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.

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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

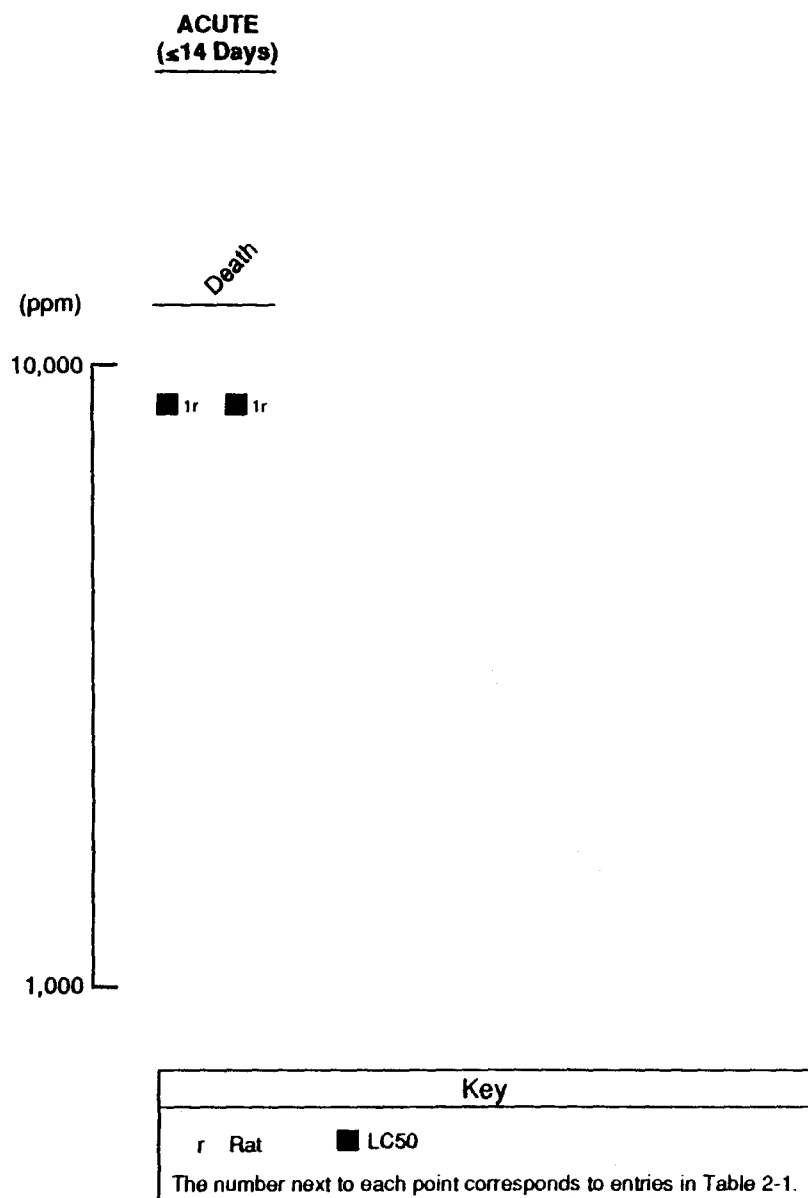No studies were located regarding immunological effects in humans or animals after inhalation exposure to pyridine.

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

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect)		Reference
					Less serious (ppm)	Serious (ppm)	
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

ACUTE
(≤14 Days)

(ppm)

Death
────────

10,000 ┌─

■ 1r   ■ 1r

1,000 └─

Key
r   Rat   ■ LC50
The number next to each point corresponds to entries in Table 2-1.

2. HEALTH EFFECTS

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

2. HEALTH EFFECTS

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
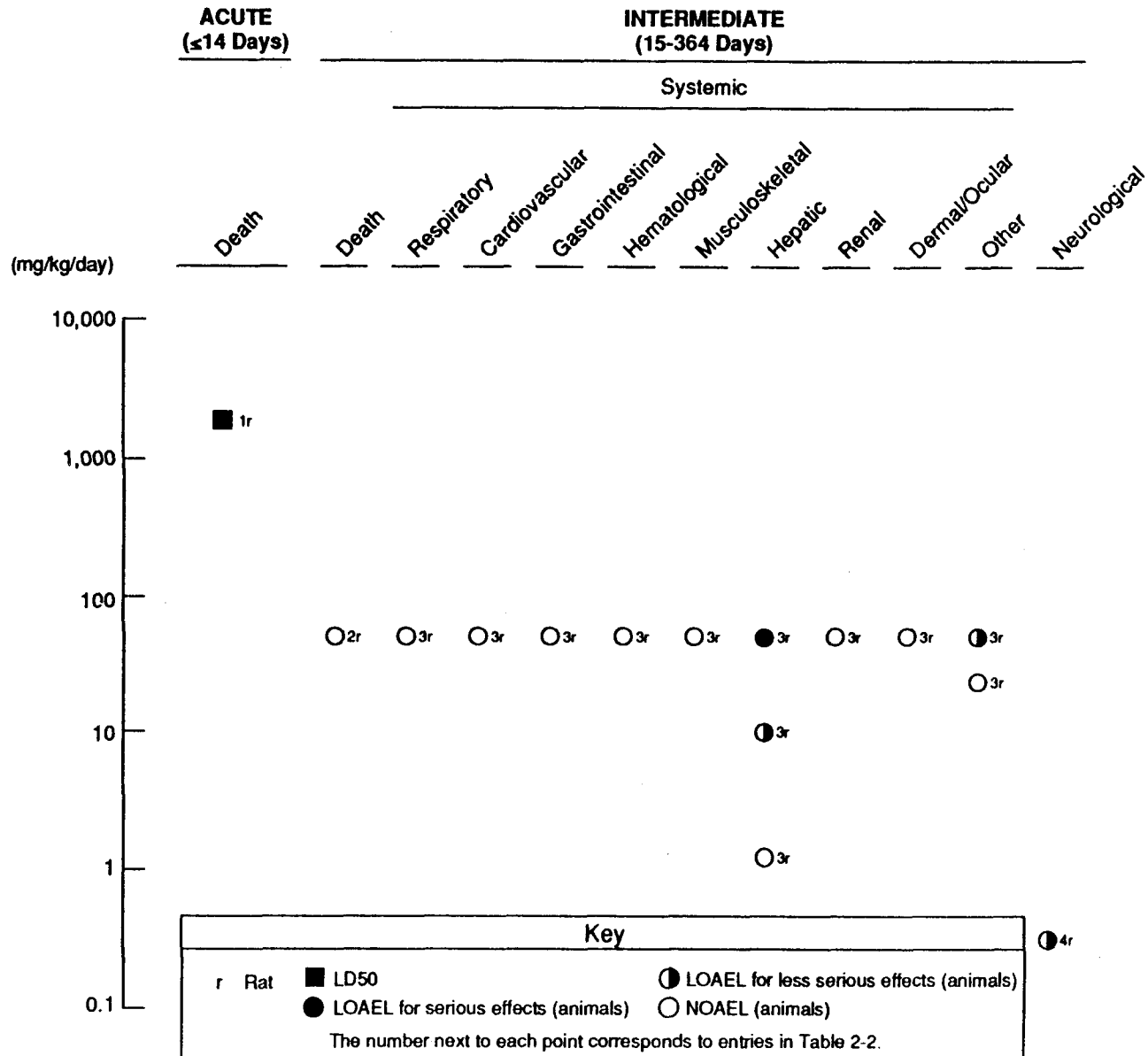
2. HEALTH EFFECTS

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.

2. HEALTH EFFECTS

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.

2. HEALTH 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. HEALTH EFFECTS

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. HEALTH EFFECTS

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.

2. HEALTH EFFECTS

There was no evidence of carcinogenicity due to pyridine administration in rats that received subcutaneous injections 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 animals 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
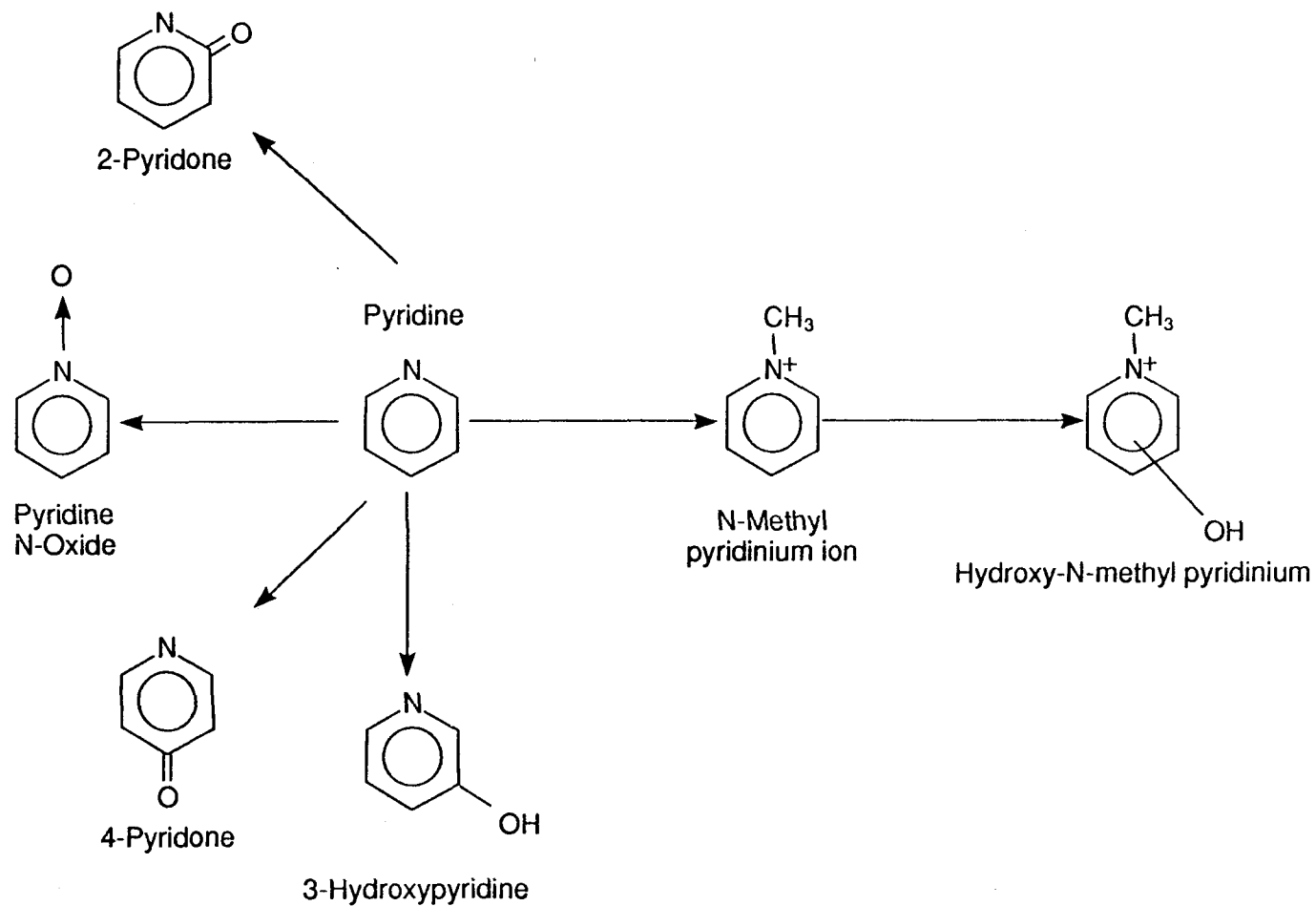
2. HEALTH EFFECTS

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*

2-Pyridone

Pyridine
N-Oxide

Pyridine

4-Pyridone

3-Hydroxypyridine

N-Methyl
pyridinium ion

Hydroxy-N-methyl pyridinium

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

2. HEALTH EFFECTS

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

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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

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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.

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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

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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 E. coli	343/113 pol A⁻ KMBL 1787/pol A⁻	DNA damage	-	-	Riebe et al. 1982
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

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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.

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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.

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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

HUMAN

ANIMAL
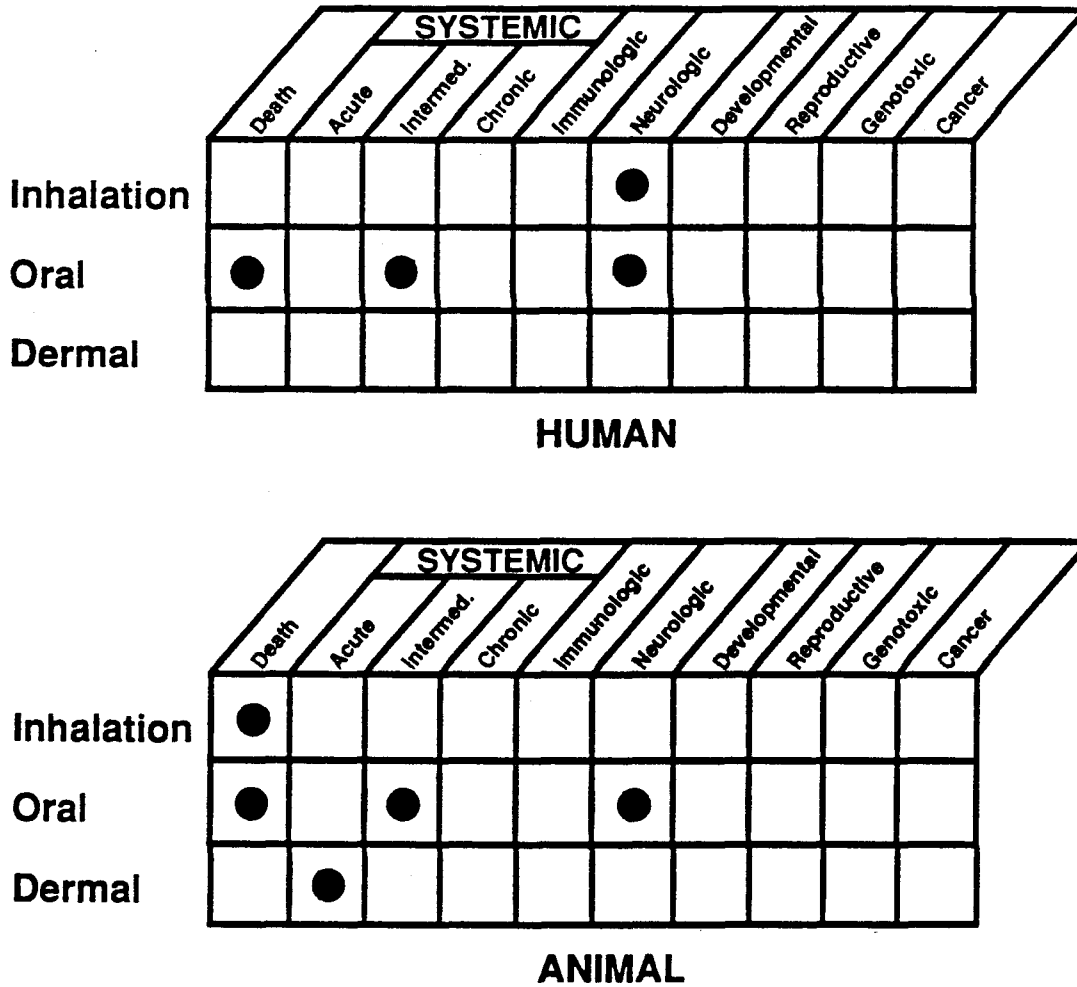
● Existing Studies

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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

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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.

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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