee Eastman Company	Kingsport, TN	100,000-999,999	As a processing aid; in ancillary or other uses
Monsanto Company	Alvin, TX	10,000-99,999	In ancillary or other uses
Ici Americas Inc. Bayport Site	Pasadena, TX	1,000,000-9,999,999	As a reactant
Dan River Inc. Chemical Products Division	Danville, VA	1,000-9,999	As a reactant
Rhone-Poulenc Incorporated Ag Company	Institute, WV	100,000-999,999	As a processing aid

[a]Derived from TRI 1989

produced today is used as an intermediate in making various insecticides and herbicides for agricultural applications (ACGIH 1986; Harper et al. 1985; Santodonato et al. 1985). Approximately 20% goes into the production of piperidine (Harper et al. 1985; Santodonato et al. 1985) which is commercially significant in the preparation of chemicals used in rubber vulcanization and agriculture (NSC 1978). Pyridine is also used as an intermediate in the preparation of drugs (antihistamines, steroids, sulfa-type and other antibacterial agents) dyes, water repellents, and polycarbonate resins (ACGIH 1986; Harper et al. 1985; NSC 1978; Santodonato et al. 1985). Pyridine is also approved by the Food and Drug Administration (FDA) for use as a flavoring agent in the preparation of foods (Harper et al. 1985; HSDB 1989) (for additional information about pyridine in foods, see Chapter 5).

4.4 DISPOSAL

Waste pyridine, when present as a constituent of a commercial chemical product or chemical intermediate, is considered to be a hazardous waste, as is any residue, soil, water, or other debris resulting from the clean-up of this waste. Disposal of these materials must be managed according to state and federal regulations (HSDB 1989). Restrictions that apply to the disposal of waste pyridine are listed in Chapter 7.

Current practices for the disposal of waste pyridine include rotary kiln incineration at 820°-1,600°C (HSDB 1989). Waste pyridine is a potential candidate for liquid injection incineration (650° - 1,600°C) or fluidized bed incineration at a temperature range of 450°-980°C (HSDB 1989).

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Pyridine is an organic liquid with an unpleasant odor; it is very soluble in water. It is released to the environment from industrial sources that manufacture and use it and as fugitive emissions from facilities such as coal gasification and oil shale processing. Pyridine may be removed from the atmosphere by photooxidation or wet deposition (precipitation). Pyridine in water is unlikely to volatilize appreciably, but may sorb to soils and sediments or biodegrade. Bioconcentration of pyridine in aquatic organisms is not likely to be important.

Pyridine has rarely been detected in ambient air, water, or soil, except in the vicinity of industrial sources. Several foods may contain pyridine, and ingestion of these foods is the most likely route of pyridine exposure for the general population. Occupational exposure to pyridine may be high. Populations living in the vicinity of hazardous waste sites where pyridine has been detected may also be exposed. The EPA has identified 1,177 NPL sites. Pyridine has been found at 4 of the sites evaluated for this chemical. However, we do not know how many of the 1,177 NPL sites have been evaluated for this chemical. As more sites are evaluated by the EPA, the number may change (View 1989). The frequency of these sites within the United States can be seen in Figure 5-l.

5.2 RELEASES TO THE ENVIRONMENT

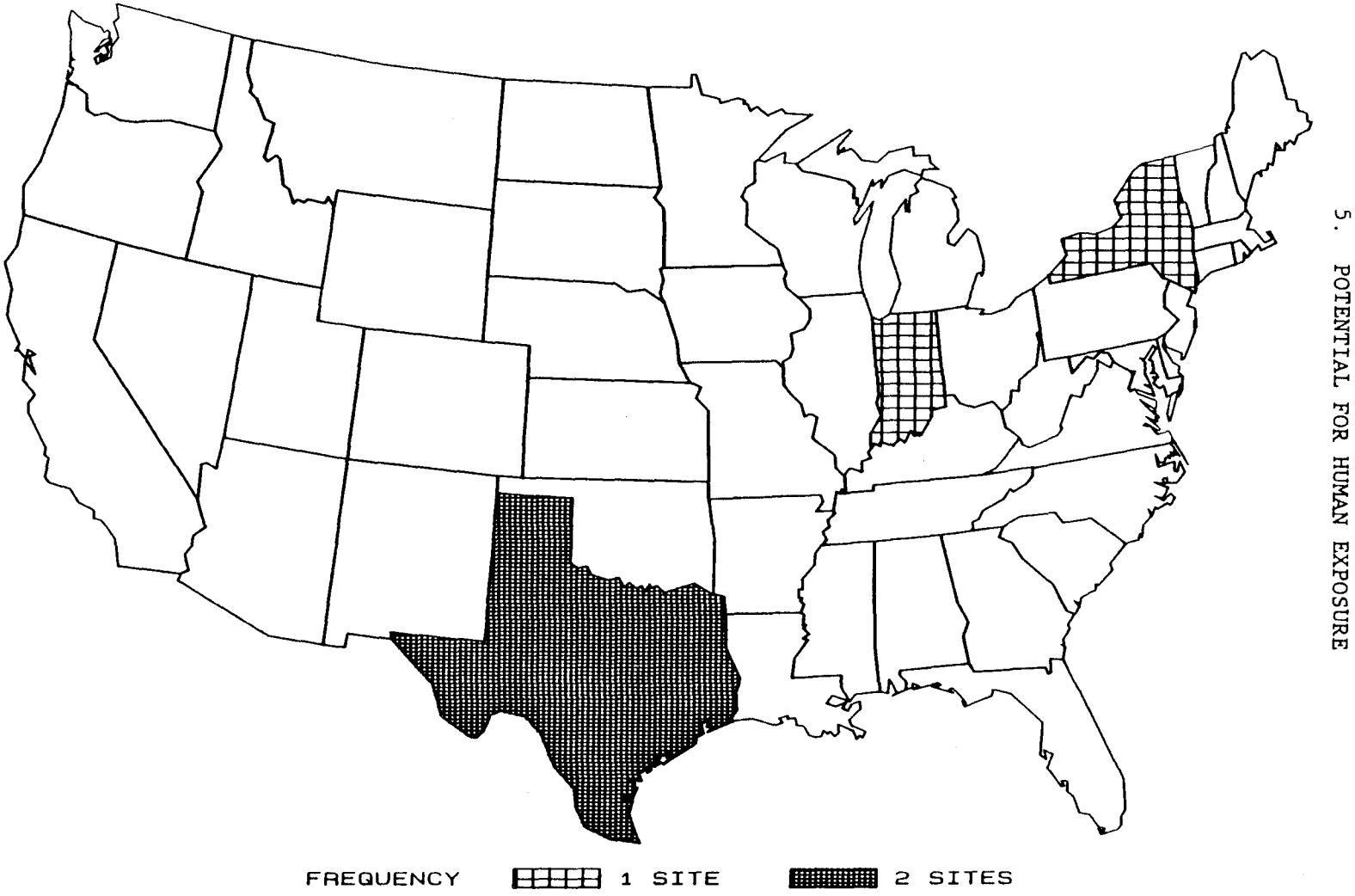
Manufacturers, processors, and users of pyridine are required to report quantities of releases of this substance to environmental media annually (EPA 1988a). According to the SARA Section 313 Toxics Release Inventory (TRI), an estimated total of 635,374 pounds of pyridine were released to the environment from manufacturing and processing facilities in the United States in 1987 (TRI 1989). The TRI data should be used with caution since the 1987 data represent first-time reporting by these facilities. Only certain types of facilities were required to report. This is not an exhaustive list. The 28 facilities reporting releases in 1987 are presented in Table 5-l.

Additional releases of pyridine may occur from oil shale processing and coke oven facilities, but these releases are not included in the TRI. Releases of pyridine relevant to specific media are discussed below.

5.2.1 Air

Pyridine is released to the atmosphere from facilities that manufacture and use this compound and from oil shale processing and coke oven facilities. Releases of an estimated 298,438 pounds of pyridine to air from domestic industrial sources were reported in 1987 (TRI 1989). Atmospheric emissions of pyridine from shale oil waste waters ranged from 0.44 to 30 μg/mL of wastewater (Hawthorne and Sievers 1984).

FIGURE 5-1. FREQUENCY OF NPL SITES WITH PYRIDINE CONTAMINATION *



* Derived from View 1989

TABLE 5-1. Releases to the Environment from Facilities That Manufacture or Process Pyridine[a]

Facility	Location	Total (lbs)						
		Air	Underground injection	Water	Land	Environment	POTW[b] transfer	Off-site transfer
Arkansas Eastman Company	Batesville, AR	4,400	0	570	0	4,970	No Data	0
Pfizer Inc. Groton Site	Groton, CT	0	0	0	0	0	0	250
Eli Lilly And Company Clinton Laboratories	Clinton, IN	3,250	0	250	250	3,750	0	0
Reilly Tar & Chemical Corporation	Indianapolis, IN	31,009	0	0	2	31,011	57,225	3,906
Air Products & Chemicals, Inc.	Wichita, KS	250	250	No Data	No Data	500	No Data	No Data
Union Carbide Corporation Industrial Chemicals	Hahnville, LA	884	No Data	0	0	884	0	0
Olin Corporation Lake Charles Plant	Lake Charles, LA	500	0	500	250	1,250	0	250
Dow Chemical Louisiana Division	Plaquemine, LA	0	0	1,900	0	1,900	0	0
The Upjohn Company Portage Site	Portage, MI	13,250	43,400	0	0	56,650	No Data	0
Burroughs Wellcome Co.	Greenville, NC	121,700	0	0	0	121,700	250	297,000
Kollsman	Merrimack, NH	0	0	0	0	0	0	0
Hoffmann-La Roche Inc.	Nutley, NJ	5,100	0	0	27,900	33,000	0	No Data
Nepera, Inc.	Harriman, NY	10,022	0	0	0	10,022	0	0
Eastman Kodak Company Kodak Park	Rochester, NY	17,800	0	610	4	18,414	0	0
Olin Corporation	Rochester, NY	19,890	0	0	0	19,890	12,610	0
The Wool Bureau, Inc.	Woodbury, NY	0	0	0	0	0	250	0
Du Pont Circleville Plant	Circleville, OH	28,760	0	50	No Data	28,810	No Data	33,150
Orsynex	Columbus, OH	1	0	0	0	1	0	20,000
Bp Chemicals America, Inc.	Lima, OH	250	260,000	0	250	260,500	0	0
American Cyanamid Company	Marietta, OH	250	0	0	0	250	0	0
New Boston Coke Corporation	New Boston, OH	163	No Data	0	0	163	0	0
The Upjohn Company	Barceloneta, PR	500	0	0	0	500	0	0
Schering Industrial Development Corporation	Manati, PR	500	0	0	0	500	250	0
Tennessee Eastman Company	Kingsport, TN	2,434	0	390	0	2,824	0	0
Monsanto Company	Alvin, TX	0	0	0	0	0	0	0
Ici Americas Inc. Bayport Site	Pasadena, TX	21,958	0	0	0	21,958	139,295	0
Dan River Inc. Chemical Products Division	Danville, VA	12,250	0	0	0	12,250	0	0
Rhone-Poulenc Incorporated Ag Company	Institute, WV	3,317	0	360	No Data	3,677	0	0
Totals		298438	303650	4630	28656	635374	209880	354556

[a]Derived from TRI 1989
[b]POTW -- publicly-owned treatment works

5.2.2 Water

Releases of pyridine to ambient waters have been reported. Industrial releases to surface water and groundwater (underground injection) reported in 1987 were estimated to be 4,630 pounds and 303,650 pounds, respectively (TRI 1989). In addition, 209,880 pounds of pyridine were disposed of in publicly owned treatment works (POTWs) in 1987 (TRI 1989). Some fraction of the quantity treated at POTWs is probably released to the environment. Pyridine was detected in one of two oi1 shale processing effluents at a concentration of 152 μg/L (ppb), but not in coal gasification plant effluents (Pellizzari et al. 1979). It was also detected in effluents from coke-oven quenching operations at 11 mg/L (EPA 1982b) and detected, but not quantified, in four industrial effluents (Shackelford and Keith 1976). Pyridine was also found in oil-shale retort water in Australia at a concentration of about 5 mg/L (Dobson et al. 1985).

Data from the Contract Laboratory Program (CLP) Statistical Database indicate that none of the hazardous waste sites sampled were positive for pyridine in surface water or groundwater (Eckel 1990).

5.2.3 Soil

Pyridine releases to land from industrial sources totalled an estimated 28,656 pounds in 1987 (TRI 1989). Additional releases of pyridine to soil may occur from spillage of oil shale waste waters on land surfaces (Leenheer and Stuber 1981). No other information was located on pyridine releases to soil. Pyridine was not detected in soil samples from hazardous waste sites (Eckel 1990).

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

Pyridine exists in the atmosphere as a vapor. Its vapor pressure is approximately 0.027 atm (20.6 mmHg) at 25°C (Chao et al. 1983). Because of its high water solubility, a large fraction of vapor-phase pyridine released to the atmosphere would tend to dissolve in water vapor (such as clouds and rain drops). A Henry's law constant estimates the tendency of a chemical to partition between its vapor state and water. The Henry's law constant for pyridine was measured as 1.1×10^{-5} atm-m^3-$mole^{-1}$ at 25°C for aqueous solutions (5 mg/L) (Hawthorne et al. 1985). The magnitude of this value indicates that much of the pyridine in the atmosphere is removed by wet deposition (precipitation).

Pyridine is highly soluble in water (Jori et al. 1983). The magnitude of Henry's law constant (1.1×10^{-5} atm-m^3-$mole^{-1}$ for aqueous solutions) suggests that pyridine in water will not volatilize into the atmosphere quickly. In addition, the equilibrium partitioning of pyridine between water and air was

found to be influenced by the pH of the water; a decrease in pH resulted in less partitioning from solution (Hakuta et al. 1977). The rate of pyridine volatilization from water has not been experimentally measured.

Pyridine in water may partition to soils and sediments to an extent that depends on the pH of the water, and to a lesser extent, the organic-carbon content of the soil. Pyridine is a weak organic base in solution; its ionization constant is 5.23×10^{-6} at 20°C (Albert et al. 1948). Consequently, pyridine is predominantly in a cationic electrolyte form (pyridinium ion) in acidic solutions, whereas it is a neutral molecule in alkaline media.

The extent of pyridine adsorption by pure-clay minerals was greatest in the pH range of 4-5.5, whereas adsorption was negligible in alkaline solutions (pH greater than 7) (Baker and Luh 1971). The magnitude of pyridinium adsorption was correlated with the cation-exchange capacity of the clays. The rate of pyridinium desorption from the clays was slower than that of adsorption (Luh and Baker 1971).

Pyridine was weakly adsorbed by sandstone at 38°C (Donaldson et al. 1975), but these authors did not report any pH measurements. Pyridine adsorption by an alkaline soil was negligible (Felice et al 1984); Zachara et al. (1987) also found that pyridine adsorption was more significant in acidic soils because of salt formation.

The extent of adsorption of neutral organic molecules by soils is often correlated with the organic-carbon content of the soil (Hassett et al. 1983). When adsorption is expressed as a function of organic-carbon content, an organic carbon/water partition coefficient (K_{oc}) can be calculated and may be used to classify the relative mobility of the chemical in soil. Based on its octanol-water partition coefficient (Table 3-2), an estimated K_{oc} for pyridine is 7 (Roy and Griffin 1985). An experimentally derived K_{oc} of about 40 can be calculated from the adsorption data in Zachara et al. (1987). As compared with K_{oc} values listed for other compounds, these low K_{oc} values suggest that pyridine is very highly mobile in soil, whereas pyridine as pyridinium will be less mobile, particularly in acidic soils.

Pyridine may not partition to organisms in water. An octanol/water partition coefficient (K_{oW}) estimates the likelihood of a chemical to partition to organisms in an aquatic environment. Octanol is believed to best imitate the fatty structures in plants and animal tissues (Kenaga and Goring 1980). The K_{oc} of pyridine has been measured as 4 (Leo et al. 1971). This low value indicates that pyridine will not partition to fatty tissues in plants or animals.

A bioconcentration factor (BCF) relates the concentration of a chemical in the tissues of aquatic organisms to the concentration of the chemical in the media in which they live. BCFs for pyridine have not been experimentally measured, but they may be less than 5, based on the empirical regressions of

Kenaga (1980) and Neely et al. (1974). These low BCFs suggest that pyridine is probably not bioconcentrated by aquatic plants and animals and therefore probably not biomagnified in terrestrial or aquatic food chains.

5.3.2 Transformation and Degradation

5.3.2.1 Air

Atmospheric pyridine may be slowly photodegraded by hydroxyl radicals in the troposphere. The rate constant for this reaction at 23°C has been measured as $5x10^{-13}$ cm^3/molecule-s, and the estimated atmospheric life time of pyridine may range from 23 to 46 days, depending on the concentration of hydroxyl radicals (Atkinson et al. 1987). Reaction by-products were not studied. It appears that the rate of ozone-initiated decay of pyridine is too slow to be an important mechanism for removing pyridine from the atmosphere. The decay rate of pyridine by ground-state oxygen ($O(^3P)$) has been measured as $1.7x10^{-13}$ cm^3/molecule-s (Mani and Sauer 1968). If the mean concentration of ground-state oxygen radicals is $5x10^{-4}$ molecules/cm^3 (Cupitt 1980), then the half-life of this reaction (2.6 years) may also be too slow to be important.

5.3.2.2 Water

Biodegradation may be the most important mechanism that can degrade pyridine in water. Pyridine may oxidize in water, but the reactions are very slow. The rate constant for pyridine oxidation by alkylperoxy radicals (RO_2) was estimated as approximately 0.67/M-s at 50°C (Mill et al. 1979). Because of the low concentration of these radicals in photolyzed natural waters, the half-life of this reaction may be on the order of decades. The rate constant for hydroxyl radical-initiated decay in water has been measured as $1.8x10^9$/M-s at 21°C, pH 7 (Dorfman and Adams 1973). radicals is 10^{-17} mole/L (Mill et al. If the mean concentration of hydroxyl 1979), the half-life of this reaction would be about 1.2 years. No information was located that suggests that pyridine hydrolyzes in water nor should it be anticipated from its chemical structure.

Most pyridine biodegradation studies have been concerned with transformations in soils and sewage sludges (see Section 5.3.3). In a study of pyridine biodegradation in unfiltered river water, the rate of removal depended on the initial concentration of pyridine, but in general, at lower concentrations (less than 20 mg/L), pyridine degradation was virtually complete in 8 days or less (Cassidy et al. 1988). No information concerning the microorganisms present in the water was given, but this study suggests that biodegradation may be a much more rapid mechanism for the removal of pyridine from the environment than are abiotic mechanisms.

5.3.2.3 Soil

It is very likely that pyridine biodegrades in soils and sewage sludges, but the rate and extent of the process is uncertain. Pyridine has been found to biodegrade readily in laboratory-screening tests (Gerike and Fischer 1979, 1981; Ruffo et al. 1984). For example, about 94%-100% of the pyridine added to municipal wastewater biodegraded in 2-21 days, depending on the specific test procedure used. Other studies have reported that pyridine biodegraded in sewage water or sludge, but that the process was slow (Battersby and Wilson 1989; Cooper and Catchpole 1973; Ettinger et al. 1954; Gomolka and Gomolka 1978; Malaney 1960). For example, pyridine was found to be only partially degraded in dilute sewage sludge, and the process required a month before significant removal was detected (Battersby and Wilson 1989).

There is evidence that pyridine can be biodegraded in soil. A branching bacteria (Proactinomyces) that can utilize pyridine as a sole-source of carbon and nitrogen, and energy has been isolated (Moore 1949). Pyridine was biodegraded in an aqueous extract of a garden soil, but the process was slow (Naik et al. 1972). Complete degradation under aerobic conditions required 66-170 days, whereas l-2 months were required under anaerobic conditions. However, in a soil incubated with low concentrations of pyridine, the compound was completely degraded in about 8 days (Sims and Sommers 1985). The halflife of the process was approximately 3 days.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

Pyridine has not been detected in ambient outdoor air, except in the vicinity of industrial sources. Pyridine was not found in rural or urban air (Hawthorne and Sievers 1984; Shah and Heyerdahl 1988). However, pyridine was detected at a concentration of 13 $\mu g/m^3$ in air in the vicinity of an oil shale wastewater facility (Hawthorne and Sievers 1984; Shah and Heyerdahl 1988). Pyridine was also present in indoor air at the same oil shale facility at a concentration of 41 $\mu g/m^3$ (Hawthorne and Sievers 1984). The concentration of pyridine in indoor air contaminated with cigarette smoke may be as high as 16 $\mu g/m^3$ (Brunnemann et al. 1991).

Pyridine has been detected in workplace air at pyridine manufacturing plants and chemical plants using pyridine as an intermediate at time-weighted average (TWA) concentrations ranging from 0.02 to 3.2 mg/m^3 (EPA 1982b).

5.4.2 Water

Pyridine is rarely detected in ambient waters. It was present in surface water of the Cuyahoga River in Ohio (IJC 1983). The compound was not detected in groundwater samples in Wyoming (detection limit 0.1-0.5 ppb) (Pellizzari et al. 1979; Stuermer et al. 1982). However, it was detected in

groundwater 15 months after completion of coal gasification activities at a Wyoming site at concentrations ranging from 0.82 to 53 ppb (Stuermer et al. 1982). Pyridine was detected in 2 of 17 drinking water concentrates (Lucas 1984).

5.4.3 Soil

No information was located on pyridine concentrations in ambient soils. Pyridine was detected in creosote-contaminated sediments in Puget Sound, Washington at a concentration of 0.22 μg/g (Krone et al. 1986).

5.4.4 Other Environmental Media

Pyridine may be present in foods from both natural and anthropogenic sources. Pyridine was detected among the natural volatile components of several foods, including fried chicken, Beaufort cheese, sukiyaki, fried bacon, and frozen mango (Dumont and Adda 1978; Ho et al. 1983; MacLeod and Snyder 1.988; Shibamoto et al. 1981; Tang et al. 1983). The concentration was reported only for mango at 1.0 μg/g (MacLeod and Snyder 1988). Pyridine is approved by the Food and Drug administration (FDA) for use as a flavoring agent (Table 7-l) and, therefore, may be present in other foods as well. Pyridine has also been identified as a component of tobacco smoke (Curvall et al. 1984; Florin et al. 1980; Riebe et al. 1982) and is a coffee aroma constituent (Aeschbacher et al. 1989).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Humans may be exposed to pyridine by inhalation, ingestion, or dermal contact. However, in the United States the general population is most likely to be exposed to pyridine by the ingestion of foods naturally containing this compound or, possibly, by inhalation of tobacco smoke. EPA (1978) reported that total pyridine is estimated to be ingested in the United States at about 500 mg/year, per person, mainly from food. The presence of pyridine in expired air is not necessarily an indicator of exposure to this chemical since pyridine has been detected in the expired air (detection limits not specified) of nonsmoking subjects described as prediabetic (i.e., nine offspring of diabetic parents and five subjects having one diabetic parent and several diabetic relatives) (Krotoszynski and O'Neill 1982). Pyridine was not detected in the expired air of 20 nonsmoking control (nondiabetic) or 28 diabetic subjects.

The greatest potential for exposure to pyridine occurs in the workplace. Occupational exposures, usually by inhalation or dermal absorption, may occur during pyridine production or its use as a chemical intermediate or solvent (Santodonato et al. 1985). Additional exposures may occur at coke-oven and oil-shale processing facilities. Reported workplace TWA concentrations range from 0.02 to 3.2 mg/m^3 (ppm) (EPA 1982b), but these data do not include cokeoven plants. It has been estimated that maximum long-term workplace exposures

to pyridine will not exceed 3.2-16 mg/m^3, except for possible brief exposures to higher concentrations (Santodonato et al. 1985). The National Institute for Occupational Health and Safety (NIOSH) estimated that the number of workers exposed to pyridine increased from about 29,000 during the early 1970s (NOHS 1990) to about 41,000 during the early 1980s (NOES 1990). These estimates also do not include workers at coke-oven plants. Neither the NOHS nor the NOES databases contain information on the frequency, concentration, or duration of exposure of workers to any of the chemicals listed therein. These surveys provide only estimates of the number of workers potentially exposed to chemicals in the workplace.

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Workers in industrial facilities that manufacture, use, or produce fugitive emissions of pyridine have the highest potential for exposure to this compound. Other populations with potentially higher than average exposure are those living in the vicinity of these facilities or of hazardous waste sites at which pyridine has been identified.

5.7 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of pyridine is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of pyridine.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

5.7.1 Data Needs

Physical and Chemical Properties. Most of the physical/chemical properties required to predict the environmental fate and transport of pyridine have been measured. However, it appears that the volatility and sorption of pyridine from water varies considerably with the pH of the water (Baker and Luh 1971). Additional data on the effect of pH on the Henry's law constant, volatilization rate, and K_{oc} would be useful to predict more accurately the environmental fate of pyridine.

5. POTENTIAL FOR HUMAN EXPOSURE

Production, Import/Export, Use, and Disposal. Information is generally available regarding the production, use, and disposal of pyridine in commercial facilities (Harper et al. 1985; HSDB 1989). The production locations, major uses, and disposal methods have been identified, and land disposal of pyridine is restricted by EPA. However, current production, import, and disposal volumes were not located. Releases from manufacturing and use facilities are reported in the TRI, but fugitive emissions from cokeoven and oil-shale processing facilities have not been reported. These data would be useful in evaluating both occupational exposures and exposures of the populations living in the vicinity of these facilities.

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 1987, became available in May of 1989. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

Environmental Fate. The available data are insufficient to predict accurately the environmental fate of pyridine. Pyridine most likely partitions to soils and sediments and from the atmosphere to water vapor. Additional data regarding the K_{oc} of pyridine, especially in nonacidic environments, would be useful in confirming the likelihood of pyridine partitioning among environmental media.

Data on transport and degradation are limited. Data on the composition and fate of the products of the atmospheric photodegradation of pyridine would enhance our understanding of the atmospheric fate of this compound, and additional studies on the biodegradation of pyridine in water and soil would be helpful in evaluating the fate of pyridine in these media.

Bioavailability from Environmental Media. Pyridine is very soluble in water (Sax and Lewis 1987). Human and animal data indicate that it is well absorbed by the oral route (D'Souza et al. 1980). It is expected to be available when it is present in natural waters. Under acidic conditions, it will adsorb to soils and sediments to some degree (Baker and Luh 1971). However, ingestion of soil-bound pyridine is an unlikely route of exposure. Information on dermal absorption from water would be useful in assessing the potential effects of recreational use of natural waters contaminated with pyridine. Information on absorption of inhaled pyridine released to the air would also be useful in assessing its bioavailability from that medium.

Food Chain Bioaccumulation. Because of pyridine's low K_{ow} (Verschueren 1983) and high water solubility (Sax and Lewis 1987), it probably will not bioconcentrate in plants, aquatic organisms, or animals. However, no data on bioconcentration factors or biomagnification in terrestrial or aquatic food

chains were located. Additional information on bioconcentration and biomagnification is needed to confirm the predicted limited importance of these processes in the environmental fate of pyridine.

Exposure Levels in Environmental Media. Although pyridine has been identified in air, water, and sediments, data regarding pyridine concentrations in environmental media are sparse. The available data are insufficient to evaluate the potential for human exposure to this compound; therefore, human intake levels of pyridine from environmental media have not been estimated. Additional monitoring data for this compound in all media in the vicinity of identified potential pollution sources and at hazardous waste sites would be useful in assessing the potential for human exposure. In addition, identification and monitoring of those foods to which pyridine is added as a flavoring agent would increase the accuracy of estimates of human intake by this route of exposure.

Exposure Levels in Humans. It would be useful to collect information on levels of exposure to pyridine in the environment that are associated with blood, urine, or tissue levels of pyridine and/or its metabolites in the exposed populations. Additional information relating those levels to the subsequent development of health effects would also be extremely useful.

Exposure Registries. No exposure registries for pyridine were located. This compound is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The compound will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to the exposure to this compound.

5.7.2 On-going Studies

Remedial investigations and feasibility studies conducted at the 4 NPL humans sites known to be contaminated with pyridine will add to the available database on exposure levels in environmental media, exposure levels in and exposure registries.

No other on-going studies were located regarding the environmental transport, or potential for human exposure to pyridine.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting and/or measuring and monitoring pyridine in environmental media and in biological samples. The intent is not to provide an exhaustive list of analytical methods that could be used to detect and quantify pyridine. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used to detect pyridine in environmental samples are the methods approved by federal agencies such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that refine previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

As a volatile to semivolatile material, pyridine can be determined by gas chromatography (GC) analysis using mass spectrometric (MS) detection. Pyridine is usually collected from the gas phase on a column of solid sorbent, such as Tenax® Pyridine can be removed from aqueous or slurry samples by purge-and-trap techniques or as headspace gas. Cryogenic (low temperature) collection and sorption in organic liquids are also possible.

6.1 BIOLOGICAL MATERIALS

In biological systems in which pyridine may have been metabolized or may itself be a metabolite, consideration should be given to the possible binding of the analyte by endogenous substances in the biological system. However, no information was found in the literature pertaining to such binding or to the release of biologically bound pyridine prior to analysis.

Sensitive and selective methods are available for the qualitative and quantitative measurement of pyridine after it is separated from its sample matrix. Gas chromatography, using either sensitive and highly specific MS or highly sensitive flame ionization detection (FID), is the analytical method most commonly used. Capillary gas chromatography, also known as highresolution gas chromatography (HRGC), has facilitated the analysis of compounds such as pyridine that can be measured by gas chromatography and has resulted in improvements in resolution and sensitivity. It has made the choice of a stationary phase less important than was previously the case with packed columns. The instrumental capability to separate volatile analytes by HRGC is, for the most part, no longer the limiting factor in their analysis. High-performance liquid chromatography (HPLC) has been used to measure isotopically labelled pyridine and its metabolites in urine (Shaker et al. 1982). This method has the advantage of compatibility with the liquid matrix of biological samples.

6. ANALYTICAL METHODS

In biological samples, after pyridine is released from the sample matrix, it is usually determined by gas chromatography. Methods for the detection of pyridine in biological materials are summarized in Table 6-l.

6.2 ENVIRONMENTAL SAMPLES

For the determination of pyridine in air, the analyte is usually trapped and concentrated from a large volume of air on a solid sorbent, such as Tenax® or activated carbon, from which it can be released thermally or eluted with a solvent such as dichloromethane for subsequent measurement. For aqueous samples, pyridine is purged with an inert gas, collected on a solid such as Tenax®, or cryogenically collected, followed by thermal desorption and measurement. Gas chromatography using sensitive and highly specific MS or highly sensitive FID are the analytical methods of choice for the determination of pyridine in environmental samples.

Methods for the determination of pyridine in environmental samples are summarized in Table

6.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of pyridine is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of pyridine.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.3.1 Data Needs

Sensitive and selective methods are available for the qualitative and quantitative measurement of pyridine after it is separated from its sample matrix.

An area of continuing interest is the ability to transfer analytes that have been isolated from a biological or environmental matrix quantitatively and in a narrow band to the HRGC; therefore this is an area of on-going study.

TABLE 6-1. Analytical Methods for Determining Pyridine in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Urine	Extraction through a membrane of Teflon impregnated with n-undecane	GC	1 ppb	3.5-4% repeatability	Audunsson 1988
Urine	Direct injection or injection after protein precipitation using acetonitrile	HPLC	No data	No data	Shaker et al. 1982
Biological liquids	Direct injection or headspace analysis	GC/FID	No data	No data	Dubowski 1975

FID = flame ionization detection; GC = gas chromatography; HPLC = high-performance liquid chromatography

TABLE 6-2. Analytical Methods for Determining Pyridine in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Collection on silver-impregnated adsorbent	HPLC	12 ng	No data	Frei et al. 1974
Air	Collection on charcoal, desorption with dichloromethane	GC	0.02 mg/sample	109%± 3.6%	NIOSH 1984
Indoor air	Collection on adsorbent resin, thermal desorption	HRGC/MS	No data	No data	Bayer and Black 1987
Tobacco smoke	Collection by diffusion denuder samplers	GC/MS	No data	No data	Eatough et al. 1989
Coal conversion oil	Extraction with dichloromethane	HPLC/GC	No data	No data	Haugen et al. 1982
Combustion products	Sorption on XAD-2, thermal desorption	GC/MS	0.5 ng	No data	James et al. 1985
River water	Distillation from sodium hydroxide, collection in dilute sulfuric acid, concentration by evaporation	GC	1 µg/L	90%	Sasai and Tsukioka 1981
River water	Distillation from sodium hydroxide, collection in dilute sulfuric acid, concentration by evaporation	GC	10 µg/L	84%	Sasai and Tsukioka 1981
Low level soil, sediment	Purge by helium, collection on solid, thermal desorption	GC/MS	5 µg/L	No data	EPA 1986a
Nonwater miscible waste	Purge by helium, collection on solid, thermal desorption	GC/MS	2.5 mg/kg	No data	EPA 1986a

GC = gas chromatography; HPLC = high-performance liquid chromatography; HRGC = high-resolution gas chromatography; MS = mass spectrometry

Another area of interest is to identify and accurately measure the quantity of compounds in the HRGC peaks. Mass spectrometric detection and Fourier transform infrared spectroscopy (FTIR) have been useful for this purpose.

The metabolites of pyridine in biological materials are difficult to determine in routine practice because of the lack of standardized methods for their measurement. In addition, not all of the pyridine metabolites have been identified and characterized, and this must first be accomplished.

Methods for Determining Biomarkers of Exposure and Effect. As with most xenobiotics, the identification of biomarkers of exposure to pyridine would be helpful in detecting exposure to this compound before adverse morphological or clinical effects occur. There is no available information in the literature that can be used to correlate levels of exposure to pyridine with resulting levels in urine or other biological fluids. Once biomarkers are identified, research on methods to detect them would be useful.

Similarly, no methods have been identified that are sensitive enough to correlate levels in biological media with levels at which biological effects occur. The development of these methods would be useful in the protection of populations exposed to pyridine.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. The media of most concern for human exposure to pyridine are drinking water (primarily from groundwater sources) and air. As illustrated by the data presented in Table 6-2 (e.g., Frei et al. 1974; NIOSH 1984; Sasai and Tsukioka 1981), the methods available for the determination of pyridine in water and air are not adequate to determine natural background levels of this compound. However, these background levels may well be insignificantly low. Methods are certainly adequate to measure the levels of pyridine at which known health effects occur. In general, the precision, accuracy, reliability, and specificity of methods to determine pyridine in water and air are not adequately documented. Additional work in this area would be useful.

Methods for determining pyridine in water, air, and waste samples are undergoing constant improvement. For example, research is on-going to develop a "Master Analytical Scheme" for the determination of organic compounds, including pyridine, in water (Michael et al. 1988). The goal of this project is to detect and quantitatively measure organic compounds at 0.1 μg/L in drinking water, 1 μg/L in surface waters, and 10 μg/L in effluent waters. Analytes are to include numerous nonvolatile compounds and some compounds that are only semisoluble in water, as well as volatile compounds (bp <150°C).

Sampling methodologies for compounds such as pyridine continue to pose problems such as nonrepresentative samples, insufficient sample volumes, contamination, and the need for labor-intensive, tedious extraction and purification procedures (Green and Le Pape 1987). Although HPLC methods have

simplified these procedures, it is desirable to have the means to measure organic compounds such as pyridine in situ in water and in other environmental media without the need for these sampling and extraction procedures to isolate the analyte prior to analysis.

6.3.2 On-going Studies

The Environmental Health Laboratory Sciences Division of the Center for Environmental Health and Injury Control, Centers for Disease Control, is developing methods for the analysis of pyridine and other volatile organic compounds in blood. These methods use high resolution gas chromatography and magnetic sector mass spectrometry which gives detection limits in the low parts per trillion range.

The Cooperative Institute for Research in Environmental Sciences (CIRES) at the University of Colorado, Boulder, is conducting research to improve methods of analysis for pyridine and related compounds in environmental samples.

Improvements continue to be made in chromatographic separation and detection. Problems associated with the collection of pyridine on a sorbent trap, followed by thermal sorption, may be overcome with direct purging to a capillary column with whole column cryotrapping (Pankow and Rosen 1988) or by trapping on a very thick film (about 100 pm) of cross-linked silicone (Roeraade and Blomberg 1989). Current activities in the areas of supercritical fluid extraction (King 1989) and supercritical fluid chromatography (Smith 1988) include determination of compounds such as pyridine in biological samples and environmental media. Fourier transform infrared flow cell detectors are sensitive and selective for the detection of compounds such as pyridine that have been separated by supercritical fluid chromatography (Wieboldt et al. 1988). Immunoassay methods of analysis are also promising for the determination of various organic substances, and it is reasonable to assume that pyridine and its metabolites are candidates for this type of analysis.

7. REGULATIONS AND ADVISORIES

Because of its potential to cause adverse health effects in exposed people, a number of regulations and guidelines have been established for pyridine by various national and state agencies. These values are summarized in Table 7-1.

7. REGULATIONS AND ADVISORIES

TABLE 7-1. Regulations and Guidelines Applicable to Pyridine

Agency	Description	Information	References
NATIONAL			
Regulations:			
a. Air:			
OSHA	PEL TWA	5 ppm (15 mg/m^3)	OSHA 1989 (29 CFR 1910.1000) Table Z-1-A
b. Food:			
FDA	Food additive - synthetic flavoring substance component of polycarbonate resins - indirect food additive	Yes	21 CFR 172.515
		Yes	21 CFR 177.1580
c. Other:			
EPA OERR	Reportable quantity	1,000 lbs	EPA 1989c (40 CFR 302.4)
EPA OSW	Hazardous Waste Constituent (Appendix VIII)	Yes	EPA 1980 (40 CFR 261)
	Groundwater monitoring list (Appendix IX)	Yes	EPA 1987 (40 CFR 264)
	Land disposal restrictions (proposed)	Yes	EPA 1989b (40 CFR 268)
EPA OTS	Toxic chemical release reporting rule	Yes	EPA 1988a (40 CFR 372)
	Health and safety data reporting rule	Yes	EPA 1988b (40 CFR 716.120)
	Preliminary assessment information reporting rule	Yes	EPA 1982a (40 CFR 712.30)
Guidelines:			
a. Air:			
ACGIH	TLV TWA STEL	5 ppm (15 mg/m^3) 10 ppm (30 mg/m^3)	ACGIH 1986
NIOSH	IDLH	3,600 ppm	NIOSH 1985
b. Other:			
EPA	Oral RfD	1x10^{-3} mg/kg/day	IRIS 1989
STATE			
Regulations and guidelines:			
a. Air:	Acceptable ambient air concentrations		NATICH 1989
Connecticut		300 µg/m^3 (8 hr)	
Florida (Tampa)		0.3 µg/m^3 (8 hr)	
Indiana		150 µg/m^3 (8 hr)	
Kansas		35.7 µg/m^3 (annual)	
Nevada		0.357 µg/m^3 (8 hr)	
New York		2.0 µg/m^3 (1 yr)	
North Dakota		0.30 µg/m^3 (18 hr)	
Vermont		0.15 µg/m^3 (8 hr)	
Virginia		357 µg/m^3 (annual) 250 µg/m^3 (24 hr)	

ACGIH = American Conference of Governmental Industrial Hygienists; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; IDLH = Immediately Dangerous to Life or Health Level; NIOSH = National Institute for Occupational Safety and Health; ODW = Office of Drinking Water; OERR = Office of Emergency and Remedial Response; OSHA = Occupational Safety and Health Administration; OSW = Office of Solid Wastes; OTS = Office of Toxic Substances; PEL = Permissible Exposure Limit; RfD = reference dose; STEL = Short Term Exposure Limit; TLV = Threshold Limit Value; TWA = Time-Weighted Average

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9. GLOSSARY

Acute Exposure -- Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption Coefficient (K_{oc}) -- The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (K_d) -- The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Bioconcentration Factor (BCF) -- The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Cancer Effect Level (CEL) -- The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen -- A chemical capable of inducing cancer.

Ceiling Value -- A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure -- Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Developmental Toxicity -- The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Embryotoxicity and Fetotoxicity -- Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

EPA Health Advisory -- An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard,

but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH) -- The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

Intermediate Exposure -- Exposure to a chemical for a duration of 15-364 days as specified in the Toxicological Profiles.

Immunologic Toxicity -- The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

In Vitro -- Isolated from the living organism and artificially maintained, as in a test tube.

In Vivo -- Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{50}) -- The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration $_{(50)}$ (LC_{50}) -- A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{50}) -- The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50}) -- The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50}) -- A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL) -- The lowest dose of chemical in a study or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Malformations -- Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level -- An estimate of daily human exposure to a chemical that is likely to be without an appreciable risk of deleterious effects (noncancerous) over a specified duration of exposure.

9. GLOSSARY

Mutagen -- A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

Neurotoxicity -- The occurrence of adverse effects on the nervous system following exposure to chemical.

No-Observed-Adverse-Effect Level (NOAEL) -- The dose of chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow}) -- The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

Permissible Exposure Limit (PEL) -- An allowable exposure level in workplace air averaged over an 8-hour shift.

q_1* -- The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually μg/L for water, mg/kg/day for food, and $\mu g/m^3$ for air).

Reference Dose (RfD) -- An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ) -- The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are: (1) 1 lb or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity -- The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are Dependent on the integrity of this system.

9. GLOSSARY

Short-Term Exposure Limit (STEL) -- The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

Target Organ Toxicity -- This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen -- A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV) -- A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

Time-weighted Average (TWA) -- An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose (TD_{50}) -- A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Uncertainty Factor (UF) -- A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIX A

USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in nontechnical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or substance release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the substance.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-2, and 2-3) and figures (2-l and 2-2) are used to summarize health effects by duration of exposure and endpoint and to illustrate graphically levels of exposure associated with those effects. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELS), Lowest-Observed- Adverse-Effect Levels (LOAELs) for Less Serious and Serious health effects, or Cancer Effect Levels (CELs). In addition, these tables and figures illustrate differences in response by species, Minimal Risk Levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper-bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text.

The legends presented below demonstrate the application of these tables and figures. A representative example of LSE Table 2-l and Figure 2-l are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-l

(1). **Route of Exposure** One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exist,

three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-l) and oral (LSE Figure 2-2) routes.

(2.) **Exposure Duration** Three exposure periods: acute (14 days or less); intermediate (15 to 364 days); and chronic (365 days or more) are presented within each route of exposure. In this example, an inhalation study of intermediate duration exposure is reported.

(3.) **Health Effect** The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table.

(4.) **Key to Figure** Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to define a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in Figure 2-l).

(5.) **Species** The test species, whether animal or human, are identified in this column.

(6.) **Exposure Frequency/Duration** The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to [substance x] via inhalation for 13 weeks, 5 days per week, for 6 hours per day.

(7.) **System** This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated in this study.

(8.) **NOAEL** A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "c").

(9.) **LOAEL** A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest exposure level used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to

quantify the adverse effect accompanies the LOAEL. The "Less Serious" respiratory effect reported in key number 18 (hyperplasia) occurred at a LOAEL of 10 ppm.

(10). **Reference** The complete reference citation is given in Chapter 8 of the profile.

(11). **CEL** A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiological studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses which did not cause a measurable increase in cancer.

(12). **Footnotes** Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "c" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See LSE Figure 2-1

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure levels for particular exposure duration.

(13). **Exposure Duration** The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

(14). **Health Effect** These are the categories of health effects for which reliable quantitative data exist. The same health effects appear in the LSE table.

(15). **Levels Of Exposure** Exposure levels for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure levels are reported on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16). **NOAEL** In this example, 18r NOAEL is the critical end point for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates a NOAEL for the test species (rat). The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17). **CEL** Key number 38r is one of three studies for which Cancer Effect Levels (CELs) were derived. The diamond symbol refers to a CEL for the test species (rat). The number 38 corresponds to the entry in the LSE table.

APPENDIX A

(18). **Estimated Upper-Bound Human Cancer Risk Levels** This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19). **Key to LSE Figure** The Key explains the abbreviations and symbols used in the figure.

1 → TABLE 2-1. Levels of Significant Exposure to [Chemical x] - Inhalation

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
3 → Systemic	5 ↓	6 ↓	7 ↓	8 ↓	9 ↓		10 ↓
4 → 18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
Cancer						11 ↓	
38	Rat	18 mo 5d/wk 7hr/d				20 (CEL, multiple organs)	Wong et al. 1982
39	Rat	89-104 wk 5d/wk 6hr/d				10 (CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79-103 wk 5d/wk 6hr/d				10 (CEL, lung tumors, hemangiosarcomas)	NTP 1982

[a] The number corresponds to entries in Figure 2-1.

12 → [b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5×10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

CEL = cancer effect level; d = day(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

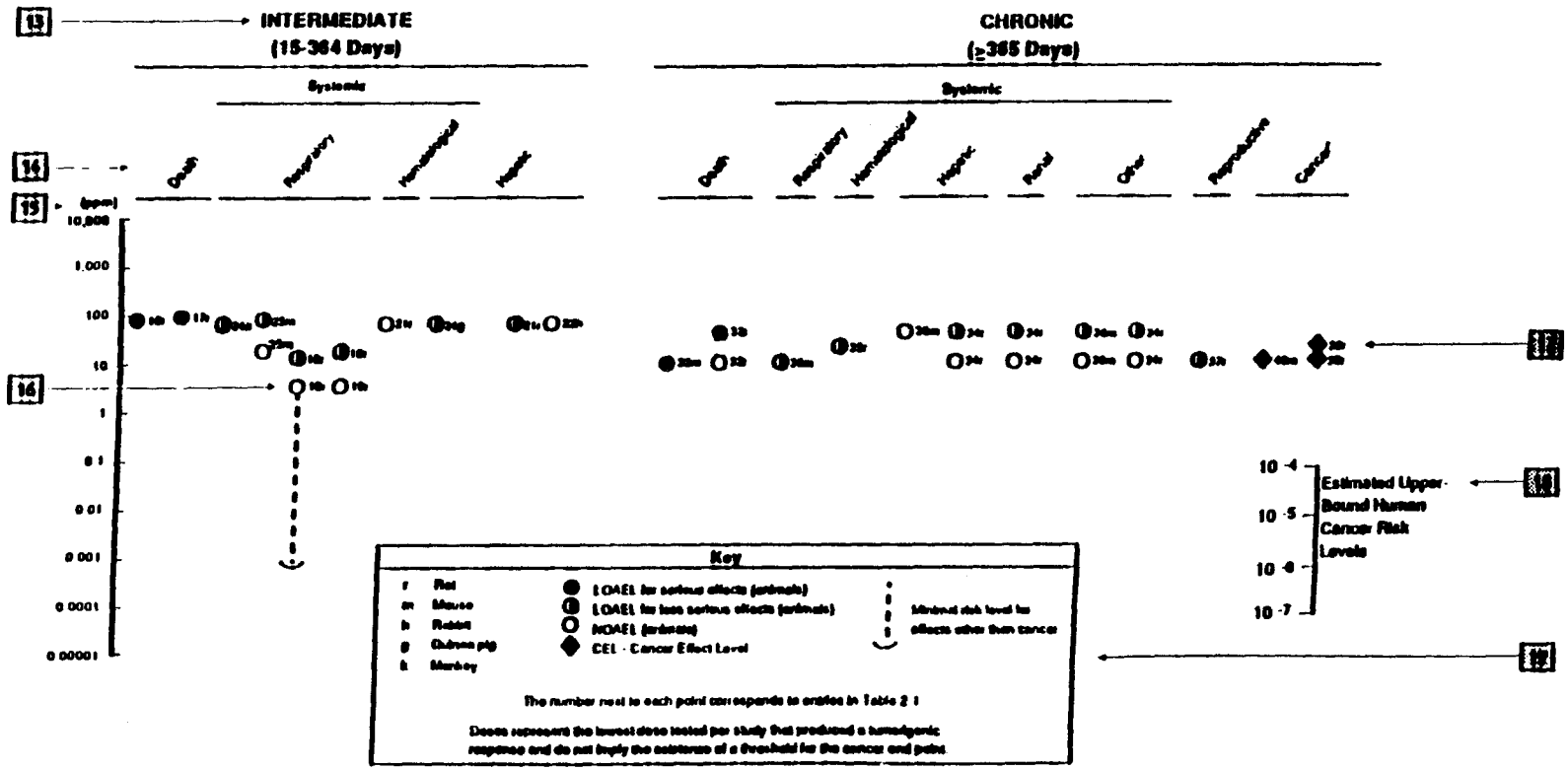

FIGURE 2-1. Levels of Significant Exposure to [Chemical X]-Inhalation

APPENDIX A

Chapter 2 (Section 2.4)

Relevance to Public Health

The Relevance to Public Health section provides a health effects summary based on evaluations of existing toxicological, epidemiological, and toxicokinetic information**.** This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The section discusses health effects by end point. Human data are presented first, then animal data. Both are organized by route of exposure (inhalation, oral, and dermal) and by duration (acute, intermediate, and chronic). In vitro data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, andcardinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. MRLs for noncancer end points if derived, and the end points from which they were derived are indicated and discussed in the appropriate section(s).

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Identification of Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information was available, MRLs were derived. MRLs are specific for route (inhalation or oral) and duration (acute, intermediate, or chronic) of exposure. Ideally, MRLs can be derived from all six exposure scenarios (e.g., Inhalation - acute, -intermediate, -chronic; Oral - acute, - intermediate, - chronic). These MRLs are not meant to support regulatory action, but to aquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a substance emission, given the concentration of a contaminant in air or the estimated daily dose received via food or water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

APPENDIX A

MRL users should be familiar with the toxicological information on which the number is based. Section 2.4, "Relevance to Public Health," contains basic information known about the substance. Other sections such as 2.6, "Interactions with Other Chemicals" and 2.7, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology used by the Environmental Protection Agency (EPA) (Barnes and Dourson, 1988; EPA 1989a) to derive reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the end point which, in its best judgement, represents the most sensitive humanhealth effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential effects (e.g., systemic, neurological, and developmental). In order to compare NOAELs and LOAELs for specific end points, all inhalation exposure levels are adjusted for 24hr exposures and all intermittent exposures for inhalation and oral routes of intermediate and chronic duration are adjusted for continous exposure (i.e., 7 days/week). If the information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. The NOAEL is the most suitable end point for deriving an MRL. When a NOAEL is not available, a Less Serious LOAEL can be used to derive an MRL, and an uncertainty factor (UF) of 10 is employed. MRLs are not derived from Serious LOAELs. Additional uncertainty factors of 10 each are used for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the adjusted inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

APPENDIX B

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
CLP	Contract Laboratory Program
cm	centimeter
CNS	central nervous system
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
f_1	first generation
fpm	feet per minute
ft	foot
FR	Federal Register
g	gram
GC	gas chromatography
HPLC	high performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
Kd	adsorption ratio
kg	kilogram
Koc	octanol-soil partition coefficient
Kow	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration low
LC_{50}	lethal concentration 50 percent kill
LD_{Lo}	lethal dose low
LD_{50}	lethal dose 50 percent kill
LOAEL	lowest-observed-adverse-effect level

APPENDIX B

LSE	Levels of Significant Exposure
m	meter
mg	milligram
min	minute
mL	milliliter
mm	millimeters
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectroscopy
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
nm	nanometer
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportional mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification
SMR	standard mortality ratio
STEL	short-term exposure limit
STORET	STORAGE and RETRIEVAL
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxic Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor

APPENDIX B

WHO	World Health Organization
>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
μm	micron
μg	microgram

APPENDIX C

PEER REVIEW

A peer review panel was assembled for pyridine. The panel consisted of the following members: Dr. Edmond LaVoie, Professor, Medicinal Chemistry, Rutgers University; Dr. James Withey, Research Scientist, Health and Welfare, Canada; Dr. Joseph Sincheiner, Professor, Toxicology, University of Michigan. These experts collectively have knowledge of pyridine's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(i)(13) of the Comprehensive Environment Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.