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TOXICOLOGICAL PROFILE FOR NITROBENZENE

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

December 1990

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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.

Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. 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, and

(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, but no less often than every three years, as required by CERCLA, as amended.

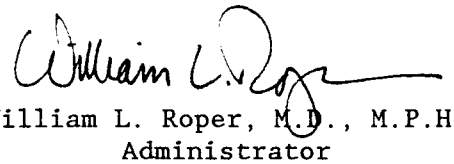
The ATSDR toxicological profile is intended to characterize succinctly the toxicological and adverse health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature (that has been peer-reviewed) that describes a hazardous substance's toxicological 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 significant health effects associated with exposure to the substance. The adequacy of information to determine a substance's health effects is described. 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 and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.



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Disease Registry

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1. PUBLIC HEALTH STATEMENT

This Statement was prepared to give you information about nitrobenzene 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). Nitrobenzene has been found at 7 of these sites. However, we do not know how many of the 1,177 NPL sites have been evaluated for nitrobenzene. As EPA evaluates more sites, the number of sites at which nitrobenzene is found may change. The information is important for you because nitrobenzene may cause harmful health effects and because these sites are potential or actual sources of human exposure to nitrobenzene.

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 substance such as nitrobenzene, 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 NITROBENZENE?

Nitrobenzene is an oily yellow liquid with an almond-like odor. It may be pale yellow-brown in appearance. It dissolves only slightly in water, but very easily in some other chemicals.

Nitrobenzene is produced in large quantities for industrial use. Approximately 98% of the nitrobenzene produced in the United States is used to manufacture a chemical known as aniline. Nitrobenzene is also used to produce lubricating oils such as those used in motors and machinery. A very small amount of nitrobenzene is used in the manufacture of dyes, drugs, pesticides, and synthetic rubber.

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Small amounts of nitrobenzene are released to the air and to bodies of water by the industries that use this chemical. However, it is broken down to other chemicals within a few days after it is released. Air and water in most areas contain no nitrobenzene or such low amounts that they cannot be measured.

More information on the chemical and physical properties of nitrobenzene can be found in Chapter 3. Its production, import, uses, and disposal are presented in Chapter 4, and its occurrence and fate in the environment are described in Chapter 5.

1.2 HOW MIGHT I BE EXPOSED TO NITROBENZENE?

Because nitrobenzene is not usually found at hazardous waste sites, it is unlikely that you will be exposed to nitrobenzene if you live near one of these sites. However, you may be exposed if you live near one of the seven waste sites where it has been found or near a manufacturing or processing plant, such as those involved in petroleum refining and chemical manufacturing. Persons in these areas may be exposed to nitrobenzene in the air they breathe. However, even in these cases, the levels of nitrobenzene have been found to be extremely low, usually less than 1 ppb (one part nitrobenzene per billion parts of air). Levels of nitrobenzene in the air of residential areas are even lower. Nitrobenzene is almost never found in drinking water. There is no information available on the levels of nitrobenzene in food.

The most common way that humans are exposed to this compound is by occupational exposure. If you work in a plant or factory that produces nitrobenzene or uses nitrobenzene to make other products such as dyes, drugs, pesticides or synthetic rubber, you may be exposed to nitrobenzene in the air that you breathe or through your skin.

For more information on human exposure to nitrobenzene, see Chapter 5.

1.3 HOW CAN NITROBENZENE ENTER AND LEAVE MY BODY?

Nitrobenzene can enter your body easily and quickly through your lungs, through your skin, or if you eat or drink contaminated food or water. Nitrobenzene is easily absorbed through the skin and this is a frequent pathway of human exposure. Drinking alcoholic beverages may result in nitrobenzene entering your body at a faster rate, no matter how you are exposed.

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Nitrobenzene and its breakdown products leave the body within a few days. These are eliminated mostly in the urine and to a smaller extent in the feces.

More information on how nitrobenzene enters and leaves the body can be found in Chapter 2.

1.4 HOW CAN NITROBENZENE AFFECT MY HEALTH?

Nitrobenzene can cause a wide variety of harmful health effects to exposed persons. Direct contact of small amounts of nitrobenzene with the skin or eyes may cause mild irritation. Repeated exposures to a high concentration of nitrobenzene can result in a blood condition called methemoglobinemia. This condition affects the ability of the blood to carry oxygen. Following such an exposure, the skin may turn a bluish color. This may be accompanied by nausea, vomiting and shortness of breath. Effects such as headache, irritability, dizziness, weakness, and drowsiness may also occur. If the exposure level is extremely high, nitrobenzene can cause coma and possibly death unless prompt medical treatment is received. Consuming alcoholic beverages during nitrobenzene exposure may increase the harmful effects of nitrobenzene.

In studies with laboratory animals, a single dose of nitrobenzene fed to male rats resulted in damage to the testicles and decreased levels of sperm. This suggests that decreased fertility may be a concern in humans. There is very little information available about the effects of long-term exposure of humans or animals to nitrobenzene, and it is not known whether exposure to nitrobenzene can cause cancer.

Further information on the health effects of nitrobenzene in humans and animals can be found in Chapter 2. More information on nitrobenzene breakdown products can be found in Chapter 2. There are populations that are unusually susceptible to nitrobenzene, and this is further discussed in Chapter 2.

1.5 WHAT LEVELS OF EXPOSURE HAVE RESULTED IN HARMFUL HEALTH EFFECTS?

Tables 1-1 through 1-4 show the relationship between exposure to nitrobenzene at certain levels and known health effects. The exposure of laboratory animals to nitrobenzene through skin contact has resulted in harmful effects similar to those seen in laboratory animals by other routes of exposure. In general, the longer the period of contact with the skin, the more severe the effects.

Nitrobenzene can be smelled in water when it is present at 0.11 mg/L (milligrams of nitrobenzene per liter of water) or in air at 0.018 ppm (0.018 parts of nitrobenzene per million parts of air). It has an odor characteristic of bitter almonds or shoe polish.

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TABLE 1-1. Human Health Effects from Breathing Nitrobenzene

Short-term Exposure (less than or equal to 14 days)		
Levels in Air	Length of Exposure	Description of Effects
		The health effects resulting from short-term exposure of humans to air containing specific levels of nitrobenzene are not known.
Long-term Exposure (greater than 14 days)		
Levels in Air	Length of Exposure	Description of Effects
		The health effects resulting from long-term exposure of humans to air containing specific levels of nitrobenzene are not known.

TABLE 1-2. Animal Health Effects from Breathing Nitrobenzene

Short-term Exposure (less than or equal to 14 days)		
Levels in Air (ppm)	Length of Exposure	Description of Effects*
10	10 to 14 days	Increased liver, kidney and spleen weights and methemoglobinemia in rats.
125	14 days	Brain lesions in mice; death in rats.
Long-term Exposure (greater than 14 days)		
Levels in Air (ppm)	Length of Exposure	Description of Effects*
5	90 days	Damage to the kidneys and increased methemoglobinemia in rats.
50	90 days	Damage to the spleen, liver, and testes of rats.

*These effects are listed at the lowest level at which they were first observed. They may also be seen at higher levels.

TABLE 1-3. Human Health Effects from Eating or Drinking Nitrobenzene

Short-term Exposure (less than or equal to 14 days)		
Levels in Food	Length of Exposure	Description of Effects
		The health effects resulting from short-term exposure of humans to food containing specific levels of nitrobenzene are not known.
Levels in Water		The health effects resulting from short-term exposure of humans to water containing specific levels of nitrobenzene are not known.
Long-term Exposure (greater than 14 days)		
Levels in Food	Length of Exposure	Description of Effects
		The health effects resulting from long-term exposure of humans to food containing specific levels of nitrobenzene are not known.
Levels in Water		The health effects resulting from long-term exposure of humans to water containing specific levels of nitrobenzene are not known.

TABLE 1-4. Animal Health Effects from Eating or Drinking Nitrobenzene

Short-term Exposure (less than or equal to 14 days)		
Levels in Food (ppm)	Length of Exposure	Description of Effects*
4,000	1 day	Methemoglobinemia in rats.
6,000	1 day	Testicle damage in rats.
11,000	1 day	Brain hemorrhage in rats.
Levels in Water		The health effects resulting from short-term exposure of animals to water containing specific levels of nitrobenzene are not known.
Long-term Exposure (greater than 14 days)		
Levels in Food	Length of Exposure	Description of Effects
		The health effects resulting from long-term exposure of animals to food containing specific levels of nitrobenzene are not known.
Levels in Water		The health effects resulting from long-term exposure of animals to water containing specific levels of nitrobenzene are not known.

*These effects are listed at the lowest level at which they were first observed. They may also be seen at higher levels.

More information on the health effects associated with exposure to nitrobenzene is presented in Chapter 2.

1.6 WHERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO NITROBENZENE?

Nitrobenzene reacts with red blood cells in the body to produce methemoglobin. If you have recently been exposed to nitrobenzene, the levels of methemoglobin in your blood will be elevated. This level can be measured. However, many toxic chemicals produce methemoglobin, and this method does not give specific information about nitrobenzene exposure.

In cases of long-term exposure to nitrobenzene, the presence of its breakdown products, p-nitrophenol and p-aminophenol, in the urine is an indication of nitrobenzene exposure. These tests require special equipment and cannot be routinely done in a doctor’s office. The results of these tests cannot be used to determine the level of nitrobenzene exposure or if harmful health effects can be expected to occur.

Information regarding tests for the detection of nitrobenzene in the body is presented in Chapters 2 and 6.

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

The federal government has developed regulations and guidelines in order to protect individuals from the possible health effects of nitrobenzene in drinking water. The Environmental Protection Agency (EPA) has concluded that the amount of nitrobenzene in drinking water should not exceed 19.8 mg/L and that any release in excess of 1,000 pounds should be reported.

The Occupational Safety and Health Administration (OSHA) has set a legal limit (Permissible Exposure Limit, or PEL) of 1 ppm in workroom air to protect workers during an 8-hour shift in a 40-hour workweek.

1.8 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 give you information on the location of the nearest occupational and environmental health clinics. Such clinics specialize in recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

2. HEALTH EFFECTS

2.1 INTRODUCTION

This chapter contains descriptions and evaluations of studies and interpretation of data on the health effects associated with exposure to nitrobenzene. Its purpose is to present levels of significant exposure for nitrobenzene based on toxicological studies, epidemiological investigations, and environmental exposure data. This information is presented to provide public health officials, physicians, toxicologists, and other interested individuals and groups with (1) an overall perspective of the toxicology of nitrobenzene and (2) a depiction of significant exposure levels associated with various adverse health effects.

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 data in this section are 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, intermediate, and chronic.

Levels of significant exposure for each exposure route and duration (for which data exist) are presented in tables and illustrated in figures. The points in the figures showing no-observed-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, determine whether or not the intensity of the effects varies 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 on 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 or with the identification of persons with the potential to develop such disease may be interested in levels of exposure associated with "serious" effects. Public health officials and project managers concerned with response actions at Superfund 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) are of interest to health professionals and citizens alike.

2.2.1 Inhalation Exposure

Health effects in humans following inhalation exposure to nitrobenzene have been described. However, as described in this section, these studies are limited in detail and technical content. There are several reliable animal studies using this route of exposure.

Table 2-l and Figure 2-l describe the health effects observed in laboratory animals associated with inhalation of nitrobenzene at varying exposure levels and durations; the results are discussed below.

2.2.1.1 Death

No studies were located regarding lethal effects of nitrobenzene in humans after inhalation exposure.

Strain and species differences in response to nitrobenzene exposure were demonstrated by Medinsky and Irons (1985). At an exposure level of 125 ppm nitrobenzene, there was a 40% rate of lethality in Sprague-Dawley (CD) rats and morbidity necessitating early sacrifice of all B6C3Fl mice. Fischer-344 rats, however, tolerated this level for 2 weeks without any adverse clinical signs. The relevance of these findings to human exposure is not known.

2.2.1.2 Systemic Effects

Hematological Effects. The outstanding toxic effect of inhalation exposure to nitrobenzene is methemoglobinemia. When the iron component of hemoglobin is converted from the ferrous state to the ferric state (oxidized), the resultant methemoglobin is no longer capable of releasing oxygen to the tissues of the body. This lowered oxygen capacity, or hypoxia, is generally associated with fatigue, weakness dyspnea, headache, and dizziness as oxygen-poor blood reaches the brain. Even under normal conditions, some (1 to 4%) methemoglobin is formed in the lungs as blood is oxygenated. Toxic or "secondary", methemoglobinemia can occur following exposure to nitrobenzene and other chemicals.

Methemoglobinemia has been reported in three-week-old twins (a male and a female) (Stevens 1928) and in a 12-month-old girl (Stevenson and Forbes 1942) exposed to nitrobenzene in insect exterminator sprays. In each case, the exposure lasted several hours and the exposure level was neither known nor estimated. Severe methemoglobinemia was reported in a 47-year-old woman who was occupationally exposed to nitrobenzene at unmeasured levels for 17 months (Ikeda and Kita 1964).

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

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (ppm)	LOAEL (Effect) Less Serious (ppm)	LOAEL (Effect) Serious (ppm)	Reference
ACUTE EXPOSURE							
Death							
1	Rat	14 d 5d/wk 6hr/d				125[a] (LD50 males)	Medinsky and Irons 1985
Systemic							
2	Rat	14 d 5d/wk 6hr/d	Renal		10[a] (incr. kidney wt.)		Medinsky and Irons 1985
3	Rat	10 d Gd6-15 6hr/d	Other		10[a] (incr. spleen wt.)		Tyl et al. 1987
4	Rat	14 d 5d/wk 6hr/d	Hepatic		10[a] (incr. liver wt.)		Medinsky and Irons 1985
5	Rat	14 d 5d/wk 6hr/d	Hemato		10[a] (methemoglobinemia)	35 (incr. WBC's)	Medinsky and Irons 1985
6	Mouse	14 d 5d/wk 6hr/d	Other		10 (splenic hemosiderosis)	35 (lymphoid aplasia)	Medinsky and Irons 1985
Neurological							
7	Mouse	14 d 5d/wk 6hr/d				125[a] (cerebellar lesions)	Medinsky and Irons 1985
Developmental							
8	Rat	10 d Gd6-15 6hr/d		40			Tyl et al. 1987

TABLE 2-1 (Continued)

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (ppm)	LOAEL (Effect) Less Serious (ppm)	LOAEL (Effect) Serious (ppm)	Reference
INTERMEDIATE EXPOSURE							
Systemic							
9	Rat	21 d 5d/wk 6hr/d	Other	50			Kligerman et al. 1983
10	Rat	90 d 5d/wk 6hr/d	Renal		5[a] (nephrosis)	50 (necrosis)	Hamm 1984
11	Rat	90 d 5d/wk 6hr/d	Other		5 (splenic hyperplasia)	50 (splenic lesions)	Hamm 1984
12	Rat	90 d 5d/wk 6hr/d	Hemato		5 (methemoglob-inemia)		Hamm 1984
13	Rat	90 d 5d/wk 6hr/d	Hepatic			50[a] (necrosis)	Hamm 1984
14	Mouse	90 d 5d/wk 6hr/d	Other		5 (adrenal lesions)		Hamm 1984
15	Mouse	90 d 5d/wk 6hr/d	Hemato			50 (methemoglob-inemia)	Hamm 1984
16	Rat	10 wk (2 gen) 5d/wk 6hr/d	Other	10			Dodd et al. 1987
Reproductive							
17	Rat	90 d 5d/wk 6hr/d				50[a] (testicular degeneration)	Hamm 1984

TABLE 2-1 (Continued)

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (ppm)	LOAEL (Effect) Less Serious (ppm)	LOAEL (Effect) Serious (ppm)	Reference
18	Mouse	90 d 5d/wk 6hr/d		50			Hamm 1984
19	Rat	10 wk (2 gen) 5d/wk 6hr/d		10		40 (testic. lesions, decr. fertility)	Dodd et al. 1987

[a]Presented in Table 1-2.

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; ppm = parts per million; d = day; LD_{50} = lethal dose, 50% mortality; wk = week; hr = hour; incr. = increase; wt = weight; Gd = gestation day; hemato = hematological; WBC's = white blood cells; gen = generation; testic. = testicular; decr. = decreased.

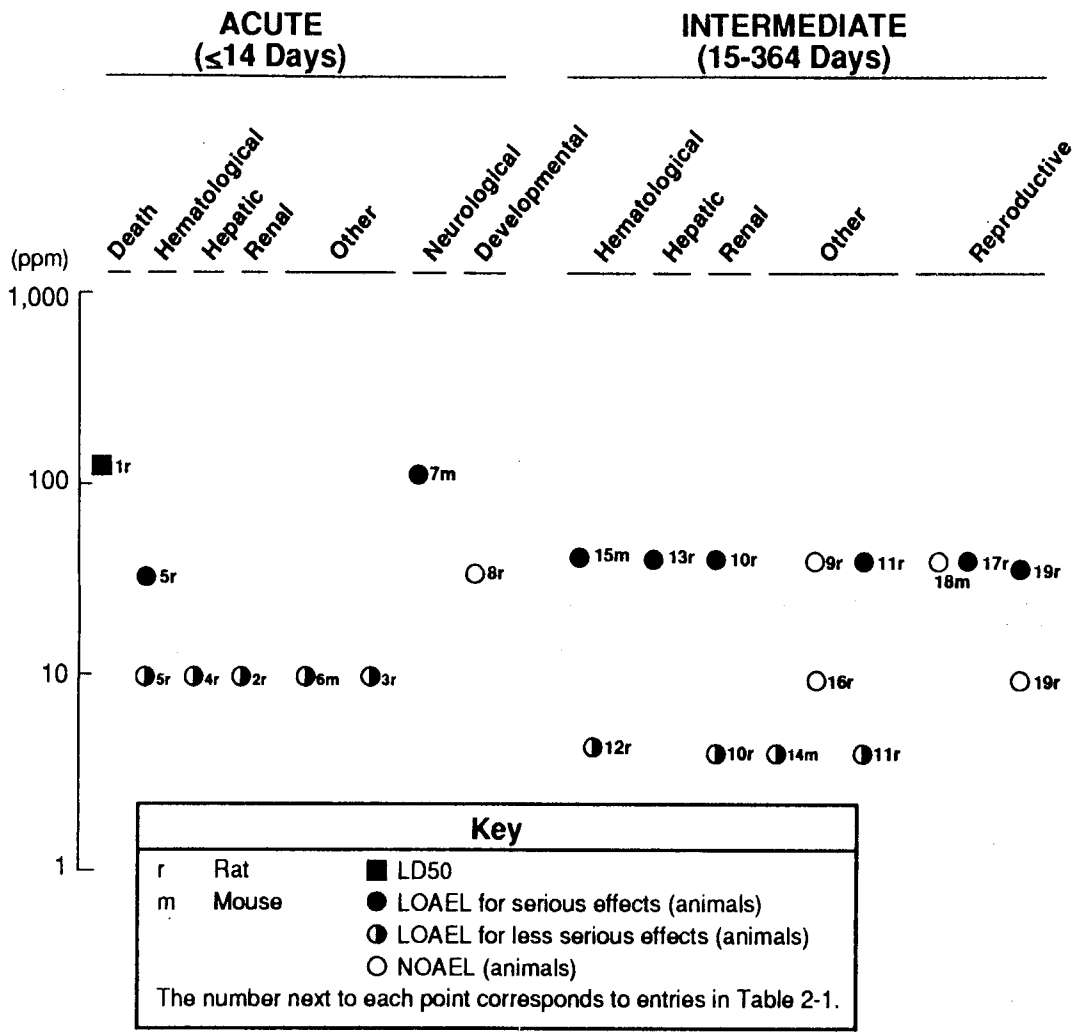


FIGURE 2-1. Levels of Significant Exposure to Nitrobenzene – Inhalation

2. HEALTH EFFECTS

Increased levels of blood methemoglobin have been reported in rate Exposed to nitrobenzene at levels as low as 10 ppm for two weeks Medinsky and Irons 1985) or 5 ppm for 90 days (Hamm 1984).

Hepatic Effects. There is some evidence that the human liver is Damaged after chronic inhaltion of nitrobenzene. The liver was Enlarged and tender and the results of liver function tests were Abnormal in a woman who was occupationally exposed to nitrobenzene for 17 months (exposure levels not measured or estimated) (Ikeda and Kita 1964).

Liver lesions reported in animals studies include hepatocyte Necrosis in male Sprague-Dawley (CD) rats exposed to nitrobenzene at 35 ppm for 2 weeks (Medinsky and Irons 1985) and increased liver weight, hepatocyte hyperlasia, and multinucleated hepatocytes in male B6C3F1 mice exposed to nitrobenzene at 16 ppm for 90 days (Hamm 1984).

Renal Effects. No studies were located regarding renal effects in Human after inhalation exposure to nitrobenzene.

Dose-related increases in kidney weights were observed in Fischer-344 rats (both sexes), but not in Sprague-Dawley (CD) rats Exposed to nitrobenzene at 10 to 125 ppm for 14 days (Medinsky and Irons 1985). At 125 ppm, hydropic degeneration of the cortical tubular cells was observed only in Sprague-Dawley rats (20% of males; 90% of females), and hyaline nephrosis only in Fischer-344 rats (100% of males; 20% of females). Renal effects reported in B6C3F1 mice in this study included minimal to moderate multifocal degenerative changes in tubular epithelium of males exposed to 35 ppm for 2 weeks. However, neither hydropic degeneration of the cortical tubular cells nor hyaline nephrosis was seen in mice even at the highest exposure level (125 ppm). Using the same three animal models exposed to nitrobenzene at 5 to 50 ppm for 90 days, dose-related real lesions were observed in both rat strains but not in mice (Hamm 1984).

Difference in species and possibly strain susceptibility to the Renal effects of nitrobenzene exposure may exist, but their relevance to The potential renal effects in humans is not clear. The occurrence of Renal effects in male rats, but not female rats or mice of either sex, in response to exposure to chemical toxicants is not unique to nitrobenzene. These differences have also been found with exposure to 1,4,-dichlorobenzene, isophorone, and unleaded gasoline (Charbonneau and Wwenberg 1988) and have been attributed to the production of high Concentrations of the protein alpha-2μ-globulin in the kidneys of male Rats, but not in female rats, mice, or humans. These observations Suggest that the severe renal effects observed in male rats exposed to Nitrobenzene will probably not occur in exposed humans.

Other Systemic Effects. No studies were located regarding cardiovascular, respiratory, gastrointestinal, musculoskeletal, dermal or ocular effects in humans or animals after inhalation exposure to nitrobenzene.

Dose-related splenic lesions have been reported to occur in B6C3Fl mice exposed to nitrobenzene at 10 to 125 ppm for 14 days (Medinsky and Irons 1985) and in F-344 and Sprague-Dawley (CD) rats at 5 to 50 ppm for 90 days (Hamm 1984). These lesions were described as sinusoidal congestion, an increase in extramedullary hematopoiesis and hemosiderin-laden macrophages infiltrating the red pulp, and the presence of proliferative capsular lesions. The results of these studies suggest that the spleen may also be a sensitive organ in cases of human inhalation exposure to nitrobenzene.

2.2.1.3 Immunological Effects

No studies were located regarding immunological effects in humans or animals after inhalation exposure to nitrobenzene. Splenic lesions observed in studies in rats and mice (see Section 2.2.1.2) suggest that potential immunologic effects may warrant further attention.

2.2.1.4 Neurological Effects

Neurological effects have been noted in the case of a woman who was occupationally exposed to nitrobenzene for 17 months at an unknown level. These effects included headache, nausea, vertigo, confusion, and paresthesia (Ikeda and Kita 1964).

Neurologic signs were not observed in mice or rats exposed to 5, 16, or 50 ppm nitrobenzene in air for 90 days. These animals were observed twice daily for clinical abnormalities (Hamm 1984).

When Sprague-Dawley (CD) rats and B6C3Fl mice were exposed to nitrobenzene at 125 ppm daily for two weeks, damage to the hindbrain (cerebellar peduncle), including bilateral cerebellar perivascular hemorrhage and malacia (cell breakdown), was observed in 8/19 mice (both sexes) and in 14/19 rats (both sexes) (Medinsky and Irons 1985). No brain lesions were found in Fischer rats exposed to the same levels. The reason for these strain differences under similar conditions is not apparent.

2.2.1.5 Developmental Effects

No studies were located regarding developmental effects in humans after inhalation of nitrobenzene.

Studies in animals indicate that inhalation exposure to nitrobenzene does not result in fetotoxic, embryotoxic or teratogenic effects at concentrations up to 40 ppm in rats (Tyl et al. 1987) and up to 100 ppm in rabbits (Bio/dynamics Inc. 1984). While the mean numbers of resorption sites and percentage of resorptions/implants in rabbits were higher in the 100 ppm group than in concurrent controls, these parameters were within the historical control range. However, animal data from these studies indicate that nitrobenzene is maternally toxic. In rats, spleen weights increased in the mothers (dams) at 10 ppm, and there was transient reduction in body weight gain in the 40 ppm group (Tyl et al. 1987). In rabbits, maternal effects noted at 40 ppm and above were increased methemoglobin levels and increased liver weights (Bio/dynamics Inc. 1983). Since no developmental toxic effects occurred in animals even at doses producing some maternal toxicity, developmental toxicity may not be a major concern in humans.

2.2.1.6 Reproductive Effects

No studies were located regarding reproductive effects in humans following inhalation exposure to nitrobenzene.

In a two-generation study in rats, nitrobenzene exposure (10 weeks) resulted in a decrease in fertility indices at 40 ppm for F_0 and F_1 generations, while other reproductive parameters were unaltered (Dodd et al. 1987). The study data suggested that the decrease was caused by effects in males. Atrophy of seminiferous tubules, spermatocyte degeneration and reduced testicular and epididymal weights were reported in F_0 and F_1 generations. A five-fold increase (above levels during exposure) in the fertility index was reported after 9 weeks of recovery from inhalation exposure to nitrobenzene, but reversibility was not studied histologically. Maternal toxicity was not observed. Hamm (1984) reported that both F-344 and Sprague-Dawley (CD) rats exposed to nitrobenzene at 50 ppm for 90 days had testicular atrophy, bilateral degeneration of the seminiferous tubules, and a reduction in or absence of mature sperm in the epididymis. No testicular lesions were observed in B6C3Fl mice under the same exposure conditions.

The testicular effects observed in these studies suggest that reproductive toxicity may be an area of concern for occupationally exposed humans.

2.2.1.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans after inhalation exposure to nitrobenzene.

Cytogenetic analyses of lymphocytes in the peripheral blood or in splenic blood of rats exposed to nitrobenzene at 5 to 50 ppm for 21 days did not reveal an increase in sister chromatid exchange (SCE) or chromosome breakage (Kligerman et al. 1983).

2.2.1.8 Cancer

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

2.2.2 Oral Exposure

Table 2-2 and Figure 2-2 describe the health effects observed in laboratory animals associated with oral exposure to nitrobenzene at varying levels and exposure durations.

2.2.2.1 Death

Although the early literature describes many "poisonings" and deaths that were attributed to nitrobenzene ingestion, the lack of reliable chemical identification makes it impossible to determine the actual cause of death in some of these cases. In early case studies that describe such events, nitrobenzene may have been identified only by its odor; in other cases, aniline may have been identified in the stomach contents. Because nitrobenzene is reduced to aniline by the microflora in the intestines, the presence of aniline in the stomach may more reasonably be attributed to the ingestion of aniline. In addition, due to prompt and aggressive medical attention when these incidents have occurred, most of the available case studies report that the victim has survived. Therefore, firm conclusions cannot be drawn about the potential lethal effects of nitrobenzene ingestion by humans.

An LD_{50} of 600 mg/kg in rats was reported by Smyth et al. (1969).

2.2.2.2 Systemic Effects

Hematological Effects. When nitrobenzene is ingested, the outstanding systemic effect is methemoglobin formation. In this condition, the blood releases less oxygen to the tissues and all general body functions tend to be slowed down (WHO 1986). A latency period (after ingestion and before any signs or symptoms occur) can be as short as 30 minutes or as long as 12 hours. Usually, the higher the dose, the shorter the latency period.

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

Figure Key	Species	Route	Exposure Frequency/ Duration	Effect	NOAEL (mg/kg/day)	LOAEL (Effect) Less Serious (mg/kg/day)	LOAEL (Effect) Serious (mg/kg/day)	Reference
ACUTE EXPOSURE								
Systemic								
1	Rat	(G)	1x	Hemato	100	200[a] (methemoglobinemia)		Goldstein et al. 1984
Neurological								
2	Rat	(G)	1x				550[b] (malacia/ hemorrhage)	Morgan et al. 1985
Reproductive								
3	Rat	(G)	1x				300[c] (testic. necrosis, decr. sperm)	Levin et al. 1988

[a]Converted to an equivalent concentration of 4,000 ppm in food for presentation in Table 1-4.
[b]Converted to an equivalent concentration of 11,000 ppm in food for presentation in Table 1-4.
[c]Converted to an equivalent concentration of 6,000 ppm in food for presentation in Table 1-4.

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; mg = milligrams; kg = kilograms; (G) = gavage; x = time; hemato = hematological; testic. = testicular; decr. = decreased

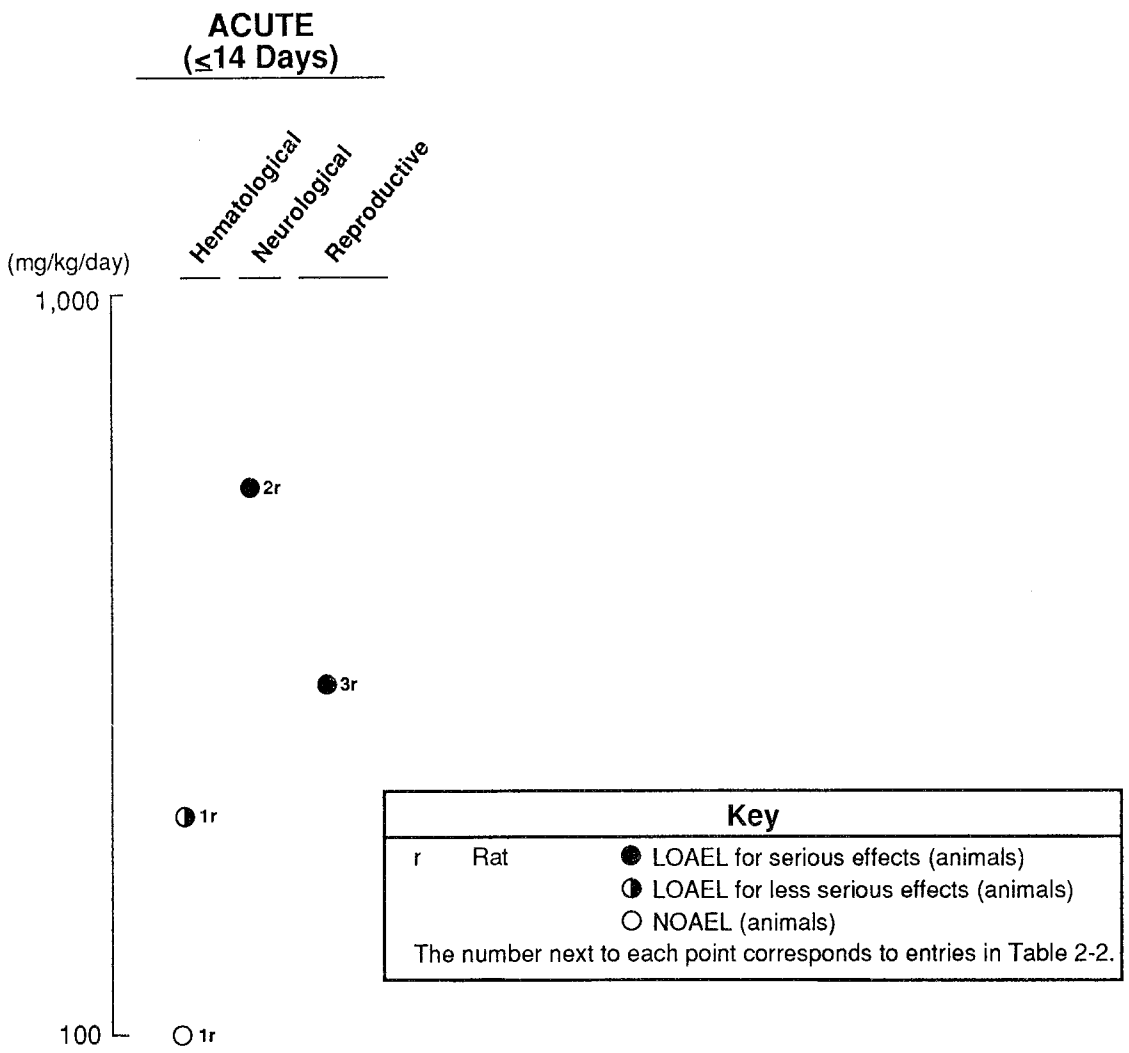


FIGURE 2-2. Levels of Significant Exposure to Nitrobenzene – Oral

No data are available to reliably estimate the level of human oral exposure to nitrobenzene that results in methemoglobinemia. Two of the case studies that were located indicate that some vague quantity, such as a few drops or a partial spoonful, was swallowed and part of that amount was vomited out before cyanosis and methemoglobinemia were observed (Carter 1936; Leader 1932). Another study (Myslak et al. 1971) estimated that a dose of 4.3 to 11 g was swallowed by a 19-year-old woman, based on the urinary levels of p-nitrophenol.

Oral administration of nitrobenzene to rats and mice results in methemoglobinemia (Goldstein et al. 1984a; Rickert 1984a).

The mouse is apparently more resistant to the methemoglobin forming properties of nitrobenzene than are other species (Shimkin 1939; Smith et al. 1967). The action of bacteria normally present in the small intestine of the rat is an important element in the formation of methemoglobin resulting from nitrobenzene exposure. Germ-free rats do not develop methemoglobinemia when orally administered nitrobenzene (Reddy et al. 1976). This observation leads to the speculation that a nitrobenzene metabolite such as aniline (which is formed by the bacterial reduction of nitrobenzene in the intestines of rats) may be involved in methemoglobin formation in this species. In addition, diet has been shown to play a role in the production of methemoglobin by influencing the intestinal microflora. The presence of cereal-based pectin in the diets of rats was shown to increase the ability of orally administered nitrobenzene to induce methemoglobinemia (Goldstein et al. 1984a).

Other Systemic Effects. No studies were located regarding hepatic, respiratory, cardiovascular, gastrointestinal, renal, musculoskeletal, dermal, or ocular effects in humans or animals after oral exposure to nitrobenzene.

2.2.2.3 Immunological Effects

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

2.2.2.4 Neurological Effects

Neurological effects following nitrobenzene ingestion by humans have been reported as headache, nausea, vertigo, confusion, unconsciousness, apnea and coma (Carter 1936; Leader 1932; Myslak et al. 1971). Levels of nitrobenzene associated with these effects cannot be reliably estimated in most of the case studies from which these descriptions have been derived.

Brain pathology was reported after a single oral administration of nitrobenzene at 550 mg/kg to male rats (Morgan et al. 1985). Observations included petechial hemorrhages in the brain stem and cerebellum and malacia (cell breakdown) in the fourth ventricle.

2.2.2.5 Developmental Effects

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

2.2.2.6 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to nitrobenzene.

No single or multigeneration reproduction studies in animals were found. However, an acute systemic study in rats indicated that the testes are sensitive to the toxic effects of nitrobenzene. Typical signs included testicular degeneration and transiently decreased sperm production following a single oral dose of 300 mg/kg (Levin et al. 1988).

Although no human studies were found and animal reproduction studies have not been performed by oral administration, the testicular degeneration in rats reported by Levin et al. (1988) suggests that reproductive toxicity may be of concern in exposed humans.

2.2.2.7 Genotoxic Effects

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

Rats gavaged with nitrobenzene at 200 or 500 mg/kg were tested for unscheduled DNA synthesis in liver slices (Mirsalis et al. 1982). No significant increase in DNA synthesis was found.

2.2.2.8 Cancer

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

2.2.3 Dermal Exposure

Cases of severe and nearly lethal toxic effects after dermal exposure to aniline-based dyes have been reported as early as 1886. These cases have involved mainly infants exposed to dye-stamped diapers and persons wearing freshly dyed shoes. The resulting condition was often termed "nitrobenzene poisoning", even though exposure to

nitrobenzene did not necessarily occur. Several conclusions and generalizations about the dermal absorption and toxic effects of nitrobenzene, especially in infants, seem to have been based on these studies which should more appropriately be considered as part of the data base for aniline.

2.2.3.1 Death

No studies were ocated regarding death in humans after dermal exposure to nitrobenzene.

Dermal applications of nitrobenzene to female C3H or male A-strain mice resulted in the death of 12 of 18 and 8 of 10 animals, respectively (Shimkin 1939). Although 2 or 3 applications were required for the C3H mice, most animals were in partial collapse within 15 minutes and dead by the third day. Most of the strain-A mice were dead within the first day. The dermal dosage was not stated.

2.2.3.2 Systemic Effects

Hematological Effects. No studies were located regarding hematological effects in humans after dermal exposure to nitrobenzene. Dermal painting of C3H female or strain-A male mice with nitrobenzene resulted in methemoglobinemia by 3 hours after application (Shimkin 1939).

Hepatic Effects. No studies were located regarding hepatic effects in humans after dermal exposure to nitrobenzene. In mice dermally exposed to nitrobenzene, the liver was the most severely affected organ. There was diffuse necrosis in the outer two thirds of the lobules of the liver (Shimkin 1939).

Renal Effects. No studies were located regarding renal effects in humans after dermal exposure to nitrobenzene.

When mice were dermally painted with nitrobenzene for 1 to 3 applications, there was slight swelling of the glomeruli and tubular epithelium upon histological examination (Shimkin 1939).

Other Systemic Effects. No studies were located regarding other systemic effects (respiratory, cardiovascular, gastrointestinal, musculoskeletal, splenic, dermal, ocular) in humans or animals after dermal exposure to nitrobenzene.

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

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

2.2.3.8 Cancer

2.3 TOXICOKINETICS

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

In humans, nitrobenzene was well absorbed through the lung in the one study located. During a 6-hour exposure of volunteers to nitrobenzene, Salmowa et al. (1963) found absorption to average 80% (73 to 87%) in 7 men breathing 6 ppm nitrobenzene. The efficiency of uptake was dose dependent, but showed considerable individual variation.

No studies were located regarding the uptake of nitrobenzene by animals after inhalation exposure.

2.3.1.2 Oral Exposure

No studies were located regarding the uptake of nitrobenzene by humans after oral exposure.

After oral administration of 250 mg/kg of nitrobenzene by stomach tube to rabbits, Parke (1956) recovered 0.5% (1.3 mg) of the administered dose of nitrobenzene from the exhaled air of the rabbit. The amount of nitrobenzene in the blood was not measured. Unchanged nitrobenzene in the urine was less than 0.1% (0.25 mg).

2.3.1.3 Dermal Exposure

The toxicokinetics of dermal exposure have not been well studied in either humans or experimental animals. Piotrowski (1967) found that approximately half of the dose of nitrobenzene was absorbed through the skin when volunteers were exposed to either 1 or 5.5 ppm nitrobenzene in air.

In animal studies, nitrobenzene appears to be absorbed after dermal application based on observations of toxic responses in the treated animals. Shimkin (1939) reported that dermal painting of mice with liquid nitrobenzene (dose not stated) resulted in the death of most test animals after 1 to 3 applications. Dermal exposure of rabbits to nitrobenzene (dose not stated) for 22 to 205 days resulted in greater neural damage than did intravenous exposure (Matsumaru and Yoshida 1959). Administration of alcohol (not further identified) by stomach tube following exposure to nitrobenzene resulted in neurotoxicity by both routes of exposure.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No studies of the distribution of nitrobenzene or its metabolites after inhalation exposure by humans or animals were found in the literature.

2.3.2.2 Oral Exposure

Radiolabeled nitrobenzene has been followed after oral administration in a number of studies in rats and mice (Goldstein and Rickert 1984; Levin and Dent 1982a; Morgan et al. 1985). In summary, these studies have shown that nitrobenzene is reduced to nitrosobenzene, phenylhydroxylamine, and aniline by the bacteria of the intestine. Metabolism of nitrobenzene resulted on covalent binding to the hepatic microsomes. Nitrosobenzene and phenylhydroxylamine were bound to the hemoglobin. Unaltered nitrobenzene was recovered from the brain at a rate of 0.02% of the administered dose. The subcellular site of nitrobenzene metabolism was not found. The major urinary metabolites were p-aminophenol and p-nitrophenol together with the sulfate and glucuronide conjugates.

In a study of rats that received radiolabeled nitrobenzene by gavage, it became bound to the tissues after the first day according to the following indices [mmol/mol Hb/dose (mmol/kg)]: blood-229, liver-129, kidney-204, lung-62. BY day 7, the same indices were: 134, 26.5, 48, 29. After the first day, 50% of the dose (radioactivity) appeared in the urine and 4% in the feces. After the fifth day, 65% of the dose had appeared in the urine and 16% appeared in the feces (Albrecht and Neumann 1985). These studies confirmed the observation of Rickert et al. (1983), that the excretion of nitrobenzene is delayed. The binding indices also indicated that 4 to 5 times as much nitrosobenzene is formed from nitrobenzene as from an equal amount of aniline.

2.3.2.3 Dermal Exposure

No studies were located regarding the distribution of nitrobenzene or its metabolites after dermal exposure.

2.3.3 Metabolism

The covalent metabolism and binding of nitrobenzene to hemoglobin was studied by Albrecht and Neumann (1985). When Wistar rats were administered 25 mg/kg radiolabeled nitrobenzene by gavage, biotransformation was first seen in the intestine where nitrobenzene was sequentially reduced to nitrosobenzene, phenylhydroxylamine and aniline. These findings were also reported in Fischer-344 rats (Levin and Dent 1982a). The observation that germ-free rats do not develop methemoglobinemia when administered nitrobenzene (Reddy et al. 1976) has led to the speculation that a nitrobenzene metabolite such as aniline may be involved in methemoglobinemia formation in this species. The nitrobenzene metabolites, nitrosobenzene and phenylhydroxylamine have been found to bind with hemoglobin in the blood of orally exposed mice and rats (Goldstein and Rickert 1984).

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

Urinary excretion rates of p-nitrophenol were found in 7 volunteers who had inhaled 6 ppm nitrobenzene for 6 hours (Salmowa et al. 1963). The rate of urinary elimination varied considerably from individual to individual, but showed a general dose dependence at 1 to 6 ppm nitrobenzene. In general, excretion was most rapid during the first two hours and then leveled off. In some cases, p-nitrophenol could be detected for as long as 100 hours after exposure to 6 ppm for 6 hours. In a 47-year-old woman who had been occupationally exposed to nitrobenzene for 17 months, p-nitrophenol and p-aminophenol were found in the urine (Ikeda and Kita 1964).

2.3.4.2 Oral Exposure

After oral exposure to nitrobenzene, the major route of excretion is the urine. In most cases of human poisoning, the metabolites excreted in the urine are p-aminophenol and p-nitrophenol (Myslak et al. 1971; Von Oettingen 1941). Five days after oral administration to rats, Albrecht and Neumann (1985) found 65% of the administered dose (25 mg/kg) in the urine and 16% in the feces.

2.3.4.3 Dermal Exposure

A unique apparatus was developed to measure skin absorption from the nitrobenzene vapor in the air without inhalation of nitrobenzene (Piotrowski 1967). At 1 ppm, about 8 mg is absorbed through the skin and about 20% is excreted in the urine the first day.

2.4 RELEVANCE TO PUBLIC HEALTH

Studies in animals, combined with observations in humans, indicate that the principal adverse health effects associated with short-term inhalation or oral exposure to nitrobenzene are methemoglobinemia, neurological effects, and liver injury. Data related to dermal exposure and to long-term exposure by any route are not considered sufficient to clearly assess the potential effects.

Death. Accidental poisonings and deaths in humans that were attributed to the ingestion of nitrobenzene have been reported; but as discussed in Section 2.2.2.1, these studies usually lack clear chemical identification of nitrobenzene as the ingested substance. In those inhalation case studies (Stevens 1928; Stevenson and Forbes 1942) and oral case studies (Carter 1936; Leader 1932; Myslak et al. 1971) in which the patients were apparently near death due to severe methemoglobinemia, termination of exposure and prompt medical intervention resulted in gradual improvement and recovery. Data relating to dermal exposure to nitrobenzene, as discussed previously in Section 2.2.3, are questionable since there may have been exposure to aniline-based dyes and little or no exposure to nitrobenzene. Data in animals indicate that nitrobenzene can be lethal via oral, inhalation or dermal exposure. Although human exposure to sufficiently high quantities of nitrobenzene can probably be lethal via any route of exposure, it is considered unlikely that levels of exposure high enough to cause death would occur except in cases of industrial accidents.

Systemic Effects. The chief systemic effect associated with human exposure to nitrobenzene is methemoglobinemia. However, it is difficult to locate clear evidence of this effect, since nitrobenzene was identified only by its odor in several early case studies. Methemoglobinemia was reported to occur in twin 3-week-old babies (Stevens 1928), in a 12-month-old girl (Stevenson and Forbes 1942), and in a 47-year-old woman (Ikeda and Kita 1964), all of whom were exposed to nitrobenzene via inhalation. However, levels of exposure were neither known nor estimated. In addition, the compound to which the 12-month-old girl was exposed also contained kerosene, turpentine, and oil of lilacine. The 3-week-old twins were exposed to nitrobenzene in a toilet deodorant called "Creco". No other ingredients were stated in the study. Oral exposure to nitrobenzene at unspecified amounts has

also resulted in methemoglobinemia (Carter 1936; Leader 1932; Myslak et al. 1971). There is no clear evidence that dermal exposure to nitrobenzene results in methemoglobinemia in humans. Reports of methemoglobinemia resulting in dermal contact with dyes allegedly containing nitrobenzene are complicated by the early confusion in nomenclature for aniline and nitrobenzene.

Methemoglobinemia has also been reported in mice and rats exposed to nitrobenzene via inhalation (Hamm 1984) and in rats and mice exposed orally (Goldstein et al. 1984a; Rickert 1984a). Dermal painting studies in mice resulted in the onset of methemoglobinemia within 3 hours after nitrobenzene application (level not stated) (Shimkin 1939). This finding suggests that methemoglobinemia may also occur in dermally exposed humans.

Liver effects have been reported in both humans and animals exposed to nitrobenzene. Hepatic enlargement and tenderness, jaundice, and altered serum chemistries were reported in a 47-year-old woman who had been occupationally exposed to nitrobenzene for 17 months (Ikeda and Kita 1964). The authors considered these changes to be related to increased destruction of hemoglobin and enlargement of the spleen. Liver effects observed in animals following nitrobenzene exposure are hepatocyte necrosis in rats (Medinsky and Irons 1985) and increased liver weight, hepatocyte hyperplasia, and multinucleated hepatocytes in mice (Hamm 1984). Hepatic effects have not been reported in oral studies. Dermal painting studies in mice resulted in diffuse necrosis in the outer two-thirds of the lobules of the liver (Shimkin 1939).

There are no data on renal effects in humans exposed to nitrobenzene by any route. In rats, strain-related differences in renal effects have been reported as a result of inhalation exposure to nitrobenzene (Hamm 1984; Medinsky and Irons 1985). Observed effects have included increased kidney weights, hydropic degeneration of the cortical tubules and hyaline nephrosis. Renal effects have not been reported in studies of animals that were orally exposed to nitrobenzene. In dermal painting studies in mice, slight swelling of the glomeruli and tubular epithelium were reported (Shimkin 1939). These findings suggest that renal damage may also occur in exposed humans.

Splenic lesions reported in inhalation studies in mice and rats have included sinusoidal congestion, an increase in extramedullary hematopoiesis and hemosiderin-laden macrophages invading the red pulp, and the presence of proliferative capsular lesions (Hamm 1984; Medinsky and Irons 1985). These findings suggest that the spleen may also be a target organ during human inhalation exposure to nitrobenzene.

2. HEALTH EFFECTS

Little information is available on the effects of inhalation, oral or dermal exposure of humans or animals to nitrobenzene on the respiratory, cardiovascular or musculoskeletal systems or on the skin or eyes.

Immunological Effects. No studies were located regarding immunologic effects in humans or animals after inhalation, oral, or dermal exposure to nitrobenzene. Splenic lesions reported in rodent inhalation studies (Hamm 1984; Medinsky and Irons 1985) suggest that this may be an area of potential concern.

Neurological Effects. Neurotoxic symptoms reported in humans after inhalation exposure to nitrobenzene have included headache, confusion, vertigo and nausea (Ikeda and Kita 1964); effects in orally exposed persons have also included those symptoms as well as apnea and coma (Carter 1936; Leader 1932; Myslak et al. 1971). Studies in animals exposed via inhalation have shown morphological damage to the hindbrain (cerebellar peduncle) (Medinsky and Irons 1985). Damage to the brainstem, cerebellum and fourth ventricle was observed in orally exposed animals. Thus, it is possible that similar neurological changes may occur in humans as a result of nitrobenzene exposure.

Developmental Effects. No studies of developmental effects in humans resulting from inhalation, oral or dermal exposure to nitrobenzene have been reported. Studies conducted via inhalation exposure did not result in fetotoxic or teratogenic effects in rats or rabbits (Bio/dynamics 1984; Tyl et al. 1987). No studies have been conducted using the oral or dermal routes. Developmental effects are not expected to be of concern to humans exposed to the typical levels in the environment or in occupational settings.

Reproductive Effects. The effects of nitrobenzene on reproduction have not been studied in humans by inhalation, oral or dermal routes of exposure. In rats, inhalation of nitrobenzene has resulted in testicular degeneration and decreased sperm levels (Dodd et al. 1987; Hamm 1984). Cessation of spermatogenesis, followed by a slow and incomplete recovery, was observed in rats following a single oral dose of nitrobenzene (Levin et al. 1988). These findings suggest that reproductive effects may also be an area of concern for men exposed to nitrobenzene in occupational settings.

Genotoxic Effects. The genotoxicity of nitrobenzene has been investigated in both in vitro and in vivo studies. The results of in vitro studies are presented in Table 2-3. In vivo studies are described in Sections 2.2.1.7 and 2.2.2.7. The results of these studies are generally negative and do not suggest potential human health concerns.

TABLE 2-3. Genotoxicity of Nitrobenzene In Vitro

End Point	Species (Test System)	Results: With Activation	Results: Without Activation	Reference
Prokaryotic organisms:				
Gene mutation	Salmonella typhimurium	-	-	Garner and Nutman 1977
Gene mutation	S. typhimurium	-	-	Shimizu et al. 1983
Gene mutation	S. typhimurium	-	ND	Ho et al. 1981
Gene mutation	S. typhimurium	-	-	Haworth et al. 1983
Gene mutation	S. typhimurium	-	ND	Anderson and Styles 1978
Gene mutation	S. typhimurium	-	-	Hughes et al. 1984

- = negative result; ND = no data.

Cancer. No studies were located regarding carcinogenic potential in humans or animals after inhalation, oral, or dermal exposure to nitrobenzene.

2.5 BIOMAREERS 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 or cell 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 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 (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 been eliminated from 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 nitrobenzene 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 as physiologic 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 nitrobenzene 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. 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 Nitrobenzene

The presence of p-nitrophenol in the urine can be used to indicate exposure to nitrobenzene (Ikeda and Kita 1964). Measurement of p-nitrophenol, however, cannot be used to determine the level of nitrobenzene exposure or if harmful effects can be expected to occur. The nitrobenzene metabolites, nitrosobenzene and phenylhydroxylamine, have been found to bind with hemoglobin in the blood of orally exposed mice and rats (Goldstein and Rickert 1984). The presence of these hemoglobin adducts in human blood may also serve as a potential biomarker of exposure to nitrobenzene.

2.5.2 Biomarkers Used to Characterize Effects Caused by Nitrobenzene

The presence of methemoglobinemia can indicate exposure to nitrobenzene as well as to any of several other toxic substances. Therefore, this condition in itself cannot be used as a biomarker of effect for nitrobenzene.

2.6 INTERACTIONS WITH OTHER CHEMICALS

Synergism between orally administered nitrobenzene and six other common industrial compounds was demonstrated in rat studies using dea as the end point (Smyth et al. 1969). The combinations of chemicals showed increased lethality that varied from 20 to 47%. The compounds were: formalin, 20%; butyl ether, 28%; aniline, 32%; dioxane, 39%; acetone, 47%; and carbon tetrachloride, 47%.

Alcohol also has the potential for enhancing the toxicity of nitrobenzene; however the toxicokinetic mechanism is not known. It is clear, however, that alcohol does not simply enhance the absorption of nitrobenzene. When alcohol was given orally and nitrobenzene is given intravenously, there was increased toxicity in rabbits. Alcohol also enhanced the neural toxicity of nitrobenzene in rabbits when nitrobenzene was applied to the skin (Matsumaru and Yoshida 1959).

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

Populations that are considered unusually susceptible to nitrobenzene toxicity are those groups that are susceptible to methemoglobinemia. The newborn infant is especially vulnerable to methemoglobinemia due to the following factors (Goldstein et al. 1969; Von Oettingen 1941):

1. Fetal hemoglobin, which remains in the blood for some time after birth, is more prone to conversion to methemoglobin than is adult hemoglobin.

2. Umbilical cord blood is deficient in the enzyme glucose-6-phosphate dehydrogenase and thus cannot readily convert the methemoglobin that is formed "naturally" back to hemoglobin as is readily done in adults.

A condition described as "hereditary methemoglobinemia" may result from a genetic defect (Goldstein et al. 1969). The enzyme methemoglobin reductase is absent and persons are hypersensitive to any substances such as nitrite or aniline derivatives capable of producing methemoglobinemia. The trait is inherited as an autosomal recessive allele. Thus either sex may exhibit the trait which is ordinarily detected by the presence of cyanosis at birth. Such individuals would be extremely sensitive to the effects of nitrobenzene.

A more common genetic defect was also described in which the enzyme glucose-6-phosphate dehydrogenase has decreased activity (Goldstein et al. 1969). The pattern of inheritance of this trait is linked to one of several alleles on the X chromosome. The phenotype is expressed as an incomplete dominant trait. Thus, female heterozygotes are not known to have severely depressed enzyme levels and males may have a wide range of activity. These phenotypes express a wide range of levels of glucose-6-phosphate dehydrogenase enzyme in the red blood cell. This defect is ordinarily without adverse effects. It is only when these individuals are challenged with compounds that oxidatively stress erythrocytes (such as primaquine) that there is a hemolytic response. Reactors to primaquine (and fava beans) are found predominantly among groups that live in or trace their ancestry to malaria-hyperendemic areas such as the Mediterranean region or Africa. The incidence of "primaquine sensitivity" among Kurds, a Middle Eastern population, is 53%. Among American blacks, the incidence is 13%. Thus, individuals already exhibiting primaquine sensitivity would be expected to be more vulnerable to the additional hemolytic crisis that often follows 5 to 6 days after nitrobenzene exposure (Gosselin et al. 1984; Von Oettingen 1941).

The presence of susceptible populations in the workplace is obviously of great concern since chronic and potentially high levels of exposure to nitrobenzene combined with a genetic predisposition toward methemoglobinemia can put certain individuals at very high risk (Linch 1974).

2.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, 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 nitrobenzene 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 nitrobenzene.

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.

2.8.1 Existing Information on Health Effects of Nitrobenzene

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to nitrobenzene are summarized in Figure 2-3. The purpose of this figure is to illustrate the existing information concerning the health effects of nitrobenzene. 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.

2.8.2 Identification of Data Needs

Acute-Duration Exposure. Case studies of acute-duration human exposure to nitrobenzene via inhalation and the oral route indicate that methemoglobinemia is the major adverse effect found in humans. No data are available on human dermal exposure. Acute-duration studies conducted in rats via the inhalation and oral routes and in mice via the dermal route have also resulted in methemoglobinemia as well as various other systemic, neurological, and testicular effects. The data are not considered to be appropriate to use in calculating an MRL by any route because species- and strain-related differences in sensitivity have been noted in intermediate-duration inhalation studies in mice and rats, and

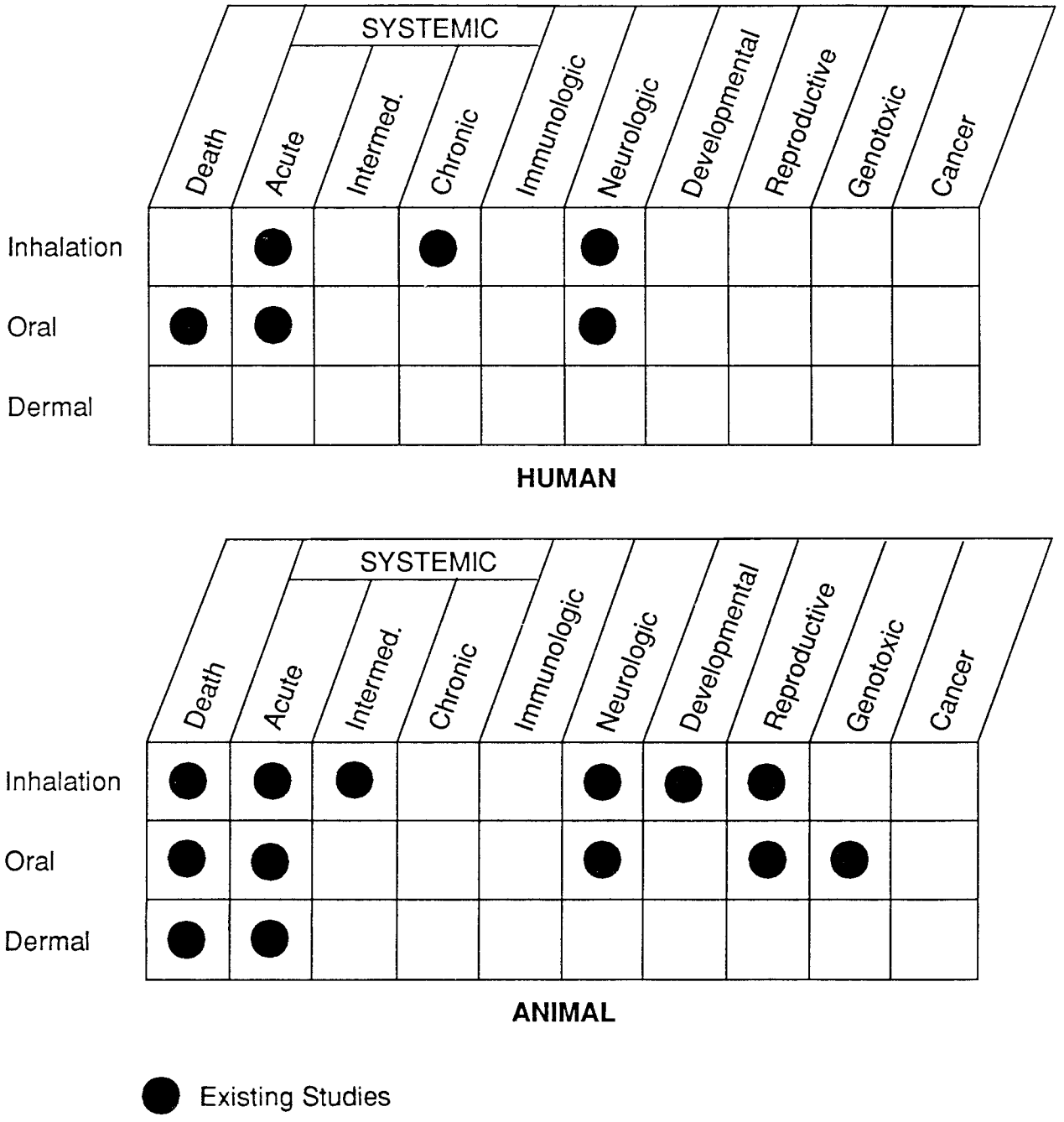


FIGURE 2-3. Existing Information on Health Effects of Nitrobenzene

it is possible that human sensitivity to methemoglobin formation may greatly exceed that of the test animals used in these studies. The available toxicokinetic data do not provide insight as to the possible reasons for the observed differences in rodent studies. However, there is no apparent need for further animal studies by any route of exposure for this duration period.

Intermediate-Duration Exposure. No data are available on human exposure to nitrobenzene by any route for this duration period. Data in animals are limited to two inhalation studies in rodents. Effects in rats included methemoglobinemia, renal and hepatic necrosis, splenic lesions, and testicular necrosis. Methemoglobinemia and adrenal lesions were reported in mice. The available data were not considered to be adequate to use in calculating an MEL for this route, because the database is very limited and because the different levels of sensitivity observed in mice and rats suggest that relative human sensitivity should be closely studied before calculations of MELs are attempted. There are no toxicokinetic data that provide a potential explanation for these differences. However, there is no apparent need for further inhalation studies for this duration period. A 90-day study via the oral route may provide useful information. However, the available information does not clearly establish that oral or dermal exposure to nitrobenzene are likely to occur in humans.

Chronic-Duration Exposure and Cancer. Available chronic-duration studies in humans are limited to a case report of a woman who was occupationally exposed to nitrobenzene and developed methemoglobinemia and hepatic and neurological effects. Chronic duration data in animals are limited to a two-generation inhalation study in rats that resulted in testicular lesions. No studies using the oral or dermal routes have been located and the available data are not considered appropriate to use in calculating an MRL by any route. The results of a Chemical Industry Institute of Toxicology (CIIT) inhalation bioassay using rats and mice which was completed in 1987 should provide useful information on the potential risks associated with chronic exposure to nitrobenzene in the vicinity of hazardous waste sites and, to a greater extent, in the workplace. Although nitrobenzene appears to be well absorbed via the oral route, there are no data to suggest that long-term oral exposure would be of concern in these populations. Dermal absorption of nitrobenzene in the air has been demonstrated in toxicokinetic studies in humans. Based on the results of the CIIT two-year inhalation study, chronic-duration dermal application studies may be useful in assessing the possible effects of dermal contact with nitrobenzene in the workplace.

There are no available carcinogenicity data in humans or animals using any route of exposure. Data from the CIIT inhalation bioassay should provide valuable information on the carcinogenic potential of airborne nitrobenzene. There is currently no apparent need for studies using the oral or dermal route. However, as stated above, the results of the CIIT bioassay may provide insight into the possible need for dermal application studies.

Genotoxicity. There are no data on the genotoxic potential of nitrobenzene in humans exposed via any route. The results of in vivo tests in rats exposed via inhalation or orally and in vitro tests have generally been negative and do not suggest a potential concern for exposed humans. Further studies in this area do not appear to be needed.

Reproductive Toxicity. There are no data on the potential reproductive effects in humans exposed to nitrobenzene via any route. Data in animals include a 90-day inhalation study in rats that resulted in testicular degeneration, a two-generation inhalation study in rats that resulted in testicular lesions and decreased fertility, and a single-dose gavage study in rats that resulted in testicular necrosis and temporarily decreased sperm levels. These data suggest that similar information on men exposed to nitrobenzene in the area of hazardous waste sites or in the workplace would be extremely useful. In addition, in any further animal studies conducted by any route and for any duration period, data on reproductive organ histopathology resulting from nitrobenzene exposure as well as toxicokinetic data on the distribution of nitrobenzene to the reproductive organs would be valuable information.

Developmental Toxicology. There are no available data on the developmental effects of nitrobenzene in humans exposed via any route for any duration period. The results of inhalation studies in rats and rabbits have been negative. There is no apparent need for further studies in this area. However, if any further developmental studies are conducted, it would be useful to have data on animals exposed earlier in the gestation period than day 6 (which was the earlier gestation day in the two available inhalation studies).

Immunotoxicity. No studies were located relating to immunotoxic effects in humans or animals exposed to nitrobenzene via any route. However, splenic lesions have been reported in mice and rats exposed to nitrobenzene via inhalation in both acute- and intermediate-duration studies. These results suggest that a battery of immune function tests in animals exposed via inhalation and orally would provide useful information. The results of the CIIT bioassay, however, may provide some information on this end point.

Neurotoxicity. Neurological effects including headache, nausea, vertigo, and confusion have been reported in case studies of humans exposed to nitrobenzene by inhalation. In orally exposed persons, apnea and coma have additionally been reported. No data are available in humans exposed via the dermal route. In animal studies, brain lesions have been observed in mice and rats exposed by inhalation and in rats that received a single oral dose. No data are available in animals exposed via the dermal route. Toxicokinetic studies in mice and rats provide evidence that nitrobenzene is distributed to brain tissue. Both the human and animal data provide clear evidence that nitrobenzene is a neurotoxic substance. Further studies in this area do not appear to be needed. In addition, results of the CIIT two-year bioassay may provide further information on this end point.

Epidemiological and Human Dosimetry Studies. No epidemiological studies were located regarding human health effects from nitrobenzene exposure. Studies of occupationally exposed populations would probably provide useful information. Areas of major interest would include methemoglobin levels, effects on reproductive function, immunological status, and neurobehavioral function.

Biomarkers of Exposure and Effect. The presence of p-nitrophenol in urine serves as a satisfactory biomarker of nitrobenzene exposure. Because nitrobenzene metabolites, nitrosobenzene and phenylhydroxylamine, bind to hemoglobin in the blood of rats and mice, the presence of these hemoglobin adducts in human blood may also serve as biomarkers of nitrobenzene exposure. More information on this possibility would be useful.

The presence of increased levels of methemoglobin can indicate exposure to nitrobenzene as well as to any of several other toxic substances. Therefore, methemoglobinemia by itself would not serve as a satisfactory biomarker of effect for nitrobenzene. Further study in this area does not appear to be potentially useful.

Absorption, Distribution, Metabolism, Excretion. Absorption data for humans exposed to nitrobenzene via inhalation and the dermal route indicate that it is efficiently absorbed by these routes. Although absorption studies using the oral route have not been located for humans, the available case studies suggest that it can also be absorbed via ingestion. However, quantitative data are lacking. Similarly, in animals, quantitative absorption studies using inhalation or dermal application are not available, but the available toxicity data using these routes suggest that absorption does take place. This does not appear to be a priority area for further research.

No distribution data are available for humans exposed to nitrobenzene via any route. Data in animals are limited to oral studies in rats and mice that indicate that there is some distribution to the blood, liver, brain, kidney, and lung. Not all tissues have been analyzed in these studies. Comprehensive distribution studies for nitrobenzene administered to mice and rats via all three routes would be very helpful in predicting the organ systems at potential risk in exposed humans.

Metabolism data available for nitrobenzene suggest that species and/or strain differences in toxicity may be related to the metabolic activities of intestinal bacteria that convert it to its toxic metabolite aniline. This is an area in which further study may be helpful in making comparisons of human sensitivity with that of other animals and thus may aid in the interpretation of the currently available animal studies and their relevance to humans.

Excretion data are available for humans exposed to nitrobenzene via the inhalation, oral, and dermal routes. The available animal studies have used the oral route. Urine appears to be the major route of excretion, although this has not been clearly established. There is no apparent need for further studies in this area.

Comparative Toxicokinetics. Species and strain differences in response to nitrobenzene exposure have been noted in inhalation studies using mice and rats. The reason for these differences and the toxicokinetics involved are not understood. Additional toxicokinetic studies in species other than rodents and attempts to estimate the sensitivity of humans relative to these test species would be valuable aids in interpreting the results of available toxicity studies and in understanding individual differences noted in response to nitrobenzene exposure.

2.8.3 On-going Studies

The CIIT has been preparing a final report on their two-year carcinogenicity studies of nitrobenzene administered to mice and rats via inhalation. No other research activities on nitrobenzene are known to be currently in progress.

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

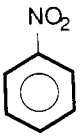
Table 3-1 lists common synonyms, trade names and other pertinent identification information for nitrobenzene.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

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

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-1. Chemical Identity of Nitrobenzene

	Value	Reference
Chemical name	Nitrobenzene	NLM 1988
Synonyms	Nitrobenzol; Oil of Mirbane	MLM 1988
Trade name	Caswell No. 600	NLM 1988
Chemical formula	$C_6H_5NO_2$	NLM 1988
Chemical structure		
Identification numbers:		
CAS Registry	98-95-3	NLM 1988
NIOSH RTECS	DA6475000	HSDB 1988
EPA Hazardous Waste	U169, F004	NLM 1988, HSDB 1988
OHM/TADS	7216821	HSDB 1988
DOT/UN/NA/IMCO Shipping	UN 1662	NLM 1988
HSDB	104	NLM 1988
NCI	C60082	NLM 1988

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

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-2. Physical and Chemical Properties of Nitrobenzene

Property	Value	Reference
Molecular weight	123.11	Weast 1985
Color	Yellow	Verschueren 1983
Physical state	Liquid	Verschueren 1983
Melting point	5.7°C	Weast 1985
Boiling point	210.8°C	Weast 1985
Density at 20°C	1.2037	Weast 1985
Odor	Bitter almonds, shoe polish	Verschueren 1983
Odor threshold:		
Water	0.11 mg/L	Amoore and Hautala 1983
Air	0.092 mg/m^3	Amoore and Hautala 1983
Solubility:		
Water at 20°C	1900 mg/L	Mabey et al. 1982
Organic solvents	Soluble in alcohol, ether, acetone, benzene	Weast 1985
Partition coefficients:		
Log K_{ow}	1.87	Mabey et al. 1982
Log K_{oc}	1.56	Mabey et al. 1982
Vapor Pressure at 20°C	0.15 mmHg	Mabey et al. 1982
Henry's law constant	1.31×10^{-5} atm-m^3/mol	Mabey et al. 1982
Autoignition temperature	482°C	Sax and Lewis 1987
Flashpoint	87.7°C	Sax and Lewis 1987
Flammability limits	No data	
Conversion factors	1 ppm = 5.12 mg/m^3	Verschueren 1983
	1 mg/m^3 = 0.20 ppm	Verschueren 1983

4 PRODUCTION, IMPORT, USE, AND DISPOSAL

4.1 PRODUCTION

Nitrobenzene is produced commercially by the exothermic nitration of benzene with fuming nitric acid in the presence of a sulfuric acid catalyst at 50 to 65°C. The crude nitrobenzene is passed through washer-separators to remove residual acid and is then distilled to remove benzene and water.

There has been a gradual increase in nitrobenzene production volume in the United States from 73,600 metric tons (kkg) in 1960 to 434,900 kkg in 1986. Based on increased production capacity and increased production of aniline (the major end-product of nitrobenzene) in 1987, it is likely that nitrobenzene production volume will continue to increase (Collins et al. 1982; Dunlap 1981; EPA 1985a; SRI 1985, 1986, 1987, 1988; USITC 1987, 1988).

Currently, there are four United States producers of nitrobenzene: E. I. DuPont de Nemours 6 Company, Inc., Beaumont, Texas; Mobay Corporation, New Martinsville, West Virginia; First Chemical Corporation, Pascagoula, Mississippi; and ICI Americas, Inc., Geismar, Louisiana (SRI 1988; USITC 1988).

4.2 IMPORT

No recent data documenting import or export volumes of nitrobenzene were located. However, it is estimated that these quantities are negligible, based on the 1978 import volume of 38 kkg and 1980 export volume of 36 kkg, which represent less than 1% of United States production during those years (Collins et al. 1982).

4.3 USE

The primary use of nitrobenzene is in the captive production of aniline, with about 97.5% of nitrobenzene production consumed in this process. The major use of aniline is in the manufacture of polyurethanes. Nitrobenzene is also used as a solvent in petroleum refining, in the manufacture of cellulose ethers and acetate, and in Friedel-Crafts reactions to hold the catalyst in solution. It is also used in the synthesis of other organic compounds including acetaminophen, which is an over-the-counter analgesic commonly known as Tylenol®.

Nitrobenzene is used as a flavoring agent, a perfume for soaps and as a solvent for shoe dyes (Collins et al. 1982; Dunlap 1981; EPA 1985a; HSDB 1988).

4.4 DISPOSAL

Because nitrobenzene is listed as a hazardous substance, disposal of waste nitrobenzene is controlled by a number of federal regulations (see Chapter 7). Land disposal restrictions (treatment standards) apply to wastes containing nitrobenzene. These wastes may be chemically or biologically treated or incinerated by the liquid injection or fluidized bed methods (EPA 1988a, 1989; HSDB 1988). No data were located on the amounts of nitrobenzene disposed of by any of these methods. The EPA does not believe that releases of nitrobenzene to the environment are substantial (EPA 1984).

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Human exposure to nitrobenzene results from releases to air and wastewater from industrial sources and from nitrobenzene as an air pollutant in ambient air, especially in urban areas. Its low volatility and weak sorption on soil suggest that surface waters and groundwater could be a route of exposure for the general population. Exposure is mitigated by environmental degradation, including photolysis and microbial biodegradation. Nitrobenzene is poorly bioaccumulated and not biomagnified through the food chain. A number of fairly stable degradation products of nitrobenzene are formed during environmental degradation; some have similar effects, while others operate by different mechanisms. Moreover, whether or not nitrobenzene will be completely broken down (mineralized) at a particular site seems to be questionable. Nitrobenzene may not be degraded in a given sewage treatment plant, and, when present at high concentrations, it also may inhibit the biodegradation of other wastes.

Occupational exposure is of great concern, since nitrobenzene can be taken up very readily through the skin as well as by inhalation. Monitoring studies reveal low and highly variable exposures through air and, more rarely, drinking water, with a generally downward trend in exposure levels over the past two decades. At this time, nitrobenzene has been found in 7 of the 1,177 NPL hazardous waste sites in the United States (VIEW 1989). The frequency of these sites within the United States can be seen in Figure 5-l.

Because of the relative ease of measurement of many of nitrobenzene's properties and its ready detectability by both chemical analysis and human olfaction (sense of smell), its release, transport and fate, and the consequent exposure of human beings have been studied over a considerable period of time. Thus, the potential for human exposure to nitrobenzene is better understood than that of many other chemicals.

5.2 RELEASES TO THE ENVIRONMENT

Most (97% to 98%) of the nitrobenzene produced is retained in closed systems for use in synthesizing aniline and other substituted nitrobenzenes and anilines (Dorigan and Hushon 1976; Chemical Marketing Reporter 1987). Most of these products go into the manufacture of various plastic monomers and polymers (50%) and rubber chemicals (27%); a smaller proportion goes into synthesis of hydroquinones (5%), dyes and intermediates (6%), drugs (3%), and pesticides and other specialty items (9%) (Dunlap 1981). A small fraction of the production is used directly in other processes or in consumer products (principally metal and shoe polishes).

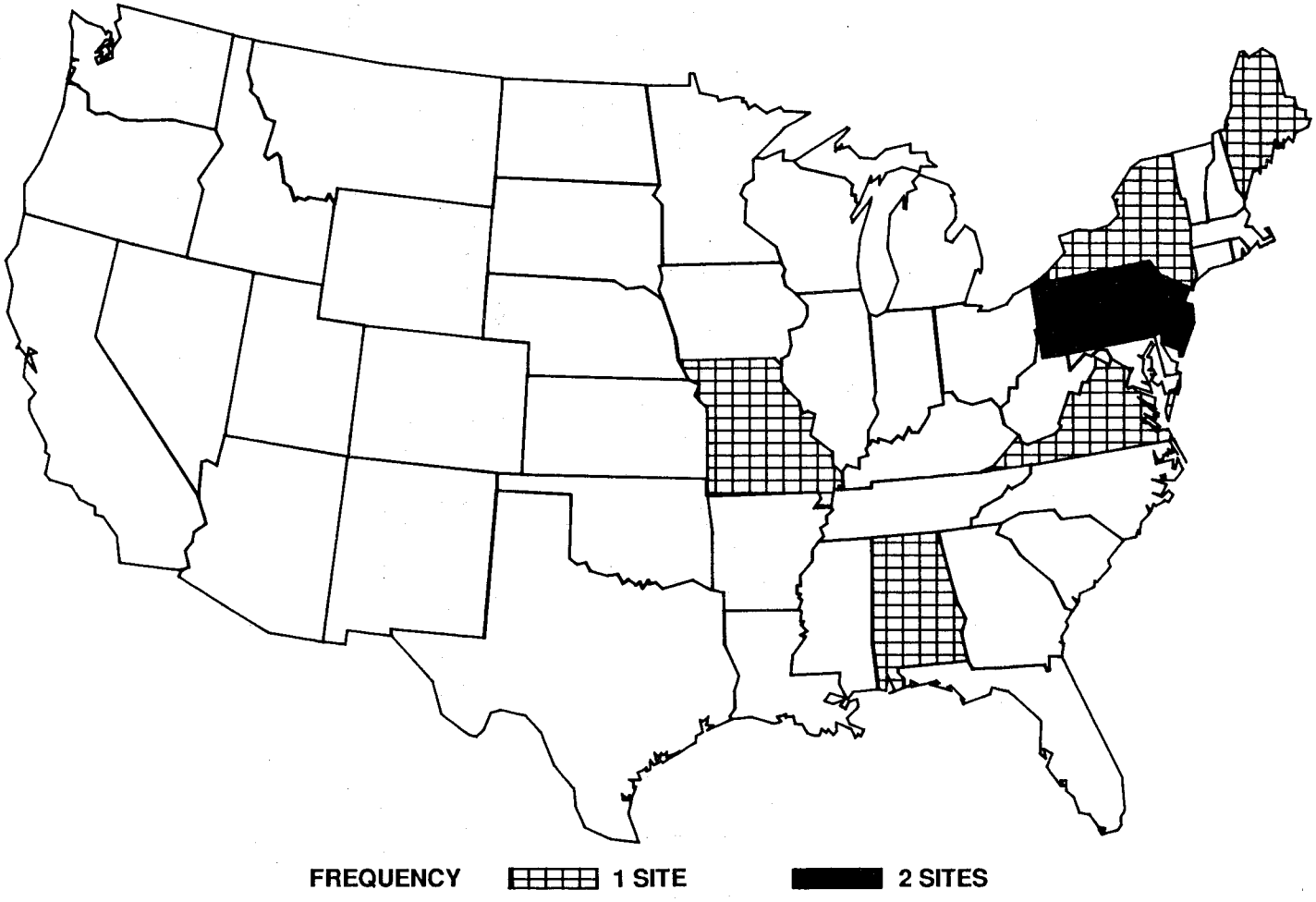


FIGURE 5-1. Frequency of Sites with Nitrobenzene Contamination

5. POTENTIAL FOR HUMAN EXPOSURE

The nitration of benzene in air leads to variable ambient levels in urban areas, making the assessment of releases to the air from waste sites difficult. Nevertheless, limited studies of municipal waste disposal facilities and the more complete evaluation of hazardous waste sites have found nitrobenzene infrequently present and, when present, concentrations have been generally low.

5.2.1 Air

Direct release of nitrobenzene to air during its manufacture is minimized by the passage of contaminated air through activated charcoal (EPA 1980a), and its subsequent use in closed systems as an intermediate similarly limits direct exposure during industrial processing. Nevertheless, as much as 8.3 million lbs/yr may be released from industrial processes (Dorigan and Hushon 1976). The fraction of these manufacturing losses to air is not known.

Use of nitrobenzene as a chemical intermediate or in consumer products such as metal and shoe polishes could contribute to losses via fugitive emissions, wastewater, spills, and end product usage. The extent to which these sources contribute to human exposure has not been evaluated quantitatively.

The third principal source of nitrobenzene is the atmospheric photo-chemical reaction of nitrogen oxides with benzene, which presumably is derived from automobile fuels and, to a lesser extent, solvent uses of benzene (Dorigan and Hushon 1976). As benzene releases decline, this source (not quantified) should diminish as well. The contribution of this source is difficult to estimate since most measurements of ambient atmospheric nitrobenzene have been made in urban areas near sites of nitrobenzene manufacture, use, and disposal (see Section 5.4.1). Seasonal variations and those associated with air pollution episodes suggest that this source, although limited, may form a significant proportion of nonoccupational human exposure.

5.2.2 Water

The effluent discharge produced during nitrobenzene manufacture is the principal source of nitrobenzene release to water. Losses to wastewater have been observed to be 0.09% of production in one plant and 2.0% in another (Dorigan and Hushon 1976).

The nitrobenzene in wastewater may be lost to the air, degraded by sewage organisms or, rarely, carried through to finished water. The EPA has surveyed nitrobenzene levels reported in effluents from 4,000 publicly-owned treatment works (POTWs) and industrial sites. The highest value in effluent was >lOO ppm in the organic and plastics

industry (Shackelford et al. 1983). Nitrobenzene was detected in one of 33 industrial effluents at a concentration greater than 100 µg/L (Perry et al. 1979). Reported nitrobenzene concentrations in raw and treated industrial wastewaters from several industries range from 1.4 to 91,000 µg/L (EPA 1983a). The highest concentrations are associated with wastewaters from the organic chemicals and plastics industries.

Nitrobenzene was reported at above detectable levels in 1.8% of the 1,245 reporting industrial stations (Staples et al. 1985) and in the finished effluent of only 3 of the POTWs and one oil refinery (Ellis et al. 1982). In analysis of runoff samples from 51 catchments in 19 cities, the National Urban Runoff Program found no nitrobenzene (Cole et al. 1984).

These results suggest that commercial and industrial users of nitrobenzene are dispersed throughout the country, so that concern regarding sources must extend beyond those four states in which nitrobenzene is manufactured.

Although nitrobenzene is sparingly soluble in water [1,900 ppm at 20°C (Verschueren 1983); 2,090 ppm at 25°C (Banerjee et al. 1980)], its pungent, characteristic odor ["bitter almonds," (Windholz 1983); "shoe polish," (Ruth 1986)] is detectable at water concentrations as low as 30 ppb (EPA 1980a). Hence, human exposures to large releases or accumulations in the environment appear unlikely to escape unnoticed. Nitrobenzene was detected in groundwater at 3 of 862 hazardous waste sites at a geometric mean concentration of 1,400 µg/L according to the Contract Laboratory Program (CLP) Statistical Database (CLPSD 1988). Nitrobenzene was not detected in any surface water samples from the 862 sites.

5.2.3 Soil

As a source of nitrobenzene exposure of humans, soil appears to rank a distant third in terms of its contribution. Nelson and Hites (1980) reported 8 ppm in the soil of a former dye manufacturing site along the Buffalo River, but failed to detect nitrobenzene in river sediments, as noted above. The presence of nitrobenzene in the soils of abandoned hazardous waste sites is inferred by its presence in the atmosphere above several sites (Harkov et al. 1985; LaRegina et al. 1986). Nitrobenzene was detected in soil/sediment samples at 4 of 862 hazardous waste sites at a geometric mean concentration of 1,000 µg/kg (CLPSD 1988). No further data on nitrobenzene levels released to soils were located.

5.3 ENVIRONMENTAL FATE

Nitrobenzene has been scored in the Pre-Biologic Screen (PBS) (Gillett 1983) which estimates the environmental fate of neutral, unionized organic chemicals and the implications for ecotoxic and, to a lesser extent, health effects. Based on a three-dimensional matrix [for which the components are P (Log K_{ow}), H_c (log of dimensionless Henry's law constant), and $t_{1/2}$ (log biodegradation half-life)], the PBS scores a candidate chemical in each of the four following categories: A) bioaccumulation and multi-species/multi-media effects; B) bioaccumulation and chronic action; C) chronic action in the water column, including plant uptake and soil leaching; and D) indirect atmospheric action, including inhalation and plant fumigation. For nitrobenzene, the values in the PBS are P = 1.83 (Banerjee et al. 1980) and H_c = -3.02 (Hine and Mookerjee 1975). These values correspond well with observations that nitrobenzene is not bioaccumulated, does not accumulate in soils and sediments, can be taken up by plants, has been reported in groundwater, and has not been associated with either direct or indirect effects in the atmosphere. Half-life values for nitrobenzene indicate that it can be readily biodegraded aerobically in 7 days ($t_{1/2}$ = 0.06) (Tabak et al. 1981); it is degraded anaerobically in 22 days ($t_{1/2}$ = 1.34) (Hallas and Alexander 1983); and at high concentrations in water is resistant to biodegradation ($t_{1/2}$ = > 2) (Korte and Klein 1982).

5.3.1 Transport and Partitioning

The movement of nitrobenzene in soil, water and air is predicted by its physical properties: (1) water solubility (1,900 ppm) (Verschueren 1983); (2) moderate volatility (0.15 mmHg at 20°C) (Mabey et al. 1982); (3) low octanol-water partition coefficient (log K_{ow} = 1.84) (Geyer et al. 1984); and (4) soil/sediment sorption coefficient (K_{sed} = 36) (Mabey et al. 1982), (K_{om} = 50.1) (Briggs 1981). The dimensionless Henry's law constant for nitrobenzene (9.6×10^{-4}) suggests that transfer from water to air will be significant, but not rapid (EPA 1985a; Lyman et al. 1982). Sediment sorption and bioconcentration into aquatic and terrestrial animals are not likely to be significant (EPA 1985a). Plant uptake might be expected in terrestrial systems (McFarlane et al. 1987a, 1987b). Leaching through soil may occur.

Vapor densities reported for nitrobenzene relative to air range from 4.1 to 4.25 (Anderson 1983; Beard and Noe 1981; Dorigan and Hushon 1976; Dunlap 1981). Removal processes of nitrobenzene in air may involve settling of vapor due to its higher density relative to air (Dorigan and Hushon 1976). Washout by rainfall (either through solution in rain drops or by removal of nitrobenzene sorbed onto particulates)

and dry fall of particulates are negligible, as estimated by Cupitt (1980) and expressly measured in field releases (Dana et al. 1984). Atmospheric residence time was estimated to be 190 days (Cupitt 1980).

Briggs (1981) compared the soil sorption coefficient (Kd) expressed in terms of organic matter (K_{om}), where $K_{om} = 100xK_d/(\%$ organic matter), for a wide variety of chemicals and soils to the octanol-water partition coefficient K_{ow}. Briggs (1973) classified soil mobility using log K_{ow} and log organic matter (om) content and compared this classification to that of Helling and Turner (1968), based on soil thin layer chromatography. Nitrobenzene would be in mobility class III (intermediate).

Jury et al. (1984) also classified nitrobenzene as intermediately mobile, but noted that its loss from soil would be enhanced by evaporation of water. Moreover, because nitrobenzene has relatively poor diffusive flux, the material would tend to move as a bolus within soil. Jury et al. (1984) hypothesized that a deposit 10 cm deep in soil would have a half-life of about 19 days.

Other results also indicate that nitrobenzene is intermediately mobile in forest and agricultural soils (Seip et al. 1986). However, nitrobenzene was somewhat more mobile in soil with lower organic carbon content. The authors attribute this to hydrogen bonding interactions of nitrobenzene with organic matter in the soil.

Piwoni et al. (1986) found that nitrobenzene did not volatilize in their microcosms simulating land-application of wastewater, but was totally degraded. Enfield et al. (1986) employed a calculated Henry's law constant of 1.30×10^{-3} kPa m^3 mol^{-1}, and arrived at a biodegradation rate coefficient greater than 8 day^{-1}. They predicted that 0.2% of the added nitrobenzene could be accounted for in volatiles. The EXAMS computer model (Burns et al. 1981) predicts volatilization half-lives of 12 days (river) to 68 days (eutrophic lake) and up to 2% sediment sorption for nitrobenzene.

In a laboratory-scale waste treatment study, Davis et al. (1981) estimated that 25% of the nitrobenzene was degraded and 75% was lost through volatility in a system yielding a loss of about 80% of initial nitrobenzene in 6 days. In a stabilization pond study, the half-life by volatilization was about 20 hours, with approximately 3% adsorbed to sediments (Davis et al. 1983).

The measured bioconcentration factors (BCF) for nitrobenzene in several organisms indicate minimal bioconcentration in aquatic organisms. Veith et al. (1979) found the 28-day flow-through test for fathead minnows yielded a BCF of 15. A less satisfactory 3-day static measurement gave a BCF of less than 10 for the golden ore (Freitag

et al. 1982). In the Metcalf model "farm pond" microcosm (Lu and Metcalf 1975), the Ecological Magnification Index (EM: ratio of concentration of parent material in organism to concentration of parent material in water) was about 8 in mosquitofish (Gambusia affinis) after a 24-hr exposure. Longer exposures of other species, however, did not increase the value; the EM in snails (Physa sp.) was 0.7, in mosquito (Culex quinquifasciatus) larvae was 0.8, in Daphnia magna was 0.15, and in alga (Oedogonium) was 0.03. Bioaccumulation from water is not considered significant at values of less than 300 (Trabalka and Garten 1981).

Nitrobenzene may bioconcentrate in terrestrial plants. The relatively rapid uptake of ^{14}C-labeled nitrobenzene into mature soybean (Glycine max L Merr) plants was reported by McFarlane et al. (1987a, 1987b) and Nolt (1988). Plant uptake is, therefore, a possible route of human exposure to nitrobenzene.

5.3.2 Transformation and Degradation

5.3.2.1 Air

p-Nitrophenol and nitrosobenzene were reported to be the principal photodegradation products of nitrobenzene vapors exposed to UV light in air (Hastings and Matsen 1948). In another study, both o- and p-nitrophenols were found when 0_2 was present and phenol was also found when 0_2 was absent (Nojima and Kanno 1977). Photolysis by reaction with hydroxyl radicals or ozone was found to be insignificant in the troposphere (Atkinson et al. 1987). Based on laboratory studies, they projected half-lives of nitrobenzene of 180 days by reaction with hydroxyl radicals and more than 6 years by reaction with ozone in "clean" air. In typical, moderately "dirty" air, these values would decrease to 90 days and more than 2 years, respectively.

As noted earlier, nitrobenzene is formed by reaction of benzene with NO_2 and Atkinson et al. (1987) reported that aniline is slowly oxidized to nitrobenzene by ozone. Further nitration of nitrobenzene appears to be negligible. These reactions are summarized in Figure 5-2.

Atmospheric photochemical decomposition is, therefore, thought to be an important removal route of nitrobenzene itself (EPA 1985a).

5.3.2.2 Water

There is no known mechanism of hydrolysis of nitrobenzene; however, photolysis and biodegradation are significant nitrobenzene degradation pathways in water (Callahan et al. 1979; Mabey et al. 1982).

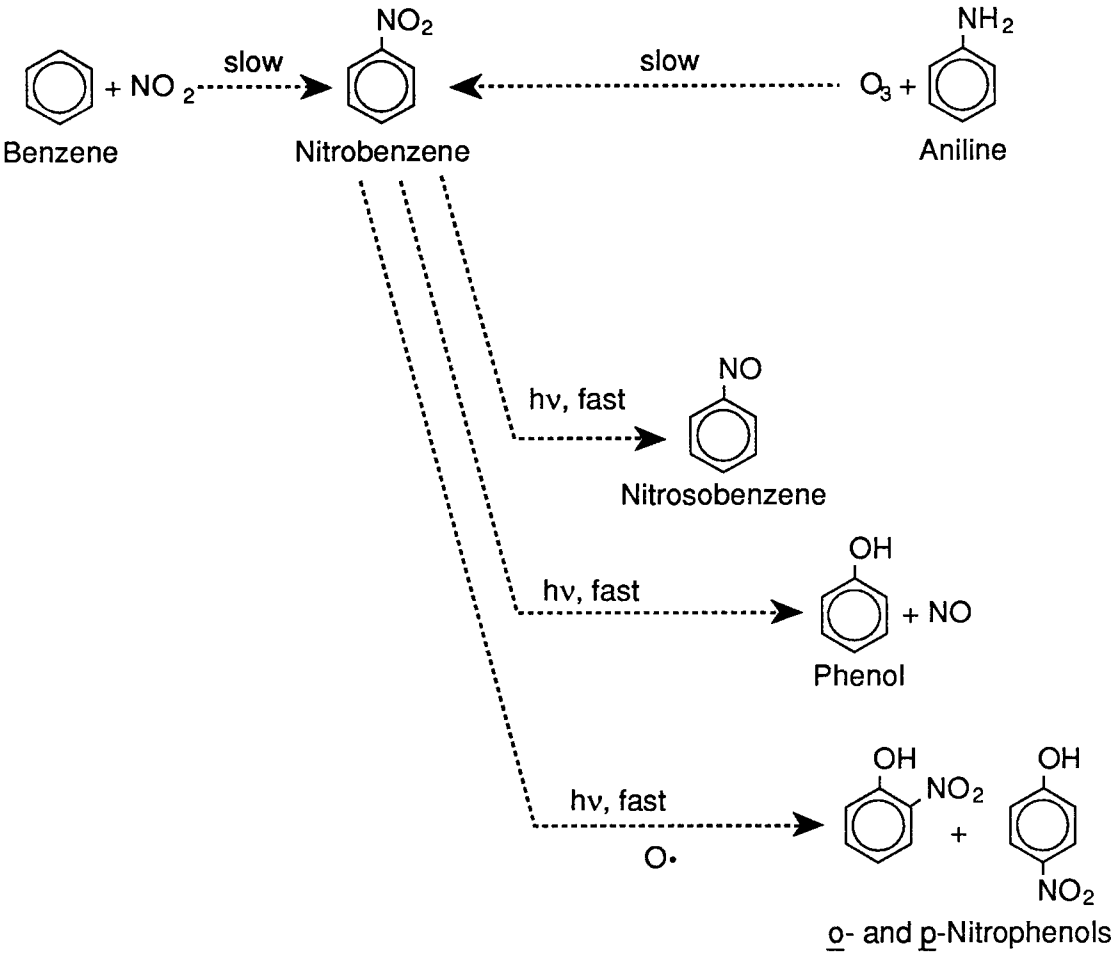


FIGURE 5-2. Atmospheric Reactions Generating and Removing Nitrobenzene

Photolysis. Photochemical oxidation of nitrobenzene by hydrogen peroxide yields p-, o-, and m-nitrophenols (Draper and Crosby 1984) with an estimated half-life of 250 days (Dorfman and Adams 1973). Direct photolysis, measured by Zepp and Scholtzhauer (1983), has a half-life of 2.5 to more than 6 days near the surface of bodies of water in the vicinity of 40°N latitude.

Under laboratory conditions, direct photolysis of nitrobenzene in solvents such as isopropanol yields phenylhydroxylamine, which can be oxidized to nitrosobenzene by oxygen (Hurley and Testa 1966, 1967). Phenylhydroxylamine and nitrosobenzene can then combine to form azoxybenzene. However, these reactions may not be important under natural conditions in the absence of hydrogen donors (Mabey et al. 1982). Callahan et al. (1979) proposed that sorption of nitrobenzene to humics could enhance photolytic destruction of nitrobenzene. Simmons and Zepp (1986), however, found that photolysis of nitrobenzene was not appreciably enhanced by either a natural humic-containing water or a commercial humic sample. Zepp et al. (1987a) reported that hydrated electrons from dissolved organic matter could significantly increase photoreduction of compounds such as nitrobenzene, and that photolysis of nitrate ions to hydroxyl radicals increased nitrobenzene photodegradation (Zepp et al. 1987b). Algae do not enhance photolysis of nitrobenzene (Zepp and Scholtzhauer 1983). Photolysis may be an important pathway in natural waters (EPA 1985a), but probably only under conditions where biodegradation is poor or absent and where both UV irradiance and appropriate facilitating molecules occur in relatively clear waters.

Biodegradation. Nitrobenzene may be almost completely removed by activated sludge treatment (EPA 1983a). Pitter (1976) obtained 98% removal of chemical oxygen demand (COD) at a rate of 14 mg COD/hr/g dry weight of activated sludge with nitrobenzene as the sole carbon source. Tabak et al. (1981) obtained 100% biodegradation in settled domestic wastewater in 7 days. Hallas and Alexander (1983) reported 100% degradation in 10 days after a 6-day lag under aerobic conditions with municipal sewage effluent. Similar results have been reported by a number of researchers (Davis et al. 1981, 1983; Kincannon et al. 1983; Patil and Shinde 1988; Stover and Kincannon 1983) using a variety of model sewage treatment reactors and wastewater sources, including adapted industrial sludges.

Nitrobenzene is also degradable by anaerobic processes, but more slowly than described above. Chou et al. (1978) reported that nitrobenzene was 81% removed in 110 days by acclimated domestic sludge in an anaerobic reactor, and Hallas and Alexander (1983) found that 50% was degraded in 12 days under similar conditions. Canton et al. (1985)

measured an 8% decrease in nitrobenzene after 8 days in unadapted media, but reported a half-life of less than 2 weeks in adapted media.

Nitrobenzene was either highly resistant to degradation or inhibited biodegradation of other components of the waste in several biodegradation studies (Barth and Bunch 1979; Davis et al. 1981; Korte and Klein 1982; Lutin et al. 1965; Marion and Malaney 1963). However, these effects were observed at concentrations (≥50 mg/L) of nitrobenzene much higher than those detected in ambient waters (see Section 5.4.2).

5.3.2.3 Soil

There is a paucity of studies of nitrobenzene in soil. Decomposition of nitrobenzene in a 1% suspension of Niagara silt loam took more than 64 days, while aniline and phenol, commonly metabolites of nitrobenzene, were completely degraded in 4 and 1 days, respectively (Alexander and Lustigman 1966). In contrast, a study of the efficacy of soil infiltration along the Rhine River in the Netherlands showed that nitrobenzene was removed completely in moving 50 cm through a peat-sand artificial dune (Piet et al. 1981).

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Monitoring of nitrobenzene in the environment reveals variably low levels in air, very infrequent occurrence in surface waters, and infrequent occurrence but higher levels in industrial wastewaters, Nitrobenzene may be present in soils at hazardous waste sites.

5.4.1 Air

Most of the information on nitrobenzene levels in air is derived from a series of reports from New Jersey, in which ambient air in urban, rural, and waste disposal areas were monitored extensively. In the initial study (Bozzelli et al. 1980), nitrobenzene was not detected above the level of 0.01 ppb in about 260 samples collected in 1979. In 1978, nitrobenzene levels averaged 0.40 ppb in industrial areas, and 0.02 and 0.09 ppb in two residential areas, but that in 1982, levels in residential areas were approximately 0.3 ppb or less, while levels in industrial areas were 0.9 ppb or more (Bozzelli and Kebbekus 1982). Again, most of the samples were negative for nitrobenzene. The highest values were 3.5 to 5.7 ppb.

Harkov et al. (1983) reported low levels of nitrobenzene (0.07 to 0.1 ppb) in approximately 85% of air samples of nitrobenzene in their study of airborn toxic chemicals in summer. Nitrobenzene was not detected during the winter (Harkov et al. 1984; Lioy et al. 1983).

Studies of air over waste disposal sites (Harkov et al. 1985) are confounded by weather and timing. Air at one landfill showed a mean nitrobenzene concentration of 1.32 ppb and another of 0.3 ppb; but at two other sites (measured during snow and/or rain), nitrobenzene was not detected. LaRegina et al. (1986) summarized these studies by noting that the highest value for nitrobenzene was 14.48 ppb at a hazardous waste site, whereas nitrobenzene was often undetectable elsewhere (especially in rural areas or at sanitary landfills) or anywhere in the air during the winter.

Very little information is available for other areas of the United States. Pellizzari (1978b) found only one positive value of 107 ng/m^3 (20 ppb) at a plant site in Louisiana. Early data (summarized in EPA 1985a) show less than 25% of United States air samples positive with a median concentration of about 0.01 ppb.

5.4.2 Water

A nitrobenzene concentration of about 20 ppb in the final effluent of a Los Angeles County municipal wastewater treatment plant in 1978 and less than 10 ppb in 1980 was reported (Young et al. 1983). Nitrobenzene was not reported in runoff samples in 1982 in a nation-wide project (Cole et al. 1984). Kopfler et al. (1977) list nitrobenzene as one of the chemicals found in finished tap water in the United States, but do not report its concentrations or locations. Levins et al. (1979) reported only one positive sample (total sample number not stated) in Hartford, Connecticut, sewage treatment plant influents, and no nitrobenzene was detected in samples taken from three other major metropolitan areas. Nitrobenzene was detected in only 0.4% of the 836 ambient surface water stations involved in EPA's STORET database (Staples et al. 1985). No data were located on occurrence of nitrobenzene in groundwater.

Nitrobenzene is detected more frequently and at higher concentrations in effluents from industrial sources. The STORET database shows that 1.8% of the 1,245 reporting stations on industrial wastewaters have had measurable values (Staples et al. 1985).

5.4.3 Soil

The only measurement of nitrobenzene in soil located was a value of 8 ppm detected is soil at one of two sampling sites along the bank of the industrially polluted Buffalo River in New York (Nelson and Hites 1980). Nitrobenzene was not detected at any of three sediment sampling sites in this study.

5.4.4 Other Media

Nitrobenzene has not been found in other environmental media. It has not been detected as a bioaccumulated material in fish samples (Staples et al. 1985). No monitoring of plant tissues has been reported, even though uptake of nitrobenzene by plants has been observed (McFarlane et al. 1987a, 1987b). Data on nitrobenzene occurrence in foods were not located in the available literature.

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Apparently general exposure of the population to nitrobenzene is limited to variable concentrations in air and possibly drinking water. Air levels can be high in the vicinity of manufacturing or production facilities (especially petroleum refining, leather finishing and some chemical manufacturers). Urban areas have much higher levels in the summer than winter due to both the formation of nitrobenzene by nitration of benzene (from motor vehicle fuels) and the higher volatility of nitrobenzene during the warmer months. Ambient exposure in the winter may be negligible.

Occupational exposure can be significantly higher than the exposure of the general population. NIOSH (1988) identified about 10,600 workers (mainly chemists, equipment servicers, and janitorial staff) as potentially exposed workers in facilities where nitrobenzene is used. Because nitrobenzene is readily absorbed through the skin, as well as taken up by inhalation and ingestion, industrial exposure necessitates worker protection, and this has been recognized for decades. At an industrial exposure level of 5 mg/m^3 (1 ppm), a worker would receive about 25 mg during an 8-hour day (Dunlap 1981).

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Based on the New Jersey air studies and on estimates of releases during manufacture, only populations in the vicinity of manufacturing activities (i.e., producers and industrial consumers of nitrobenzene for subsequent synthesis) and petroleum refining plants are likely to have any significant exposure to anthropogenic nitrobenzene. However, consideration of possible groundwater and soil contamination and uptake of nitrobenzene by plants expands the potentially high exposure group to include people living in and around abandoned hazardous waste sites.

The numbers of people actually exposed to ambient concentrations of nitrobenzene are unknown. Based on the locations of production and other manufacturing facilities, tens of millions of people might be exposed to low levels of this compound.

5.7 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, 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 nitrobenzene 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 nitrobenzene.

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 Identification of Data Needs

Physical and Chemical Properties. No specific data needs,are identified for these properties, for which available values are generally accepted.

Production, Use, Release and Disposal. Available data indicate that most nitrobenzene produced in the United States is consumed in the production of aniline, but current quantitative data on the amount of nitrobenzene released to the environment during nitrobenzene production and use are sparse. Collection of this information would be helpful in evaluating the effect of current industrial practices on environmental levels of nitrobenzene.

According to the Emergency Planning and Community Right to Know Act of 1986 (EPCRTKA), (§313), (Pub. L. 99-499, Title III, §313), industries are required to submit release information to the EPA. The Toxic Release Inventory (TRI), which contains release information for 1987, became available in May of 1989. This database will be updated yearly and should provide a more reliable estimate of industrial production and emission.

Environmental Fate. The environmental fate of nitrobenzene is fairly well understood within the context of recognition of the importance of conditions in estimating or modelling environmental concentrations. The most critical condition is the presence/absence of a viable, competent and functioning population of microorganisms for biodegradation. The next most critical factor is the amount of sunlight. For exposure assessment modelling accuracy, more data are

needed on fate in soil, both in the root zone where plants are exposed and in the saturated and unsaturated zones where groundwater may become contaminated. Metabolism in plants is poorly characterized to date, so that information on the nature and quantity of plant metabolites would assist assessment of exposure via that route.

Bioavailability from Environmental Media. The available information indicates that nitrobenzene is well absorbed following inhalation, oral or dermal exposure. It is expected to be well absorbed by persons breathing or having dermal contact with contaminated air or ingesting water, soil, plants or any environmental materials that contain it. It would be useful to have information on its absorption after dermal contact with contaminated soil or plant material.

Food Chain Bioaccumulation. Uptake and accumulation of nitrobenzene through food chains are well understood regarding animal tissues, especially fish. However, more information about plant tissues would be helpful.

Exposure Levels in Environmental Media. Because nitrobenzene is a priority pollutant, extensive data are available on its occurrence in surface waters, sediments, and aquatic animals. It would be useful to have data on its presence in soils and groundwater and correlations of measured air concentrations to soil levels and of plant levels to soil concentrations.

Exposure Levels in Humans. There is very little information on human exposure to nitrobenzene outside of the workplace. More detailed exposure analyses that take transformation pathways into account need to be performed for local sites and the potentially impacted populations. Further, it would be useful to know more about the relationship of the organoleptic properties of nitrobenzene with respect to tolerable exposures. For example, it would be useful to know whether its taste and aroma are deterents to high levels of human exposure.

Exposure Registries. No exposure registries for nitrobenzene 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

No long-term research projects or other on-going studies of occupational or general population exposures to nitrobenzene were identified.

As part of the Third National Health and Nutrition Evaluation Survey (NHANES III), the Environmental Health Laboratory Sciences Division of the Centers for Disease Control, will be analyzing human urine samples for p-nitrophenol and other phenolic compounds. Since p-nitrophenol is a major metabolite of nitrobenzene, the presence of p-nitrophenol in the urine can be used to indicate exposure to nitrobenzene. These data will give an indication of the frequency of occurrence and background levels of these compounds in the general population.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting and/or measuring and monitoring nitrobenzene 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 nitrobenzene. 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 nitrobenzene 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 a trade association 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.

6.1 BIOLOGICAL MATERIALS

Nitrobenzene is volatile; it has a boiling point of 211°C and a vapor pressure (20°C) of 0.15 mmHg. Its water solubility (20°C) is 1,900 mg/L. It has a log octanol/water partition coefficient value of 1.85, implying a relatively weak affinity for lipids. These properties affect the manner in which biological samples are analyzed for nitrobenzene. Albrecht and Neumann (1985) discussed the difficulty of analysis of nitrobenzene and its metabolite aniline in animals. Excretion of the parent compounds or some metabolites in urine has been determined, but apparently this kind of biological monitoring has so far not produced satisfactory results due to practical and methodological reasons. Nitrobenzene metabolites are bound to blood proteins, both in hemoglobin and in plasma (Albrecht and Neumann 1985). Acute poisoning by nitrobenzene is usually monitored by measuring levels of methemoglobin, which is produced by the metabolic products of nitrobenzene. However, many toxicants produce methemoglobin, and this analysis is not specific enough to be a satisfactory method for monitoring nitrobenzene in animals.

Analytical methods for the determination of nitrobenzene in biological materials are given in Table 6-l.

6.2 ENVIRONMENTAL SAMPLES

Nitrobenzene is determined in environmental samples by collection, extraction with an organic solvent and gas chromatographic analysis (EPA 1982a, 1982b; NIOSH 1984). Flame ionization detection or mass spectrometry may be used for detection.

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

Sample Matrix	Sample Preparation	Analytical Method	Sample Detection Limit	Accuracy	Reference
Urine (spiked with nitrobenzene)	Reduce nitrobenzene, form coupled dye, extract in carbon tetrachloride	Colorimetric at 450 nm	0.8 mg/L	No data	Dangwal and Jethani 1980
Urine	Measure p-nitrophenol metabolite in urine	No data	No data	No data	Ikeda and Kita 1964
Urine	Measure p-nitrophenol metabolite in urine	No data	No data	No data	Lauwerys 1983
Blood	Measure methemoglobin formation in blood	No data	No data	No data	Albrecht and Neumann 1985
Blood	Measure methemoglobin formation in blood	No data	No data	No data	Lauwerys 1983
Blood	Measure methemoglobin formation in blood	Photometric	No data	No data	Dreisbach and Robertson 1987

mg = milligram; L = liter; nm = nanometer.

6. ANALYTICAL METHODS

Analytical methods for the determination of nitrobenzene in environmental samples are given in Table 6-2.

6.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, 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 nitrobenzene 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 nitrobenzene.

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 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. Sensitive and selective methods are available for the qualitative and quantitative measurement of nitrobenzene after it is separated from its sample matrix. Capillary gas chromatography, also known broadly as high-resolution gas chromatography (HRGC), has greatly facilitated the analysis of compounds such as nitrobenzene that can be measured by gas chromatography and has resulted in vast improvements in resolution and sensitivity. It has made the choice of a stationary phase much less crucial than was the case with packed columns. The instrumental capability to separate volatile analytes by HRGC is no longer the limiting factor in their analysis. Further development of methods for the transfer of isolated analytes, quantitatively and in a narrow band, to the HRGC, and the identification and accurate measurement of compounds in the HRGC peaks would be useful. Mass spectrometry (MS) has been outstanding for the detection of various organic compounds but other techniques, particularly Fourier transform infrared spectroscopy (FTIR) may be superior for nitrobenzene. Because nitrobenzene is metabolized in biological systems, it is difficult to accurately determine in most biological samples after enough time has elapsed for these metabolic processes to take place. Therefore, although nitrobenzene itself can be easily determined in biological samples, it is rarely found in its unchanged form in these samples. Metabolites of nitrobenzene in biological materials are difficult to determine in

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

Sample Matrix	Sample Preparation	Analytical Method	Sample Detection Limit	Accuracy	Reference
Air at landfill sites	Adsorption on Tenax-GC cartridges, thermal desorption	HRGC/FID	0.05 ppb	No data	Harkov et al. 1985
Air	Adsorption on silica gel, extraction with methanol	GC/FID	0.02 mg/sample	No data	NIOSH 1984
Air	Adsorption on silica gel, extraction with methanol	GC/FID	0.5 mg/m^3	No data	NIOSH 1977
Wastewater	Direct injection of aqueous sample	GC/FID	No data	No data	Patil and Shinde 1988
Wastewater	Extract with dichloromethane, exchange to hexane, concentrate	GC/FID	3.6 µg/L	71± 5.9%[a]	EPA 1982a
Water	Extract with dichloromethane at pH 11 and 2, concentrate	GC/MS	1.9 µg/L	71±31%[a]	EPA 1982b
Soil and solid waste	Extract from sample, cleanup	GC/FID	137 mg/kg[b]	25.7-100%[a]	EPA 1986b
Soil and solid waste	Extract from sample, cleanup	GC/MS	19 mg/kg[b]	No data	EPA 1986c
Soil and solid waste	Extract from sample, cleanup	GC/FID	660 µg/kg[c]	54-158%[a]	EPA 1986d
Soil and solid waste	Extract from sample, cleanup	HRGC/FTIR	12.5 µg/L[d]	No data	EPA 1986e

[a]Relative recovery, percent, ± standard deviation.
[b]Approximate detection limit in high-level soil and sludges.
[c]Approximate detection limit in low-level soil and sediments.
[d]Detection limit in water. Detection limit in solids and wastes is several orders of magnitude higher.

HRGC = high resolution gas chromatography; FID = flame ionization detector; ppb = parts per billion; GC = gas chromatography; mg = milligram; m^3 = cubic meter; µg/L = micrograms/liter; MS = mass spectrometry; kg = kilogram; FTIR = fourier transform infrared spectrometry.

routine practice because of the lack of standardized methods for measuring these compounds and because of the difficulty of correlating the presence or levels of these metabolites directly with exposure to nitrobenzene.

The development of supercritical fluid (SCF) extraction combined with chromatographic analysis will probably be useful for meeting the goals of quantitative, rapid, easily performed, low cost and safe procedures for the determination of poorly volatile organic analytes such as nitrobenzene and its metabolites in biological samples (Hawthorne 1988).

Methods for the determination of biomarkers of effect for nitrobenzene are largely confined to measurement of methemoglobin, which is also produced by numerous toxicants other than nitrobenzene. More specific methods for biomarkers of exposure would be helpful in toxicological studies of nitrobenzene.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Methods for determining the parent compound, nitrobenzene, in water, air, and waste samples with excellent selectivity and sensitivity are well developed and constantly improving. It is desirable to have the means to measure organic compounds such as nitrobenzene in situ in water and other environmental media without the need for sampling and extraction procedures to isolate the analyte prior to analysis.

6.3.2 On-going Studies

Research is ongoing to develop a Master Analytical Scheme for organic compounds, including nitrobenzene, in water (Michael et al. 1988). The overall goal 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 "semi-soluble" in water, as well as volatile compounds (bp < 150°C). Improvements continue to be made in chromatographic separation and detection, including the areas of supercritical fluid extraction and supercritical fluid chromatography (Smith 1988). An important aspect of supercritical fluid chromatographic analysis of compounds such as nitrobenzene is detection. Fourier transform infrared flow cell detectors are promising for this application (Wieboldt et al. 1988). Immunoassay methods of analysis are promising for the determination of various organic pollutants and toxicants, and nitrobenzene may be a candidate for immunoassay techniques.

6. ANALYTICAL METHODS

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 nitrobenzene and other compounds. These methods use high resolution gas chromatography and magnetic sector mass spectrometry.

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 nitrobenzene by various international, national and state agencies. These values are summarized in Table 7-l.

7. REGULATIONS AND ADVISORIES

TABLE 7-1. Regulations and Guidelines Applicable to Nitrobenzene

Agency	Description	Value[a]	Reference
	National		
Regulations:			
a. Air:			
OSHA	PEL TWA	1 ppm (5 mg/m^3)	OSHA 1989, (29 CFR 1910.1000) Table Z-1-A
b. Water:			
EPA OWRS	General permits under NPDES	NA	40 CFR 122, Appendix D, Table II
	General pretreatment regulations for existing and new sources of pollution	NA	40 CFR 403
c. Nonspecific media:			
EPA OERR	Reportable quantity	1000 lb	EPA 1985b, (40 CFR 302.4)
	Extremely hazardous substance threshold planning quantity	10,000 lb	EPA 1987a, (40 CFR 355)
EPA OSW	Hazardous waste constituent (Appendix VIII)	NA	EPA 1980b, (40 CFR 261)
	Land disposal restrictions	NA	EPA 1988a, 1989 (40 CFR 268)
	Groundwater monitoring list (Appendix IX)	NA	EPA 1987b, (40 CFR 264)
EPA OTS	Preliminary assessment information rule	NA	EPA 1982c, (40 CFR 712.30)
	Health and safety data reporting rule	NA	EPA 1988b, (40 CFR 716.120)
	Toxic chemical release reporting	NA	EPA 1988c, (40 CFR 372)
Guidelines:			
a. Air:			
ACGIH	TLV TWA	1 ppm	ACGIH 1986 (5 mg/m^3)
NIOSH	IDLH	200 ppm	NIOSH 1985
b. Water:			
EPA OWRS	Ambient water quality criteria		
	Ingesting water and organisms	19.8 mg/L	EPA 1980b
	Oral RfD	0.0005 mg/kg/day	IRIS 1989
Other:			
EPA	Carcinogenic classification	Group D[b]	EPA 1988c

7. REGULATIONS AND ADVISORIES

TABLE 7-1 (Continued)

Agency	Description	Value	Reference
		State	
Regulations:			
a. Air:	Acceptable ambient air concentration		NATICH 1988
Connecticut		100 $\mu g/m^3$ (8 hr)	
Massachusetts		6.80 $\mu g/m^3$ (24 hr)	
Nevada		0.1190 mg/m^3 (8 hr)	
New York		16.70 $\mu g/m^3$ (1 yr)	
North Carolina		25.0 $\mu g/m^3$ (24 hr)	
North Dakota		0.05 mg/m^3 (8 hr)	
South Carolina		25.0 $\mu g/m^3$ (24 hr)	
Virginia		80.0 $\mu g/m^3$ (24 hr)	
b. Water:	Drinking water		FSTRAC 1988
Kansas		5 $\mu g/L$	
Maine		1.4 $\mu g/L$	

[a] Numerical values are provided in this column, when available. However, many regulations list chemicals and/or involve requirements too complex for inclusion here. In these cases, NA (Not Applicable) is inserted in this column. The cited references provide details of the regulations.
[b] Group D: Not classifiable as to human carcinogenicity.

OSHA = Occupational Safety and Health Administration; PEL = Permissible Exposure Limit; TWA = Time-Weighted Average; EPA = Environmental Protection Agency; OWRS = Office of Water Regulations and Standards; NPDES = National Pollutant Discharge Elimination System; NA = Not Applicable; OERR = Office of Emergency and Remedial Response; OSW = Office of Solid Wastes; OTS = Office of Toxic Substances; ACGIH = American Conference of Governmental Industrial Hygienists; TLV = Threshold Limit Value; NIOSH = National Institute for Occupational Safety and Health; IDLH = Immediately Dangerous to Life or Health Level.

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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 time period.

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

Carcinogen -- A chemical capable of inducing cancer.

Ceiling value (CL) -- 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.

9. GLOSSARY

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_{LO}) -- 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_{LO}) -- 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 which produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

9. GLOSSARY

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

Minimal Risk Level (MRL) -- 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.

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 a chemical.

No-Observed-Adverse-Effect Level (NOAEL) -- That dose of chemical at which there are 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 doseresponse 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 μg/m3 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.

9. GLOSSARY

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.

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 humans, (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

PEER REVIEW

A peer review panel was assembled for nitrobenzene. The panel consisted of the following members: Dr. Lloyd Hastings, Research Associate Professor, Department of Environmental Health, University of Cincinnati; Dr. Judith Marquis, Associate Professor, Department of Pharmacology, Boston University School of Medicine; Dr. James Popp, Head, Department of Environmental Pathology, Chemical Industry Institute of Toxicology; Dr. Rajender Abraham, Private Consultant, Brookview, NY; and Dr. Martin Alexander, Professor, Department of Agronomy, Cornell University. These experts collectively have knowledge of nitrobenzene'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 Environmental Response, Compensation, and Liability Act, as amended.

Scientists from 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 their approval of the profile's final content. The responsibility of the content of this profile lies with the Agency for Toxic Substances and Disease Registry.