

TOXICOLOGICAL PROFILE FOR
CHLOROBENZENE

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

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The use of company or product name(s) is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry.

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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1. PUBLIC HEALTH STATEMENT

This Statement was prepared to give you information about chlorobenzene 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). Chlorobenzene has been found at 97 of these sites. However, we do not know how many of the 1,177 NPL sites have been evaluated for chlorobenzene. As EPA evaluates more sites, the number of sites at which chlorobenzene is found may change. The information is important for you because chlorobenzene may cause harmful health effects and because these sites are potential or actual sources of human exposure to chlorobenzene.

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 chlorobenzene, 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 CHLOROBENZENE?

Chlorobenzene is a colorless liquid with an almond-like odor. The compound does not occur widely in nature, but is manufactured for use as a solvent (a substance used to dissolve other substances) and is used in the production of other chemicals. Chlorobenzene persists in soil (several months), in air (3.5 days), and water (less than 1 day). Additional information can be found in Chapters 3, 4, and 5.

1.2 HOW MIGHT I BE EXPOSED TO CHLOROBENZENE?

There is potential for humans to be exposed to chlorobenzene by breathing contaminated air, by drinking water or eating food

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contaminated with chlorobenzene, or by getting chlorobenzene-contaminated soil on the skin. These exposures are most likely to occur in the workplace or in the vicinity of chemical waste sites.

Occupational exposure occurs primarily through breathing the chemical. Personnel engaged in the production and handling of chlorobenzene would be at greatest risk. Levels of chlorobenzene in the air at several industrial sites during normal operations were found to be below allowable federal standards.

Exposure in humans could occur in persons living or working in the vicinity of hazardous waste sites if emissions to water, air, and soil are not adequately controlled. Chlorobenzene has been found at 97 out of 1,177 NPL hazardous waste sites in the United States. Thus, federal and state surveys suggest that chlorobenzene is not a widespread environmental contaminant. The chemical has not been detected in surface water, although a few ground water systems have been found with chlorobenzene levels in the parts per billion (ppb) range. Background levels of less than 1 ppb were detected in air samples from urban and suburban areas. No information of the occurrence of chlorobenzene in food has been found. Additional information on the potential for human exposure is presented in Chapter 5.

1.3 HOW CAN CHLOROBENZENE ENTER AND LEAVE MY BODY?

Chlorobenzene enters your body when you breathe in air containing it, when you drink water or eat food containing it, or when it comes in contact with your skin. Human exposure to contaminated water could occur near hazardous waste sites where chlorobenzene is present. Significant exposure to chlorobenzene is not expected to occur by getting chlorobenzene contaminated soil on your skin. When chlorobenzene enters your body, most of it is expelled from your lungs in the air we breathe out and in urine. Additional information is presented in Chapter 2.

1.4 HOW CAN CHLOROBENZENE AFFECT MY HEALTH?

Workers exposed to high levels of chlorobenzene complained of headaches, numbness, sleepiness, nausea, and vomiting. However, it is not known if chlorobenzene alone was responsible for these health effects since the workers may have also been exposed to other chemicals at the same time. Mild to severe depression of functions of parts of the nervous system is a common response to exposure to a wide variety of industrial solvents (a substance that dissolves other substances).

In animals, exposure to high concentrations of chlorobenzene affects the brain, liver, and kidneys. Unconsciousness, tremors and restlessness have been observed. The chemical can cause severe injury

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to the liver and kidneys. Data indicate that chlorobenzene does not affect reproduction or cause birth defects. Studies in animals have shown that chlorobenzene can produce liver nodules, providing some but not clear evidence of cancer risk. Additional information on health effects is presented in Chapter 2.

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

Harm to human health from breathing, eating or drinking chlorobenzene is not established (Tables 1-1 and 1-3). Tables 1-2 and 1-4 show the relationship between exposure to chlorobenzene and known health effects in animals. A Minimal Risk Level (MRL) is included in Table 1-3. The MRL was derived from animal data for long-term exposure, as described in Chapter 2 and in Table 2-2. The MRL provides a basis for comparison with levels that people might encounter either in the air or in food or drinking water. If a person is exposed to chlorobenzene at an amount below the MRL, it is not expected that harmful (noncancer) health effects will occur. Because this level is based only on information currently available, some uncertainty is always associated with it. Also, because the method for deriving MRLs does not use any information about cancer, a MRL does not imply anything about the presence, absence, or level of risk for cancer. Further information on the levels of chlorobenzene that have been observed to cause health effects in animals is presented in Chapter 2.

1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO CHLOROBENZENE?

Exposure to chlorobenzene can be determined by measuring the chemical or its metabolite in urine, exhaled air, blood, and body fat. Tests are not routinely available at the doctor's office. Specific tests are available that can determine if exposure is currently occurring or has occurred very recently, but not whether exposure occurred in the past. Further, levels in the various media stated above do not predict adverse health effects. Additional information on how chlorobenzene can be measured in exposed humans is given in Chapters 2 and 6.

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TABLE 1-1. Human Health Effects from Breathing Chlorobenzene*

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

*See Section 1.2 for a discussion of exposures encountered in daily life.

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TABLE 1-2. Animal Health Effects from Breathing Chlorobenzene

Short-term Exposure (less than or equal to 14 days)		
<u>Levels in Air (ppm)</u>	<u>Length of Exposure</u>	<u>Description of Effects*</u>
537	2 hours	Death in rabbits.
Long-term Exposure (greater than 14 days)		
<u>Levels in Air (ppm)</u>	<u>Length of Exposure</u>	<u>Description of Effects*</u>
75	24 weeks	Liver and kidney damage in rats and rabbits.

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

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

Short-term Exposure (less than or equal to 14 days)		
<u>Levels in Food</u>	<u>Length of Exposure</u>	<u>Description of Effects</u>
		The health effects resulting from short-term exposure of humans to food containing specific levels of chlorobenzene are not known.
<u>Levels in Water</u>		The health effects resulting from short-term exposure of humans to water containing specific levels of chlorobenzene are not known.
Long-term Exposure (greater than 14 days)		
<u>Levels in Food (ppm)</u>	<u>Length of Exposure</u>	<u>Description of Effects</u>
15	91 days	Minimal Risk Level (based on animal studies; see Section 1.5 for discussion).
<u>Levels in Water</u>		The health effects resulting from long-term exposure of animals to water containing specific levels of chlorobenzene are not known.

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

Short-term Exposure (less than or equal to 14 days)		
<u>Levels in Food (ppm)</u>	<u>Length of Exposure</u>	<u>Description of Effects*</u>
7,692 - 20,000	1-14 days	Death in mice and rats.
<u>Levels in Water</u>		The health effects of short-term exposure of animals to water containing specific levels of chlorobenzene are not known.
Long-term Exposure (greater than 14 days)		
<u>Levels in Food (ppm)</u>	<u>Length of Exposure</u>	<u>Description of Effects*</u>
1,923 - 5,000	91 days	Liver and kidney damage in mice. Liver injury rats.
1,923	13 weeks	Injury to organs of the immune system in mice.
1,923	13 weeks	Death in mice.
<u>Levels in Water</u>		The health effects resulting from long-term exposure of animals to water containing specific levels of chlorobenzene 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.

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

The Federal Government has developed regulatory standards and advisories to protect individuals from potential health effects of chlorobenzene in the environment. The Environmental Protection Agency has proposed that the maximum level of chlorobenzene in drinking water be 0.1 parts per million (ppm). For short-term exposures to drinking water, EPA has recommended that drinking water levels not exceed 2 ppm for up to ten days. The Occupational Safety and Health Administration (OSHA) has established a legally enforceable minimum limit of 75 ppm of chlorobenzene in workplace air for an 8 hour/day, 40-hour work week. Additional information regarding federal and state regulations is presented in Chapter 7.

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 Substance 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 chlorobenzene. Its purpose is to present levels of significant exposure for chlorobenzene 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 chlorobenzene 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 graphs 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

2. HEALTH EFFECTS

humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (minimal risk levels, MRLs) are of interest to health professionals and citizens alike.

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made, where data were believed reliable, for the most sensitive noncancer end point for each exposure duration. MRLs include adjustments to reflect human variability and, where appropriate, the uncertainty of extrapolating from laboratory animal data to humans. Although methods have been established to derive these levels (Barnes et al. 1987; EPA 1989a), uncertainties are associated with the techniques.

2.2.1 Inhalation Exposure

2.2.1.1 Death

No studies were located regarding lethality in humans following inhalation exposure to chlorobenzene.

The acute lethality of chlorobenzene is relatively low in animals. Exposure to concentrations of 20 mg/L (4,300 ppm) for 2 hours resulted in 100% mortality in mice (Rozenbaum et al. 1947). Rabbits died 2 weeks after chlorobenzene exposure to concentrations of about 537 ppm (Rozenbaum et al. 1947).

The highest NOAEL values and all reliable LOAEL values for death in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.2 Systemic Effects

No studies were located regarding effects on the respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular systems in humans following inhalation exposure to chlorobenzene.

As shown in Table 2-1 and Figure 2-1, animal studies indicate that chlorobenzene induces injury to the liver and kidneys following intermediate and chronic inhalation exposures.

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

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (ppm)	LOAEL (Effect)		Reference
					Less Serious (ppm)	Serious (ppm)	
ACUTE EXPOSURE							
Death							
1	Rabbit	2 hr				537 ^a	Rozenbaum 1947
2	Mouse	2 hr				4300	Rozenbaum 1947
Developmental							
3	Rat	10 d Gd6-15 6hr/d		590			John et al. 1984
4	Rabbit	13 d Gd6-18 6hr/d		590			John et al. 1984
INTERMEDIATE EXPOSURE							
Systemic							
5	Rat	120 d 5d/wk 7hr/d	Renal		75 ^a (micro. lesions)		Dilley 1977
6	Rat	120 d 5d/wk 7hr/d	Hepatic		75 ^a (decr. SGOT)		Dilley 1977
7	Rabbit	120 d 5d/wk 7hr/d	Hepatic		75 ^a (decr. LDH)		Dilley 1977

TABLE 2-1 (Continued)

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (ppm)	LOAEL (Effect)		Reference
					Less Serious (ppm)	Serious (ppm)	
CHRONIC EXPOSURE							
Systemic							
8	Rat	2 gen 7d/wk 6hr/d	Hepatic	50	150 (hypertrophy)		Nair et al. 1987
9	Rat	2 gen 7d/wk 6hr/d	Renal	50	150 (micro. changes)		Nair et al. 1987
Reproductive							
10	Rat	2 gen 7d/wk 6hr/d		450			Nair et al. 1987

^aPresented in Table 1-2.

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; ppm = parts per million; hr = hour; LC100 = lethal concentration, 100% animals exposed; d = day; Gd = gestation day; wk = week; decr = decrease; SGOT = serum glutamic oxaloacetic transaminase; micro = microscopic; LDH = lactate dehydrogenase; gen = generation

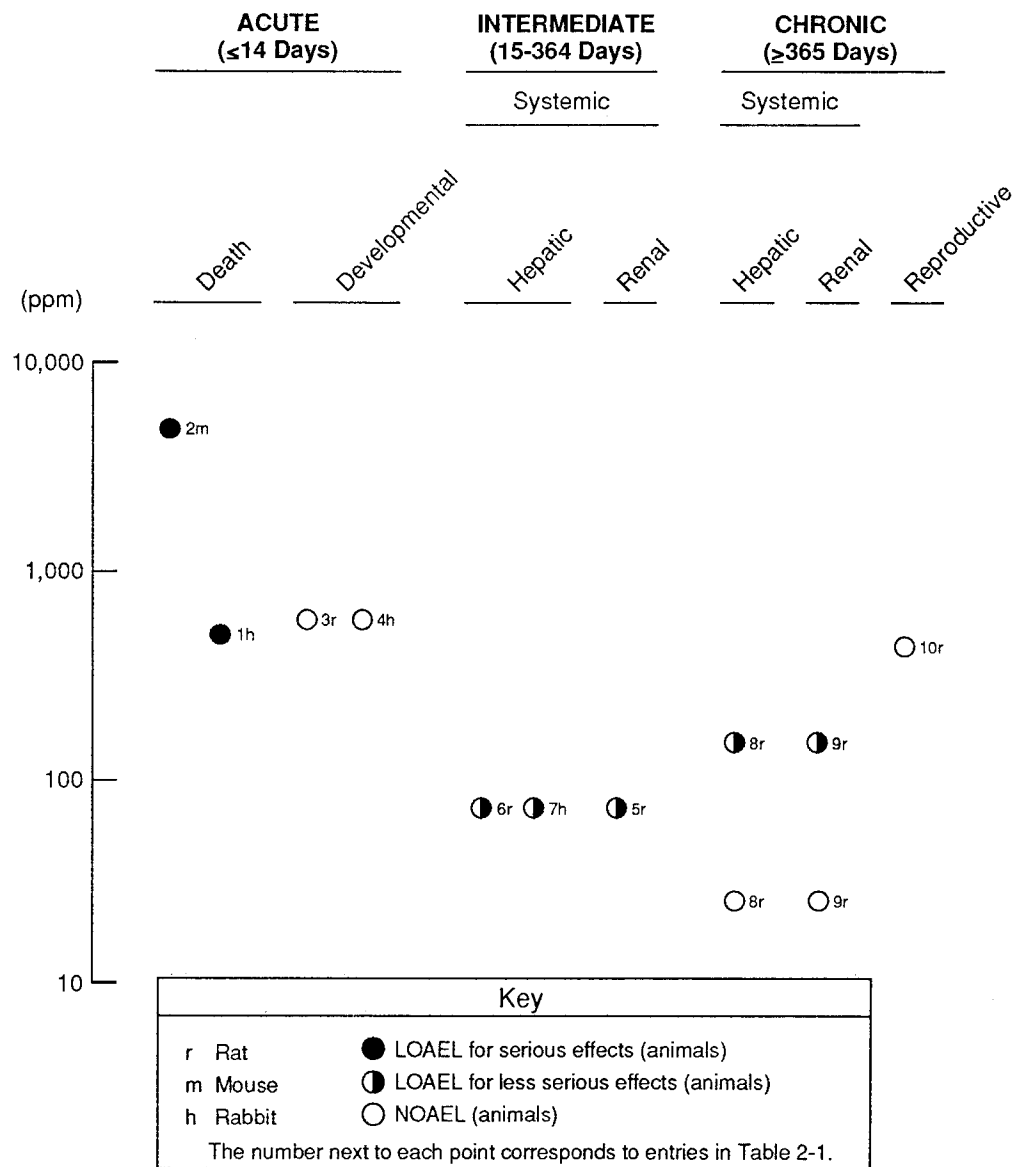


FIGURE 2-1. Levels of Significant Exposure to Chlorobenzene – Inhalation

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Hematological. Based on a small number of studies, chlorobenzene may cause hematological changes. There were dose and time-related effects on red blood cell parameters, primarily an increase in reticulocyte count which increased in rats but not in rabbits exposed to vapors of chlorobenzene at concentrations ≥ 75 ppm for 24 weeks (Dilley 1977). Other hematological parameters (red blood cell count, hemoglobins, hematocrit, and white blood cell count) were variable and were comparable to controls at the end of the test. Slight leukopenia and lymphocytosis occurred in mice exposed to chlorobenzene (0.1 mg/L) for 3 months (Zub 1978). In the absence of more detailed experimental data and information on compound purity, it is not certain if the effects in mice were compound-related. Further, these effects have not been confirmed at comparable doses in other species. Thus, it appears that hematological effects may not be sensitive indicators of chlorobenzene toxicity.

Hepatic Effects. No data were found that severe liver damage results from acute exposure to chlorobenzene vapor. Treatment-related congestion of the liver was observed in male rats and to a lesser degree in male rabbits exposed for 24 weeks to ≥ 75 ppm (Dilley 1977). Focal hemorrhages and foci of perivascular lymphocytes were observed. Decreased levels of serum enzymes (lactate dehydrogenase [LDH] and serum glutamic-oxaloacetic transaminase [SGOT]) were observed at the end of the treatment period; the significance of this response is not clear. Nair et al. (1987) reported liver hypertrophy and increased liver weights in male rats exposed to chlorobenzene vapors daily at 150 and 450 ppm for two generations. Overall, data suggest liver toxicity may be an area of concern for chlorobenzene exposure in humans.

The highest NOAEL values and all reliable LOAEL values for liver toxicity in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

Renal Effects. A small number of studies demonstrates that the kidney is also a target organ following chlorobenzene exposure and that the effects occur at levels comparable to those causing liver effects. Nair et al. (1987) reported tubular dilatation with eosinophilic material, interstitial nephritis and foci of regenerative epithelium in male rats exposed to vapors of chlorobenzene at 150 and 450 ppm for two generations. There was also treatment-related congestion of the kidneys in rabbits exposed to chlorobenzene at concentrations 275 ppm in animals sacrificed at 5 weeks of a 24 week treatment period (Dilley 1977). Interstitial foci of lymphocytes were evident. Overall, data suggest that this effect may also be an area of concern for chlorobenzene exposure in humans.

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The highest NOAEL values and all reliable LOAEL values for renal toxicity in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.3 Immunological Effects

No studies were located regarding the immunological effects in humans or animals following inhalation exposure to chlorobenzene.

2.2.1.4 Neurological Effects

Chlorobenzene affects the central nervous system. Humans occupationally exposed to chlorobenzene intermittently for up to 2 years at levels above current federal limits displayed signs of neurotoxicity including numbness, cyanosis (from depression of respiratory center), hyperesthesia, and muscle spasms (Rozenbaum et al. 1947). Specific exposure levels and histopathologic data have not been provided.

Neurological effects of chlorobenzene have also been reported in animals following inhalation. Acute inhalation exposure produced muscle spasms followed by narcosis in rabbits exposed to 5 mg/L chlorobenzene (1,090 ppm) or greater for 2 hours (Rozenbaum et al. 1947).

2.2.1.5 Developmental Effects

No studies were located regarding developmental effects in humans following inhalation exposure to chlorobenzene.

In rats and rabbits, inhalation of chlorobenzene vapors at concentrations up to 590 ppm during periods of major organogenesis did not produce structural malformations (John et al. 1984). This value has been presented in Table 2-1 and plotted in Figure 2-1. The highest dose resulted in maternal toxicity, as indicated by elevation of liver weights (both species) and decreased food consumption and body weight gain (rats only).

2.2.1.6 Reproductive Effects

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

In a two-generation study in rats, chlorobenzene in concentrations up to 450 ppm did not adversely affect reproductive performance or fertility (Nair et al. 1987). This value has been presented in Table 2-1 and plotted in Figure 2-1. A slight increase was observed in the incidence of degenerative testicular changes (unilateral and bilateral) in high-dose (450 ppm) males (F_0 and F_1 generations) and the F_1 mid-dose (150 ppm) males. The significance of this finding is

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unclear since the mean mating, pregnancy, and male fertility indices for both F_0 and F_1 generations were comparable for all groups and the incidences of testicular lesion were identical in F_0 and F_1 animals.

2.2.1.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals following inhalation exposure to chlorobenzene.

2.2.1.8 Cancer

No studies were located regarding carcinogenic effects in humans or animals following inhalation exposure to chlorobenzene.

2.2.2 Oral Exposure

2.2.2.1 Death

No studies were located regarding lethality in humans following oral exposure to chlorobenzene.

Animal studies show that chlorobenzene is lethal following acute, intermediate, and chronic oral exposures. Death occurred within 2 to 3 days after a single exposure to 4,000 mg/kg in corn oil by gavage in rats of both sexes, and in mice after a single exposure to 1,000 mg/kg (NTP 1985). Necropsy or histological examination was not performed. In a 14-day repeated-dose gavage study in rats, administration of $\geq 1,000$ mg/kg was lethal to all rats by the end of the study (NTP 1985). This dose has been converted to an equivalent concentration of 20,000 ppm in food for presentation in Table 1-4. Survival was reduced in rats of both sexes exposed to ≥ 500 mg/kg/day and ≥ 250 mg/kg/day in mice following intermediate-duration exposure (NTP 1985). The dose of 250 mg/kg/day has been converted to an equivalent concentration of 1,923 ppm in food for presentation in Table 1-4. Clinical signs of toxicity were not observed in mice and rats but histopathologic examination revealed dose-related chemical-induced changes to the liver, kidney, bone marrow, spleen, and thymus. Liver and kidney weights increased in mice and rats, while spleen weights decreased. In chronic oral studies, male rat survival at 120 mg/kg (2,400 ppm) was significantly lower than that of vehicle controls (NTP 1985); however no compound-induced toxic lesions responsible for this reduction in survival were observed.

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

2.2.2.2 Systemic Effects

No studies in humans were located regarding the effects on the respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular systems following oral exposure to chlorobenzene. The following sections describe effects observed in animals.

Hepatic Effects. Animal studies indicate that the liver is susceptible to injury by chlorobenzene following oral exposure. Typical signs include: increased serum enzymes, altered liver weights, degeneration, necrosis, and interference with porphyrin metabolism. In acute studies (5 days), effects on porphyrin metabolism occurred at 1,140 mg/kg/day by gavage (Rimington and Ziegler 1963). Intermediate and long-term exposure studies in rats and mice reported organ weight increases at 100 (Hazleton 1967) and 125 mg/kg/day (NTP 1985), while organ weight increases and microscopic lesions were detected at ≥ 250 mg/kg/day by the same route (NTP 1985). Focal hepatocytic necrosis and degenerative changes in the centrilobular hepatocytes were observed in mice. These effects were most apparent in the ≥ 500 mg/kg dose group in rats. The dose of 250 mg/kg/day has been converted to equivalent concentrations of 1,923 ppm (in mice) and 5,000 ppm (in rats) in food for presentation in Table 1-4. No effects were observed at 60 mg/kg/day. Based on this value, an intermediate oral MRL of 0.4 mg/kg/day was calculated as described in the footnote in Table 2-2. This MRL has been converted to an equivalent concentration in food (15 ppm) for presentation in Table 1-3.

Renal Effects. Animal studies demonstrate that chlorobenzene can cause injury to the kidney at doses comparable to those which cause liver effects. In a 90-day study, degeneration or focal necrosis of the proximal tubules was observed at ≥ 250 mg/kg in mice and ≥ 500 mg/kg in rats (NTP 1985). Repeated doses of ≥ 100 mg/kg/day for 90 to 99 days (Hazleton 1967) caused an increase in kidney weights.

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

Figure Key	Species	Route	Exposure Frequency/ Duration	Effect	NOAEL (mg/kg/day)	LOAEL (Effect)		Reference
						Less Serious (mg/kg/day)	Serious (mg/kg/day)	
ACUTE EXPOSURE								
Death								
1	Rat	(G)	14 d 1x/d		500		1000 ^a	NTP 1985
2	Rat	(G)	1 d 1x/d		250		4000	NTP 1985
3	Mouse	(G)	14 d 1x/d		500			NTP 1985
4	Mouse	(G)	1 d 1x/d				1000 ^b	NTP 1985
Systemic								
5	Rat	(G)	5 d	Hepatic			1140 (necrosis)	Rimington and Ziegler 1963
Neurological								
6	Rat	(G)	1 d 1x/d				4000 (prostration)	NTP 1985
7	Rat	(G)	14 d 1x/d				1000 (prostration)	NTP 1985
INTERMEDIATE EXPOSURE								
Death								
8	Rat	(G)	91 d 5d/wk		250			NTP 1985
9	Mouse	(G)	91 d 5d/wk		125			NTP 1985
Systemic								
10	Rat	(G)	91 d 5d/wk	Hepatic	60 ^c	125 (incr. wt. and serum enzymes)	250 ^d (necrosis)	NTP 1985

TABLE 2-2 (Continued)

Figure Key	Species	Route	Exposure Frequency/ Duration	Effect	NOAEL (mg/kg/day)	LOAEL (Effect)		Reference
						Less Serious (mg/kg/day)	Serious (mg/kg/day)	
11	Mouse	(G)	91 d 5d/wk	Renal	125		250 ^e (necrosis, tub. degen.)	NTP 1985
12	Mouse	(G)	91 d 5d/wk	Hepatic	60	125 (incr. wt.)	250 ^e (necrosis, degeneration)	NTP 1985
Immunological								
13	Mouse	(G)	91 d 5d/wk				250 (thymic necrosis, splenic depletion)	NTP 1985
CHRONIC EXPOSURE								
Death								
14	Mouse	(G)	103 wk 5d/wk 1x/d		120			NTP 1985
Systemic								
15	Rat	(G)	103 wk 5d/wk 1x/d	Hepatic	60		120 (necrosis)	NTP 1985

^aConverted to an equivalent concentration of 20,000 ppm in food for presentation in Table 1-4.

^bConverted to an equivalent concentration of 7692 ppm in food for presentation in Table 1-4.

^cUsed to derive intermediate oral MRL of 0.4 mg/kg/day; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans, and 10 for human variability). This MRL has been converted to an equivalent concentration in food (15 ppm) for presentation in Table 1-3.

^dConverted to an equivalent concentration of 5000 ppm in food for presentation in Table 1-4.

^eConverted to an equivalent concentration of 1923 ppm in food for presentation in Table 1-4.

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; mg = milligram; kg = kilogram; (G) = gavage; d = day; 1x = one time; wk = week; incr = increase; wt = weight; tub = tubular; degen = degeneration.

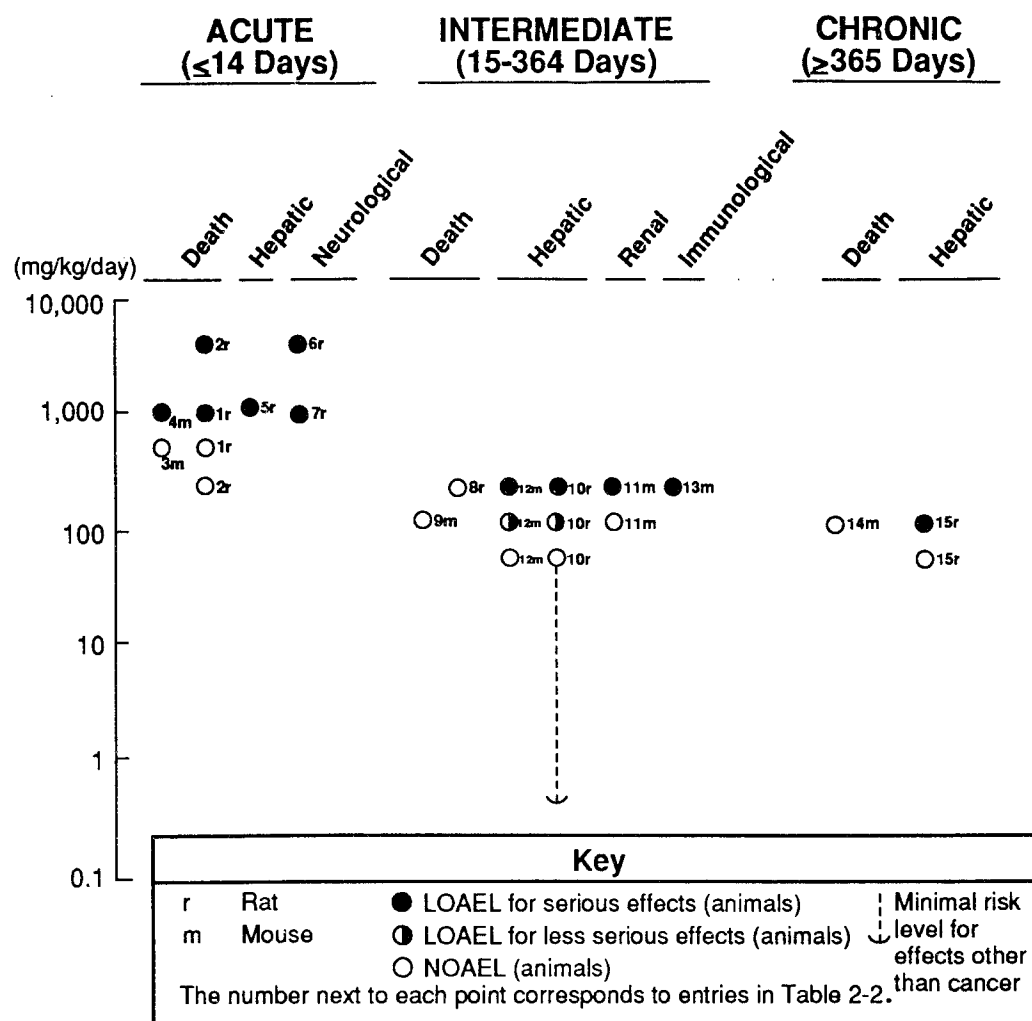


FIGURE 2-2. Levels of Significant Exposure to Chlorobenzene – Oral

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

2.2.2.3 Immunological Effects

No studies were located regarding immunological effects in humans following oral exposure to chlorobenzene.

Histological studies in mice and rats suggest that chlorobenzene has immunotoxic properties. Mice exposed to chlorobenzene at ≥ 250 mg/kg/day by gavage for 13 weeks showed thymic necrosis and lymphoid or myeloid depletion of bone marrow, spleen, or thymus (NTP 1985). While histopathologic evidence suggests that chlorobenzene is immunotoxic, a NOAEL cannot be established in this study since immune function tests were not conducted. A LOAEL of 250 mg/kg/day was determined (NTP 1985). This value has been presented in Table 2-2. Since there are no human data on immunotoxic effects and animal data are sparse, firm conclusions can not be made concerning the potential for chlorobenzene to affect the immune system in humans following oral exposure.

2.2.2.4 Neurological Effects

There is a paucity of data on the effects of chlorobenzene in humans following oral exposure. A two-year-old male swallowed 5 to 10 cc of a stain remover which consisted almost entirely of chlorobenzene. He became unconscious, did not respond to skin stimuli, showed muscle spasms, and became cyanotic. The odor of chlorobenzene could be detected in his urine and exhaled air; however, the child recovered uneventfully (Reich 1934).

No studies were located regarding neurological effects in animals following oral exposure. In the absence of dose-response data in humans and the lack of animal evidence, the potential for chlorobenzene to produce effects on the nervous system cannot be quantitatively determined.

2.2.2.5 Developmental Effects

No studies were located regarding the developmental effects in humans following oral exposure to chlorobenzene.

Limited data in animals suggest that chlorobenzene is not teratogenic. Rats were administered chlorobenzene (100 or 300 mg/kg) in corn oil by gavage from days 6-15 of gestation (IBT 1977). Fetal weight, external anomalies, and skeletal and soft tissue abnormalities

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did not differ from control animals in any of the measured parameters. Further, data on maternal weight and behavioral effects did not reveal evidence for dose-related effects.

2.2.2.6 Reproductive Effects

No studies were located regarding the reproductive effects in humans or animals following oral exposure to chlorobenzene.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or in vivo studies in animals following oral exposure to chlorobenzene.

2.2.2.8 Cancer

No studies were located regarding carcinogenic effects in humans following oral exposure to chlorobenzene.

In a chronic oral bioassay in rats and mice (NTP 1985), there was no evidence for carcinogenicity in both sexes of mice or female rats administered chlorobenzene in corn oil by gavage at dose levels up to 120 mg/kg/day. Increased tumor frequencies were not seen in female rats or in male or female mice. Male rats showed a significant ($p < 0.05$) increase in the incidence of neoplastic nodules of the liver in the 120 mg/kg/day dose group, but no increases were found at lower dose levels. While progression from nodules to carcinomas is a well characterized phenomenon, existing data are inadequate to characterize the carcinogenic potential of chlorobenzene in humans. On the basis of these data, the EPA has classified chlorobenzene as a class D carcinogen (i.e., inadequate evidence of carcinogenicity in humans and animals) (EPA 1987c).

2.2.3 Dermal Exposure

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

2.2.3.1 Death

2.2.3.2 Systemic Effects

2.2.3.3 Immunological Effects

2.2.3.4 Neurological Effects

2.2.3.5 Developmental Effects

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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

Ogata and Shimada (1983) reported that in two workers exposed to 0.84 and 0.5 ppm of chlorobenzene, the amount absorbed was 38% and 45%, respectively of the administered dose. It should be noted that the percent recovery reported in this study did not take into consideration elimination that occurred during the night nor of expired chlorobenzene. Sullivan et al. (1983) reported that rats readily absorbed ¹⁴C-labeled chlorobenzene vapor at concentrations up to 700 ppm.

2.3.1.2 Oral Exposure

Chlorobenzene is absorbed from the gastrointestinal tract. In a study with a single human volunteer, Ogata and Shimada (1983) reported that at least 31% of administered chlorobenzene was absorbed. In the same study, rats administered chlorobenzene absorbed at least 18% of the administered dose. Similar results were reported by Lindsay-Smith et al. (1972), who observed that in rabbits administered ¹⁴C-labeled chlorobenzene, at least 22% of the administered chlorobenzene was absorbed.

2.3.1.3 Dermal Exposure

No studies were located regarding dermal exposure to chlorobenzene in humans or animals.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No studies were located regarding distribution after inhalation exposure of chlorobenzene in humans.

Sullivan et al. (1983) reported the distribution of ¹⁴C-labeled chlorobenzene vapor in rat tissues following single or multiple 8-hour exposures. Some rats were maintained for 48 hours for urine collection. Others were sacrificed immediately or 16 hours after exposure for analysis of tissue radioactivity. The radioactivity in all tissues,

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except for fat, increased in proportion to the increase in exposure concentration. The amount of the radiolabel in adipose tissue increased 8 to 10 times when the concentration was increased from 100 to 400 ppm and 3 to 5 times from 400 to 700 ppm. Tissue levels of radioactivity following a single exposure were highest in epididymal and perirenal fat (16.4 and 15.3 micromoles per gram, respectively) after the 700 ppm exposure. These values were not exceeded in animals following multiple exposures. However, multi-exposed rats exhibited higher tissue burdens, 48 hours after the last exposure, than rats exposed only once. The preferential distribution of chlorobenzene to the adipose tissue reflects the lipophilic nature (log octanol/water partition coefficient: 2.84 (Verschuere 1983)) of this compound. The longevity of radioactivity in fat tissue was not determined.

2.3.2.2 Oral Exposure

No studies were located regarding the distribution of chlorobenzene after oral exposure in humans or animals.

2.3.2.3 Dermal Exposure

No studies were located regarding the distribution of chlorobenzene after dermal exposure in humans or animals.

2.3.3 Metabolism

The proposed metabolic pathway (adapted from Ogata and Shimada 1983) of chlorobenzene is shown in Figure 2-3. The main metabolites of chlorobenzene are p-chlorophenylmercapturic acid and 4-chlorocatechol.

The in vitro metabolites of chlorobenzene are o-chlorophenol, m-chlorophenol, and p-chlorophenol; the proportions differ according to the source of the mono-oxygenase system and its state of purity (Selander et al. 1975). The o- and p-chlorophenols result from isomerization of the intermediate 3- and 4-chlorobenzene oxides, respectively. The formation of m-chlorophenol appears to occur via a direct oxidative pathway (Oesch et al. 1973). In vitro conjugation of the arene oxide with glutathione or hydration is not a significant pathway (Selander et al. 1975).

Ogata and Shimada (1983) examined the urinary metabolites of chlorobenzene in human subjects. An oral dose of 0.3 mmol/kg chlorobenzene was given to a 57-year-old male subject. Metabolites were also assayed in 2 workers exposed via inhalation of either 0.84 or 0.5 ppm of chlorobenzene. They reported the occurrence of 4-chlorocatechol and p-chlorophenylmercapturic acid in the urine of humans who received chlorobenzene orally or by inhalation.

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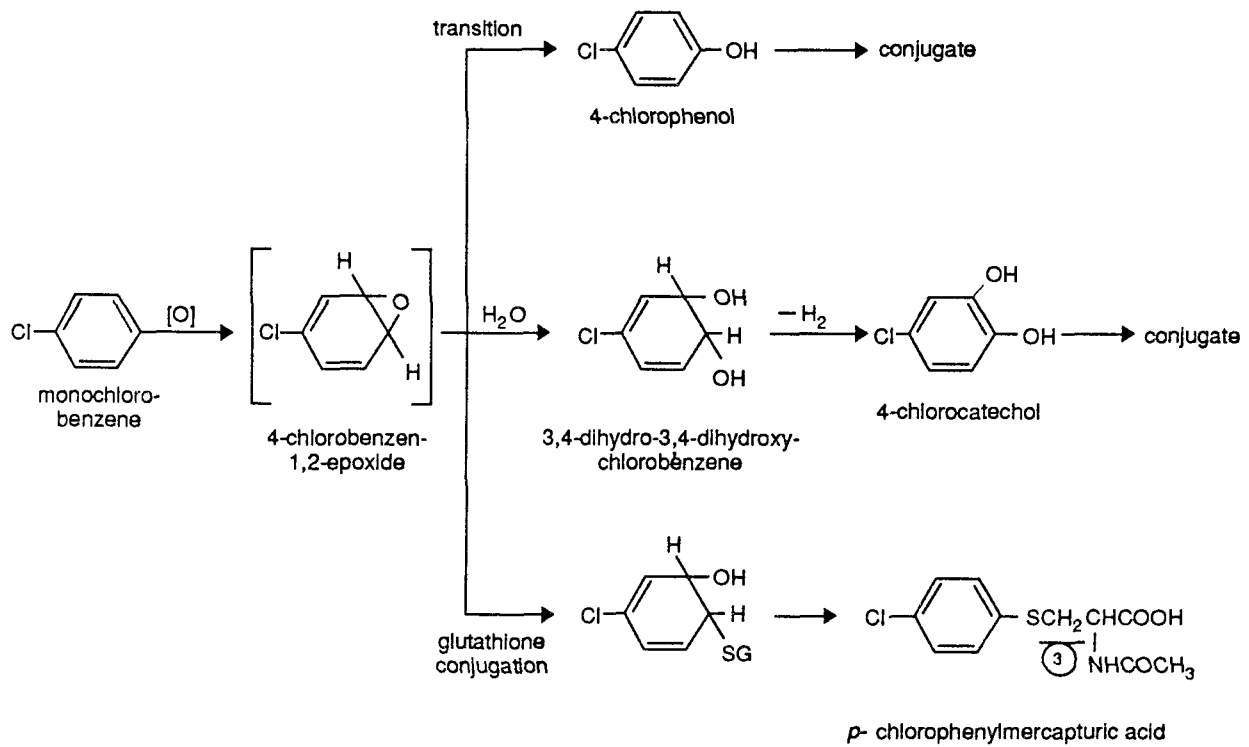


FIGURE 2-3. Metabolic Scheme for Chlorobenzene

Source: Adapted from Ogata and Shimada 1983.

2. HEALTH EFFECTS

Ogata and Shimada (1983) also examined the urinary metabolites of chlorobenzene in rats, mice, and rabbits. Rats were given oral doses of 0.3 mmol/kg, while all three species received intraperitoneal injections of 0.5, 1.0, or 2.0 mmol/kg. Urinary p-chlorophenylmercapturic acid, and 4-chlorocatechol, after hydrolysis of its conjugate, were reported.

Lindsay-Smith et al. (1972) reported that the major metabolites of chlorobenzene in the rabbit are p-chlorophenylmercapturic acid and conjugates of 4-chlorocatechol. Other urinary metabolites included quinol, 3-chlorocatechol, and o- and m-chlorophenylmercapturic acids. Oesch et al. (1973) studied the metabolism of chlorobenzene in rats administered chlorobenzene by intraperitoneal injection. Thirty-three percent of the administered dose was excreted in the urine, with p-chlorophenol as the major metabolite. Other metabolites included 4-chlorocatechol, o-chlorophenol, and m-chlorophenol.

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

Rats were exposed to ¹⁴C-chlorobenzene vapor at concentrations of 100, 400, and 700 ppm for 8 hours (Sullivan et al. 1983). The plasma concentration-time profile for chlorobenzene on cessation of exposure, as estimated by respiratory elimination of radioactivity, indicated a two compartment elimination. Increase in exposure by a factor of seven (100-700 ppm) increased the total uptake of radioactivity by a factor of about 13. This increase in body burden was associated with a decrease in total body clearance, as indicated by an approximate four fold increase in the half-life of the central compartment. The proportion of the dose excreted via the lungs (which may be presumed to be largely, if not entirely, unchanged chlorobenzene) increased nonlinearly and the proportion eliminated by hepatic metabolism decreased. Increase in the dose of chlorobenzene was associated with a decrease in the proportion cleared as the mercapturic acid derivative. Of interest, the half-life of chlorobenzene was shorter at the 700 ppm exposure level when the animals were subjected to repeated treatment daily for 5 days, as compared with that of the single 700 ppm exposure animals, raising the possibility of induction of metabolic clearance. In agreement with this possibility, the proportion cleared by metabolism in the multi-exposed animals was increased, and the proportion excreted unchanged via the lung was decreased, as compared with the 700 ppm-single exposure animals.

Ogata and Shimada (1983) reported that in two workers exposed to 0.84 and 0.5 ppm of chlorobenzene, the excretion of p-chlorophenylmercapturic acid was markedly lower than that of 4-chlorocatechol. However, the ratio of mercapturic-acid to

2. HEALTH EFFECTS

4-chlorocatechol in the urine of human subjects receiving chlorobenzene orally was similar to that of workers inhaling chlorobenzene.

2.3.4.2 Oral Exposure

Ogata and Shimada (1983) also assayed the urinary metabolites of chlorobenzene of a 57-year-old male volunteer given an oral dose of 0.3 mmol/kg of chlorobenzene. Two urinary metabolites, p-chlorophenylmercapturic acid and 4-chlorocatechol, were detected. As in the case of inhalation exposure, the excretion of p-chlorophenylmercapturic acid was reported to be markedly lower than that of 4-chlorocatechol. However, the ratio of mercapturic-acid to 4-chlorocatechol in the urine of human subjects receiving oral chlorobenzene was similar to that of workers inhaling chlorobenzene.

Lindsay-Smith et al. (1972) reported that rabbits administered ¹⁴C-labeled chlorobenzene excreted 22% of the radiolabel in the urine. The authors concluded that the remaining radiolabel was excreted in the expired air. Ogata and Shimada (1983) reported that in rats the primary urinary metabolite was p-chlorophenylmercapturic acid and that 4-chlorocatechol was a minor metabolite.

2.3.4.3 Dermal Exposure

No studies were located concerning excretion of chlorobenzene in animals or man after dermal exposure.

2.4 RELEVANCE TO PUBLIC HEALTH

Inhalation studies in humans and animals and oral studies in animals demonstrate that chlorobenzene can affect the central nervous system, liver, and kidneys. Chlorobenzene did not affect the developing fetus, was not genotoxic, and did not affect reproduction. Data has not provided clear evidence that chlorobenzene causes cancer in animals. Existing data are considered inadequate to derive human minimal risk levels for acute and chronic exposures.

Death. No case studies of human fatalities have been reported following exposure to chlorobenzene by inhalation, ingestion, or dermal contact. Death has been reported in animals at high doses for brief periods of exposure. Rabbits died within 2 weeks after removal from exposure at approximately 537 ppm (Rozenbaum et al. 1947). The cause of death has been attributed to central nervous system depression resulting in respiratory failure. Animal data suggest that lethality may not be a concern for humans unless the exposure level is very high.

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Systemic Effects. No studies were located regarding effects on the respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, or dermal/ocular systems in humans or animals by any route of exposure to chlorobenzene.

Hepatic Effects. No studies were located demonstrating that chlorobenzene causes hepatic toxicity in humans by any route of exposure. Acute and intermediate exposures in animals demonstrated that chlorobenzene causes changes in liver weights and enzyme levels, degeneration, necrosis, and alterations in microsomal enzymes. These effects were first evident during acute exposure (5 days) at 1,140 mg/kg/day by gavage (Rimington and Ziegler 1963) and intermediate exposure (5 days/wk for 24 weeks) at 75 ppm via inhalation (Dilley 1977). Similar effects were also observed following ingestion of ≥ 250 mg chlorobenzene/kg/day for 91 days. The precise mechanism for liver damage is not known; however, direct binding of chlorobenzene metabolites to cellular protein may be involved (Reid et al. 1973; Reid and Krishna 1973). There were differential sensitivities in animal species tested which may be due to differences in metabolism. Based on animal studies, liver toxicity may be an area of concern in humans.

Renal Effects. No studies were located demonstrating that chlorobenzene causes renal effects in humans by any route of exposure. Intermediate studies in animals showed effects on the kidney at doses comparable to those causing liver effects. Typical signs included tubular degeneration and necrosis as well as changes in organ weight. Changes in organ weights with accompanying histopathology occurred at ≥ 250 mg/kg/day (90 days) (Kluwe et al. 1985). The precise mechanism of kidney damage is not clear. However, necrosis was associated with covalent binding of substantial amounts of radiolabeled chlorobenzene to kidney protein in intraperitoneal studies (Reid 1973). This study also reported that autoradiograms revealed that most of the covalently bound material was localized within necrotic tubular cells (Reid 1973). Based on animal studies, renal toxicity may be an area of concern in humans.

Immunological Effects. Histopathologic evaluations in animals suggest that chlorobenzene may be immunotoxic; however, direct tests of immune function have not been performed. In the absence of functional assessment, the potential for chlorobenzene to affect the immune system in humans can not be determined.

Neurological effects. Case reports of humans demonstrated that chlorobenzene caused disturbances of the central nervous system, but there were no reports of changes in the structure of the brain and other parts of the nervous system. Effects were observed in humans who inhaled vapors of chlorobenzene in the workplace for up to 2 years (Rozenbaum et al. 1947). Effects included headaches, dizziness, and

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sleepiness. Unconsciousness, lack of response to skin stimuli, and muscle spasms were noted following accidental ingestion. While there is qualitative evidence for central nervous system effects in humans, a quantitative assessment can not be made since exposure levels were not reported. Because work practices have changed significantly since these studies, it is reasonable to assume that exposure levels in this study were higher than current permissible federal exposure levels. Acute studies in animals confirm that chlorobenzene is potentially neurotoxic. These effects appear to be the result of narcotic effects of chlorobenzene on the central nervous system. Acute inhalation exposure produced narcosis preceded by muscle spasms in rabbits at 1,090 ppm (Rozenbaum et al. 1947).

Developmental Effects. No studies were found regarding the developmental toxicity of chlorobenzene in humans. In inhalation and oral exposure studies, the animals did not demonstrate significant developmental toxicity when compared with untreated controls. Negative responses in two animal species suggest that developmental toxicity may not be an area of concern for chlorobenzene.

Reproductive Effects. No studies were found regarding the reproductive toxicity of chlorobenzene in humans. In a two-generation inhalation study, chlorobenzene did not adversely affect various reproductive parameters in rats (Nair et al. 1987). While results of this study suggest reproductive toxicity may not be an area of concern to humans, other considerations are warranted before firm conclusions can be made regarding risk to humans. The slight increase in the occurrence of degeneration of the germinal epithelium of the testes provides some evidence for further consideration. Also, the study did not provide histopathological data on other organs related to reproductive functions (i.e., epididymis, vas deferens, accessory sex glands, and pituitary). While the authors reported no treatment-related impairment of fertility, it should be noted that fertility assessments in test animals are limited by their insensitivity as measures of reproductive injury in humans.

Genotoxic Effects. No studies were located regarding the genotoxic effects of chlorobenzene in humans. No in vivo animal assays were found, except the micronuclear test in mice which was moderately positive (Mohtashamipur et al. 1987) (Table 2-3). Furthermore, in vitro tests employing bacterial and yeast assay systems with and without metabolic activation were negative (Haworth et al. 1983; NTP 1985; Prasad 1970). Chlorobenzene induced transformation in adult rat liver epithelial cells but was not genotoxic to hepatocytes (Shimada et al. 1983). Since transformations may occur through nongenotoxic mechanisms, results do not necessarily indicate that chlorobenzene is potentially genotoxic. Results of in vitro assays for chlorobenzene are presented

TABLE 2-3. Genotoxicity of Chlorobenzene In Vivo

End Point	Species (Test System)	Exposure Route	Results	Reference
Mammalian systems:				
Chromosomal	Mouse (micronuclear)	IP	+	Mohtashumipur et al. 1987

IP = intraperitoneal; + = positive result.

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in Table 2-4. Existing data suggest that genotoxicity may not be an area of concern for chlorobenzene exposure in humans.

Cancer. No studies were found regarding the carcinogenicity of chlorobenzene in humans. In a chronic bioassay in animals, chlorobenzene (up to 120 mg/kg/day) did not produce increased tumor incidences in mice of both sexes or in female rats (NTP 1985). It was noted, however, that male rats showed a statistically significant increase in neoplastic nodules at the highest dose level tested. While there is strong evidence for neoplastic nodules, existing data are inadequate to characterize the potential for chlorobenzene to cause cancer in humans and animals.

2.5 BIOMARKERS OF EXPOSURE AND EFFECT

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

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule 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 left the body by the time biologic samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to chlorobenzene 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

TABLE 2-4. Genotoxicity of Chlorobenzene In Vitro

End Point	Species (Test System)	Results		Reference
		With Activation	Without Activation	
Prokaryotic organisms:				
Gene mutation	<u>Salmonella typhimurium</u>	-	-	NTP 1985
Gene mutation	<u>S. typhimurium</u>	-	-	Haworth et al. 1983
Eukaryotic organisms:				
Fungi:				
Gene mutation	<u>Aspergillus nidulans</u>	-	No data	Prasad 1970
Mammalian cells:				
Genetic endpoint unknown	Rat (cellular transformation)	+	No data	Shimada et al. 1983
DNA Repair	Rat (UDS)	-	No data	Shimada et al. 1983

- = negative result; + = positive result; UDS = unscheduled DNA synthesis.

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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 chlorobenzene 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 Chlorobenzene

Levels of chlorobenzene and its metabolites have been measured in blood, urine, and exhaled air; however, no studies were located linking any level of chlorobenzene in humans with a biological effect. Levels ranging from 0.05 to 17 mg/L were detected in the blood and 25 to 120 µg/L in the urine of residents living near a former toxic chemical dump, while trace amounts were found in exhaled air (Barkley et al. 1980).

2.5.2 Biomarkers Used to Characterize Effects Caused by Chlorobenzene

Neurological damage is a characteristic biomarker of effect in humans exposed to chlorobenzene. Additional information on health effects associated with exposure to chlorobenzene can be found in Section 2.2. Various clinical signs and symptoms of people exposed to chlorobenzene which may be monitored include headaches, dizziness, muscle spasms, and cyanosis (from respiratory depression). No data were found on biochemical changes which may exist.

Studies in animals suggest that chlorobenzene may also cause injury to the liver. In rats, alkaline phosphatase, SGOT, and delta-amino levulinic acid levels were increased as were liver protoporphyrin and uroporphyrin. Data suggest that the kidneys may be affected following exposure to chlorobenzene as polyuria was noted in rats at high dose levels. Since other chemicals may produce similar effects, these are not specific indicators of chlorobenzene exposure.

2.6 INTERACTIONS WITH OTHER CHEMICALS

In an attempt to identify the proposed epoxide intermediate of chlorobenzene, Oesch (1973) co-administered the epoxide hydrolase

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inhibitor cyclohexane oxide together with chlorobenzene to rats. Instead of increasing the toxicity of chlorobenzene as expected, through the inhibition of epoxide hydrase, cyclohexane oxide actually decreased the metabolism of chlorobenzene and its necrotic toxicity on the liver, suggesting that the metabolism of chlorobenzene is partially responsible for its liver toxicity.

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

No studies were located regarding human populations that are unusually susceptible to chlorobenzene. By analogy to other lipophilic chlorinated benzenes such as hexachlorobenzene, which is found in human milk (Weisenberg et al. 1985), nursing infants may be susceptible to chlorobenzene toxicity.

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 chlorobenzene 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 chlorobenzene.

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 Chlorobenzene

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to chlorobenzene are summarized in Figure 2-4. The purpose of this figure is to illustrate the existing information concerning the health effects of chlorobenzene. 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.

As summarized in Figure 2-4, there is a paucity of data on health effects of chlorobenzene in humans. Existing data relate to inhalation and oral exposures. No data were found on dermal exposures.

2. HEALTH EFFECTS

	Death	SYSTEMIC			Immunologic	Neurologic	Developmental	Reproductive	Genotoxic	Carcinogenic
		Acute	Intermed.	Chronic						
Inhalation				●	●					
Oral					●					
Dermal										

HUMAN

	Death	SYSTEMIC			Immunologic	Neurologic	Developmental	Reproductive	Genotoxic	Carcinogenic
		Acute	Intermed.	Chronic						
Inhalation	●		●		●	●	●			
Oral	●	●	●	●				●	●	
Dermal										

ANIMAL

● Existing Studies

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

2. HEALTH EFFECTS

The toxicity of chlorobenzene has been studied in animals by oral and inhalation exposures, but there are no data on dermal exposures. Oral studies have focused on systemic toxicity (liver and kidney) and genotoxic and carcinogenic effects. There are inhalation studies evaluating neurologic, developmental, and reproductive effects.

2.8.2 Identification of Data Needs

Acute-Duration Exposure. No information is available on the effects of acute-duration exposure of humans to chlorobenzene by any route of exposure. Animal studies indicate that acute inhalation and oral exposures can result in death. No other treatment-related effects were reported. There are no data on effects of chlorobenzene following dermal exposure in animals. Since data on effects in humans are not available and animal data are limited to lethality, data are not sufficient to derive an acute MEL. Further studies would be useful to identify target tissues and threshold levels for effects that may exist.

Intermediate-Duration Exposure. No studies are available in humans on the effects of intermediate-duration exposure to chlorobenzene by any route. Inhalation and oral studies in animals indicate that the nervous system, liver, and kidneys are principal target tissues following exposure to chlorobenzene. An intermediate oral MRL was derived based on liver effects in rats. There are no data on effects following dermal exposure in animals. Because there is potential for exposure to chlorobenzene through skin contact, additional studies by dermal exposure would add to the database on chlorobenzene toxicity.

Chronic-Duration Exposure and Cancer. Limited studies are available on the effects in humans chronically exposed to chlorobenzene via inhalation and suggest that nervous system is a target tissue. Specific exposure data were not provided. No information is available on effects of chlorobenzene in humans following chronic oral or dermal exposure. Inhalation and oral studies in animals identified the same target tissues as for intermediate-duration exposure. One study in rats demonstrated that the immune system can also be adversely affected via oral exposure. Inhalation studies in humans and inhalation and oral studies in animals are sufficient to identify main target tissues. A chronic MRL was not derived since human exposure data were lacking and the one animal study did not evaluate a sufficient number of end points and test animals. Further studies via the dermal route would provide additional toxicity data for an assessment of potential risk to humans.

No studies were found in humans regarding the carcinogenic effect of chlorobenzene via inhalation. Since this is the primary route of environmental exposure, additional studies would be useful to assess potential risk to people who may be exposed to low levels of

2. HEALTH EFFECTS

chlorobenzene in air near hazardous waste sites. There was no evidence for carcinogenicity in both sexes of mice or female rats following oral exposure to chlorobenzene. Since the animals were tested at the maximum tolerated dose and a no-effect level for tumors in rats and mice has been determined, additional oral studies are not warranted at this time.

Genotoxicity. No studies were found on the genotoxic effects of chlorobenzene in humans by any route of exposure. Results of animal assays were mixed. Chlorobenzene induced statistically significant increases in polychromatic erythrocytes containing micronuclei in mice following intraperitoneal injections. Results of cellular transformation assays of rat liver epithelial cells were positive, but chlorobenzene did not induce unscheduled DNA synthesis in primary rat hepatocytes. Studies evaluating the mutagenic potential of chlorobenzene have been negative. Since existing data do not suggest a significant genotoxic risk associated with exposure to chlorobenzene, additional studies are not warranted at this time.

Reproductive Toxicity. No studies were found on the reproductive toxicity of chlorobenzene by any route in humans. Chlorobenzene did not affect various reproductive parameters in a two-generation inhalation study in rats. Additional animal studies employing another species would provide further information for assessing potential effects on the reproductive functions of chlorobenzene. These studies should provide histological evaluations of organs related to reproduction function (i.e., epididymis, vas deferens, accessory sex glands, and pituitary) since these organs have not been evaluated. Slight increases in the incidence of degeneration of testicular epithelium are also noteworthy for further consideration.

Developmental Toxicity. No studies have been conducted to evaluate the developmental toxicity of chlorobenzene in humans. Chlorobenzene did not affect the developing fetus following inhalation and oral exposures by rats and rabbits. While there is a potential for exposure via the dermal route, the absence of significant effects by the primary exposure route (inhalation) suggests that additional studies may not be needed at this time.

Immunotoxicity. There are no data available on the immunotoxicity of chlorobenzene in humans by any route of exposure. Histological examination of organs and tissues of the immunological system in mice and rats provide some evidence that chlorobenzene is potentially immunotoxic. Immune function tests would provide a better assessment of potential immunotoxic effects in humans.

Neurotoxicity. Limited data in humans indicate that exposure to chlorobenzene via inhalation and oral exposures can result in effects on

2. HEALTH EFFECTS

the nervous system. Clinical signs and symptoms were observed, but histological lesions were not reported. Results of inhalation studies in animals confirm clinical aberrations, but no data were found in animals following oral exposure. Further studies employing other animal species and various dose levels would be useful to determine if similar effects exist following oral and dermal exposures. Although the inhalation of contaminated air is the most probable route of exposure to chlorobenzene, there is also potential for exposure through skin contact or by consumption of contaminated water. Animal studies in which chlorobenzene is administered orally or dermally would allow determination of neurotoxicity by these routes.

Epidemiological and Human Dosimetry Studies. No epidemiological studies have been conducted to evaluate the adverse health effects of chlorobenzene. Existing studies are limited to case reports of occupational exposures and identified the nervous system as a target tissue following chronic inhalation of chlorobenzene. Reliable exposure data were not reported. Additional studies which provide quantitative exposure data would be useful in evaluating potential risk to humans and providing a better understanding of levels which lead to effects that may exist.

Biomarkers of Exposure and Effect. Parent chlorobenzene and metabolites can be detected in biological tissues and fluids. However, existing methods may not be useful for evaluating the general population as opposed to industrial situations where preexposure levels are established prior to known chlorobenzene exposure. The overall reliability of these biomarkers are further reduced since data are not available on the half-life of chlorobenzene in various biological media.

Central nervous system injury is a common effect associated with exposure to vapors of chlorobenzene in humans. Studies in animals suggest that chlorobenzene can also result in damage to the liver and kidneys. Since similar effects occur with exposure to other chemicals, additional studies are needed to identify more specific biomarkers by which to monitor populations living near hazardous waste sites.

Absorption, Distribution, Metabolism, and Excretion. The toxicokinetics of chlorobenzene have not been evaluated to any great extent in humans. Limited studies suggest that chlorobenzene can be absorbed following inhalation and oral exposures, but no data were found on absorption following dermal exposure. Based on absorption characteristics of benzene and the high lipid solubility of chlorobenzene, absorption may be significant depending on conditions. Additional studies are needed to determine absorption rates following exposure by all routes.

2. HEALTH EFFECTS

Data are also sparse on the distribution of chlorobenzene. No information is available regarding distribution of chlorobenzene in humans by inhalation, oral, or dermal exposure. There are limited animal data which suggest preferential distribution to adipose tissue in rats via inhalation. The kidneys and liver also showed significant amounts of chlorobenzene and rats that received multiple doses exhibited higher tissue burdens than rats exposed only once.

The metabolic transformation of chlorobenzene has been evaluated in humans and animals. Although ultimate products of metabolic oxidation are known, the oxidative pathway and possible intermediates have not been established. Principal metabolites have been determined but quantities and ratios differ among species. Additional studies would be useful to determine if these differences affect the toxicity of chlorobenzene.

There are limited data on the excretion of chlorobenzene. In humans exposed via the inhalation and oral routes, chlorobenzene and its metabolites were detected in urine and there were differences in excretion patterns via the two routes. Chlorobenzene and its metabolites were also detected in exhaled air of rats following inhalation and in exhaled air and urine in rabbits after oral exposure. The urinary metabolite profile appeared to be dose dependent and there were changes in excretion patterns due to multiple versus single exposures. No data on excretion following dermal exposure are available. Additional studies would be useful in determining the significance of these differences with regard to risk associated with different routes of exposure.

Comparative Toxicokinetics. Existing studies regarding toxicokinetics of chlorobenzene in humans are limited, but data do provide some understanding of the absorption, metabolism, and excretion following inhalation and oral exposures. Since studies on distribution of chlorobenzene are lacking, quantitative data correlating human exposure and tissue accumulation would be useful. In animals, quantitative data on absorption, distribution, metabolism, and excretion are very limited in extent and quality. Additional studies using a variety of species and including physiological based pharmacokinetic modeling would be useful in determining the most suitable animal model for assessing human risk.

2.8.3 On-going Studies

Chlorobenzene is one of 47 chemicals to be tested by NTP for heritable genetic effects in *Drosophila* and for mutagenesis in the mouse lymphoma cell mutagenesis assay.

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY


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

3.2 PHYSICAL AND CHEMICAL PROPERTIES

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

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-1. Chemical Identity of Chlorobenzene

Characteristic	Value	Reference
Chemical name	Chlorobenzene	NLM 1988 NLM 1988
Synonyms	Monochlorobenzene; benzene chloride; phenylchloride; MCB; chlorobenzol	NLM 1988
Trade name	Caswell no. 183A	NLM 1988
Chemical formula	C ₆ H ₅ Cl	NLM 1988
Chemical structure		
Identification numbers:		
CAS Registry	108-90-7	NLM 1988
NIOSH RTECS	CZ0175000	HSDB 1988
EPA Hazardous Waste	U037,F002	HSDB 1988
OHM/TADS	No data	
DOT/UN/NA/IMCO Shipping	UN 1134	NLM 1988
	IMCO 3.3	HSDB 1988
HSDB	55	NLM 1988
NCI	C54886	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 Chlorobenzene

Property	Value	Reference
Molecular weight	112.56	Weast 1985
Color	Colorless	Verschueren 1983
Physical state	Liquid	Verschueren 1983
Melting point	-45.6°C	Weast 1985
Boiling point	132°C	Weast 1985
Density at 20°C	1.1058	Weast 1985
Odor	Aromatic, almond-like	Sax and Lewis 1987
Odor threshold:		
Water	0.050 mg/L	Verschueren 1983
Air	1-8 mg/m ³	Verschueren 1983
Solubility:		
Water at 20°C	500 mg/L	Verschueren 1983
Organic solvents	Soluble in alcohol, ether, benzene	Weast 1985
Partition coefficients:		
Log octanol/water	2.84	Verschueren 1983
Log K _{oc}	2.52	Mabey et al. 1982
Vapor pressure at 20°C	8.8 mmHg	Verschueren 1983
Henry's law constant	3.58x10 ⁻³ atm-m ³ /mol	Mabey et al. 1982
Autoignition temperature	637°C	Sax and Lewis 1987
Flashpoint	29.4°C	Sax and Lewis 1987
Flammability limits	1.8%-9.6%	Sax and Lewis 1987
Conversion factors	1 ppm = 4.7 mg/m ³ 1 mg/m ³ = 0.22 ppm	Verschueren 1983

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.1 PRODUCTION

Production of chlorobenzene in the United States has declined by nearly 60%, from the peak production volume of 274,000 kkg in 1960 to 112,000 kkg in 1987. This decline is attributed primarily to the replacement of chlorobenzene by cumene in phenol production and the cessation of DDT production in the United States. In addition, pesticide production using chlorobenzene as an intermediate has declined and no major new uses have been found for chlorobenzene in recent years. Therefore, the decline in chlorobenzene production is expected to continue (EPA 1980c, 1985; Hughes et al. 1983; USITC 1988).

Chlorobenzene is produced by three United States chemical companies: Monsanto Chemical Company, Sauget, Illinois; PPG Industries, Inc., Natrium, West Virginia; and Standard Chlorine Chemical Co., Inc., Delaware City, Delaware. Production capacity for chlorobenzene at these plants has remained constant since 1985 although it appears that actual production has declined slightly during that period (Hughes et al. 1983; SRI 1985, 1986, 1987, 1988; USITC 1988).

Chlorobenzene is produced commercially by the chlorination of benzene in the presence of a catalyst (e.g., ferric chloride, aluminum chloride, or stannic chloride). This process yields a mixture of chlorobenzene, dichlorobenzenes, and higher analogs which are distilled and crystallized to obtain pure products (EPA 1985a; Hughes et al. 1983).

4.2 IMPORT

Import and export data for chlorobenzene are not readily available. Estimates indicate that for the last ten years, both imports and exports have been negligible (Hughes et al. 1983).

4.3 USE

The current primary uses of chlorobenzene are as a solvent for pesticide formulations, diisocyanate manufacture, degreasing automobile parts, and for the production of nitrochlorobenzene. Solvent uses accounted for about 37% of chlorobenzene consumption in the United States in 1981, nitrochlorobenzene production for 33%, and diphenyl oxide and phenylphenol production for 16% of consumption. Chlorobenzene

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

is also used in silicone resin production and as an intermediate in the synthesis of other halogenated organics. The past major use of chlorobenzene was as an intermediate in phenol and DDT production (Hughes et al. 1983).

4.4 DISPOSAL

Because chlorobenzene is listed as a hazardous substance, disposal of waste chlorobenzene is controlled by a number of federal regulations (see Chapter 7). Spent solvent wastes, which may include chlorobenzene, are prohibited from land disposal, except under specific conditions. Land disposal restrictions (treatment standards) are proposed for other wastes containing chlorobenzene. Wastes containing chlorobenzene may be disposed of by liquid injection, rotary kiln, or fluidized bed incineration (EPA 1988a, 1989b; HSDB 1988). Since chlorobenzene is a volatile compound and is used extensively as a solvent, large quantities are released to the air. Some estimates indicate that 30 to 50% of the annual production of chlorobenzene is released to the atmosphere, while less than 0.1% is found in wastewater and less than 1% is disposed of on land (EPA 1985a).

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Chlorobenzene is used as a solvent and as an intermediate in industry. A portion of that is lost to the environment in water and air discharges. Chlorobenzene adsorbs moderately to soil and is biodegraded comparatively rapidly. With a moderate index of bioaccumulation, chlorobenzene was found in almost every individual tested for it in the United States. The EPA has identified 1,177 NPL sites. Chlorobenzene has been found at 97 of the sites evaluated for the presence of this chemical. As more sites are evaluated by the EPA, the number may change. The frequency of these sites within the United States can be seen in Figure 5-1.

5.2 RELEASES TO THE ENVIRONMENT

5.2.1 Air

The production of chlorobenzene by seven major producers was reported to be 112,000 kkg in 1987. Estimates of environmental releases vary widely. The EPA (1982d) estimated the release of chlorobenzene to be about 200 tons, or 0.2% of production, while Dow Chemical Company estimated that about 50,000 tons, or 30% to 50% of their annual production was released to the air (EPA 1980a).

5.2.2 Water

The principal source of chlorobenzene in water is release from chemical manufacturing facilities. Dow Chemical Company estimated that 0.1% of its annual production enters waters (EPA 1980a). Perry et al. (1979) found chlorobenzene in 6/63 industrial effluent in concentrations up to 100 µg/L. Based on 1,338 samples collected from about 1980 to 1983, the medium concentration of chlorobenzene in waste effluent was < 3 ppb and was detected in 54 samples. The total amount released to the environment was not reported (Staples et al. 1985). Chlorobenzene has been detected in both surface and groundwater samples at hazardous waste sites. Data from the Contract Laboratory Program (CLP) Statistical Database indicate that chlorobenzene occurred in surface water at 13 sites at a geometric mean concentration of 17 ppb in positive samples and in groundwater at 28 sites at a geometric mean concentration of 62 ppb in positive samples (CLPSD 1988). It should be noted that the CLP Statistical Database includes data from both NPL and non-NPL sites.

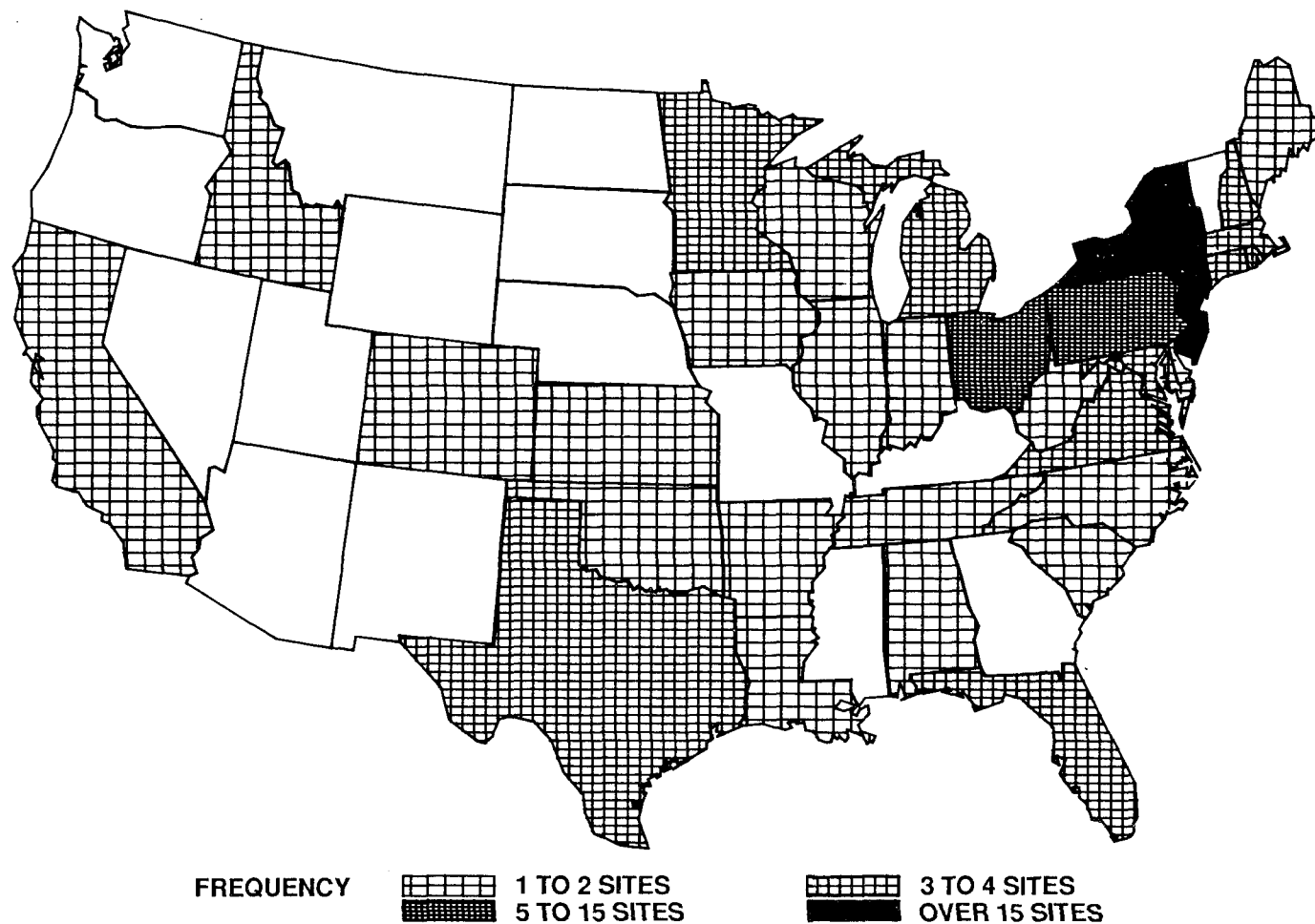


FIGURE 5-1. Frequency of Sites with Chlorobenzene Contamination

5. POTENTIAL FOR HUMAN EXPOSURE

5.2.3 Soil

Chlorobenzene was detected at 34 sites at a geometric mean concentration of 37 ppm in positive soil samples (CLPSD 1988). It should be noted that the CLP Statistical Database includes data from both NPL and non-NPL sites.

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

Chlorobenzene is volatile and has only moderate solubility in water (500 mg/L). Chlorobenzene was observed to evaporate ($\geq 99\%$) from an unaerated aqueous solution in 72 hrs (Garrison and Hill 1972). The air, undoubtedly, plays a large role in the environmental transport and degradation of chlorobenzene, although studies addressing this aspect were not found.

5.3.2 Transformation and Degradation

5.3.2.1 Air

Physical constants for chlorobenzene, especially its vapor pressure and water solubility, indicate that the air is an important and perhaps the dominant medium for the transport and transformation of chlorobenzene. As an aromatic molecule with strong UV-absorption, chlorobenzene has a half-life of 20 to 40 hrs under simulated atmospheric conditions (Dilling et al. 1976). This appears to be confirmed by the large difference between chlorobenzene measurements in urban air (3,000 ng/m³) and in rural air (not detected) in 1982 (Brodzinsky and Singh 1983).

5.3.2.2 Water

Biodegradation in a waste water inoculum was studied by Tabak et al. (1981). Among 57 environmental pollutants tested, chlorobenzene at 5 mg/L was among the more rapidly biodegraded substances with 89% degradation in a week and 100% after adaptation. Biodegradation is therefore a major degradation process in oxygenated waters while evaporation will play an additional role in surface waters.

5.3.2.3 Soil

Biodegradation of chlorobenzene is rapid, leaving no detectable residues after 1 or 2 weeks. Adaptation is also rapid (Tabak et al. 1981).

5. POTENTIAL FOR HUMAN EXPOSURE

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

Air samples at 56 localities in the United States in 1982 had mean chlorobenzene concentrations of about 3,000 ng/m³; the highest concentrations in urban and suburban areas, at much lower levels at the sites of production, but was not detectable in rural and remote areas (Brodzinsky and Singh 1983). This suggests a substantial contribution to urban air levels by small industry and consumer products but also a short residence time in the air. A study of New Jersey waste sites found similar air levels of chlorobenzene (2,500 ng/m³) (Harkov et al. 1985). However, air levels found by another study done for the United States EPA (Pellizzari 1978a) were an order of magnitude lower, with only the air over a waste site approaching the mean urban concentrations reported above. Ambient air outside homes of "Old Love Canal" (Niagara Falls, New York) contained chlorobenzene ranging from not detectable (4 sites) to traces (4 sites) and 120 ng/m³ (1 site) (Barkley et al. 1980).

5.4.2 Water

Chlorobenzene, along with other chlorinated chemicals, was found in United States' rivers at levels up to and exceeding 10,000 ng/L (Shackelford and Keith 1976; Sheldon and Hites 1978). Private wells near a hazardous waste site contained as much as 41 µg/L (Clark 1982) and tap water at Love Canal contained 10 to 60 ng/L of chlorobenzene (Barkley et al. 1980).

Chlorobenzene contamination of industrial waste waters up to and exceeding 100 µg/L was found in 6/63 samples (Perry et al. 1979) and in 147/31,194 samples with a mean concentration of 667 µg/L (EPA 1985a).

5.4.3 Soil

Staples et al. (1985) reported that the median concentration of chlorobenzene in the United States was estimated to be less than 5 ppb dry sediments. In 347 measurements recorded in the STORET data base, 2% of the samples contained detectable concentrations of chlorobenzene.

5.4.4 Other Media

No studies of chlorobenzene in food or other media are available.

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Chlorobenzene was found in 98/100 human adipose tissue samples from all regions of the United States at levels ranging from 1 to 9 ng/g (Stanley 1986). At Love Canal, Niagara Falls, chlorobenzene could be

5. POTENTIAL FOR HUMAN EXPOSURE

detected in the breath of one of nine people evaluated for exposure and in the urine of six of nine persons at 20 to 120 ng/L (Barkley et al. 1980).

Personal sampling at chemical companies (Cohen et al. 1981) indicated that chlorobenzene levels (up to 18 mg/m³) in work place air did not exceed the current federal level (350 mg/m³).

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Occupational settings provide the greatest potential for high exposures to chlorobenzene. Since chlorobenzene is a volatile compound and is used extensively as a solvent, large quantities may be released to the workplace air. Other populations who might be exposed include persons living near industrial facilities where chlorobenzene emissions are not properly controlled.

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 chlorobenzene 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 chlorobenzene.

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. Physical and chemical properties of chlorobenzene have been thoroughly measured.

Production, Use, Release, and Disposal. Data indicate that chlorobenzene production has declined dramatically over the past two decades, but current quantitative data on use (especially solvent uses) and disposal practices would be helpful in evaluating the effect of current industrial practices on environmental levels of chlorobenzene.

5. POTENTIAL FOR HUMAN EXPOSURE

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. Information on biodegradation in soil under aerobic conditions exists, but degradation products were not identified. Anaerobic biodegradation, as might occur in river bottoms and in Superfund sites, has not been studied and would be valuable. Emissions from waste lagoons have been modelled and measured in bench-top experiments and are measured as part of many Superfund Remedial Investigation/Feasibility studies, but those were not located.

Bioavailability from Environmental Media. Chlorobenzene is absorbed primarily following inhalation of contaminated air. There is also some potential for exposure from water and soil. Chlorobenzene has been detected at low levels in surface, ground, and drinking water, but no information was found on levels in food. Since chlorobenzene binds tightly to soil particles, skin contact with or ingestion of contaminated soil may be an important source of exposure, particularly in children living near hazardous waste sites. Additional studies would be useful to determine if soil-bound chlorobenzene is bioavailable.

Food Chain Bioaccumulation. No information is available regarding biomagnification within aquatic or terrestrial food chains. Additional studies would be useful in assessing potential for human exposure to chlorobenzene.

Exposure Levels in Environmental Media. There are studies on concentrations of chlorobenzene in air and water, but many of the samples measured had low levels or did not have detectable levels. Additional studies using more sensitive analytical methods would be useful.

Exposure Levels in Humans. Studies have been conducted measuring chlorobenzene levels in drinking water and air (including indoor air). Conflicting data on chlorobenzene air levels point to a need for confirmation and, possibly, validation of analytical methods. Less conflicting estimates of environmental emissions are the prerequisite for any attempt to prioritize control measures.

Exposure Registries. No exposure registries for chlorobenzene were located. This compound is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry.

5. POTENTIAL FOR HUMAN EXPOSURE

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

Studies on the migration and in situ biodegradation of chlorobenzene in hazardous waste sites are being conducted in the laboratory of Perry McCarty and others.

As part of the Third National Health and Nutrition Evaluation Survey (NHANES III), the Environmental Health Laboratory Sciences Division of the Center for Environmental Health and Injury Control, Centers for Disease Control, will be analyzing human blood samples for chlorobenzene and other volatile organic compounds. 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 chlorobenzene 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 chlorobenzene. 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 chlorobenzene in environmental samples are 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

Many of the considerations regarding the analysis of halogenated alkanes and alkenes in biological samples (Fishbein 1985) similarly apply to the determination of chlorobenzene in these samples. Although most environmentally significant halogenated alkanes and alkenes have boiling points below 100°C, chlorobenzene is relatively less volatile with a boiling point of 132°C. The water solubility (25°C) of chlorobenzene is 472 mg/L, which is lower than the water solubilities of most environmentally and toxicologically significant halogenated alkanes and alkenes. Along with many halogenated alkanes and alkenes, chlorobenzene is classified as a purgeable species for purge-and-trap analysis (EPA 1982a, 1982b). Therefore, many of the approaches and methods used for the determination of halogenated alkanes and alkenes in biological samples are applicable to chlorobenzene, although they have not been validated as a sampling method.

Because chlorobenzene is volatile, has limited water solubility, and has a moderate affinity for lipid tissue, chlorobenzene is easily lost from biological samples. Appropriate care must be exercised in handling and storing such samples for analysis of chlorobenzene.

The methods that generally are used to remove volatile organic chemicals (VOCs) from biological samples for analysis are applicable to chlorobenzene. These include headspace analysis, purge-and-trap (gas stripping) collection from aqueous solutions or slurry samples, solvent extraction, and direct collection on resins. Headspace analysis offers speed, simplicity, and good reproducibility for a particular type of

6. ANALYTICAL METHODS

sample. However, partitioning of the analyte between the headspace and the sample matrix is dependent upon the nature of the matrix and must be determined separately for different kinds of matrices (Walters 1986).

Purge-and-trap collection is well suited to biological samples that are soluble in water and is readily adapted to biological samples from techniques that have been developed for the analysis of halocarbons such as chlorobenzene in water and wastewater. For water-insoluble materials, the purge-and-trap approach is complicated by the uncertainty of partitioning the analyte between sample slurry particles and water.

Homogenization of tissue with the extractant and lysing of cells improves extraction efficiency. When multiple analytes are determined using solvent extraction, selective extraction and loss of low-boiling compounds can cause errors. The commercial availability of highly purified solvents has largely eliminated problems with solvent impurities, although high costs, solvent toxicities, and restrictions on spent solvent disposal must be considered. Directly coupled supercritical fluid extraction-gas chromatography has been used for the determination of polychlorinated biphenyls (Hawthorne 1988) and should work well for the determination of chlorobenzene in biological samples.

Analytical methods for the determination of chlorobenzene in biological samples are given in Table 6-1.

6.2 ENVIRONMENTAL SAMPLES

Purgeable organic compounds such as chlorobenzene can be determined in water by the purge-and-trap technique. This method consists of bubbling inert gas through a small volume of the sample and collecting the vapor in a trap packed with sorbent. The analytes are then removed from the trap by heating it and backflushing the analytes onto a gas chromatographic column. The two materials most widely used for adsorption and thermal desorption of volatile organic compounds collected by the purge-and-trap technique are Carbotrap® consisting of graphitized carbon black, and Tenax® a porous polymer of 2,6-diphenyl-pphenylene oxide (Fabbri et al. 1987).

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

Sample Matrix	Sample Preparation	Analytical Method	Sample Detection Limit	Accuracy	Reference
Breath, blood, urine	Breath collected on Tenax, blood and urine subjected to purge-and-trap, concentrated on cryogenic capillary trap, thermally removed to GC.	GC/MS	No data	No data	Barkley et al. 1980
Fish tissue	Grind with sodium sulfate, extract with hexane/acetone	GC/ECD	No data	No data	Oliver and Nicol 1982a, 1982b
Adipose tissue	Extraction, bulk lipid removal, Florisil fractionation	HRGC/MS	0.1 µg/g	No data	Mack and Stanley 1984
Adipose tissue	Heated dynamic headspace purge-and-trap	HRGC/MS	2 ng/g	No data	Stanley 1986
Biofluids ^a	Dilute with water, sealed vial, collection of headspace vapors	GC/ECD	No data	No data	Suitheimer et al. 1982
Blood, tissue	Macerate tissue in water, warm blood or tissue, pass inert gas through, trap on Tenax, thermal desorption	GC/MS	3 ng/mL blood 6 ng/g tissue	No data	Pellizzari et al. 1985

^a Among the compounds for which this method was used are benzene, m-xylene, carbon tetrachloride and chloroform. The method can be adapted to chlorobenzene although the procedures do not list this compound specifically as an analyte.

GC = gas chromatography; MS = mass spectrometry; ECD = electron capture detector; HRGC = High Resolution Gas Chromatography; µg/g = microgram per gram; ng/g = nanogram per gram.

6. ANALYTICAL METHODS

The introduction of capillary column chromatography has markedly improved both the sensitivity and resolution of gas chromatographic analysis of environmental samples such as chlorobenzene. Because of the very small quantities of sample required, capillary column chromatography has made sample delivery more difficult. One of the more promising approaches to sample introduction using capillary columns with purge-and-trap collection is the use of cryofocussing. Basically, this procedure consists of collecting purged analyte on a short section of the capillary column cooled to a low temperature (e.g., -100°C) temperature, followed by heating and backflushing of the sample onto the analytical column. Chlorobenzene has been determined in water by this method (Washall and Wampler 1988).

Chlorobenzene can be removed from water by adsorption on synthetic polymers contained in cartridges, followed by thermal desorption of analyte (Pankow et al. 1988). Among the products used for this purpose are Tenax-GC[®] and Tenax-TA[®].

Analytical methods for the determination of chlorobenzene 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 chlorobenzene 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 chlorobenzene.

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.

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

Sample Matrix	Sample Preparation	Analytical Method	Sample Detection Limit	Accuracy	References
Air	Collect on Tenax GC, thermal desorption, cryogenic collection on a capillary trap, thermal transfer to GC	GC/MS	0.47 parts per trillion	No data	Krost et al. 1982
Air	Coconut shell charcoal sorption, carbon disulfide desorption	GC/FID	10 µg per sample	No data	NIOSH 1984
Water	Purge-and-trap	GC/HSD	0.25 µg/L	No data	EPA 1982a
Water	Purge-and-trap	GC/MS	0.2 µg/L	No data	EPA 1982b
Water	Purge-and-trap	GC/MS	6.0 µg/L	No data	EPA 1982c
Water	Sorption on small dead volume Tenax cartridges, thermal desorption	HRGC/MS	No data	No data	Pankow et al. 1988
Contaminated soil	Purge-and-trap	GC/HSD	300 µg/kg	No data	EPA 1986a
Wastes (non-water miscible) and soil	Purge-and-trap	GC/MS	250 µg/kg	No data	EPA 1986b
Wastes (water miscible and non-water miscible) and soil	Purge-and-trap	GC/MS	250-2500 µg/kg	No data	EPA 1986c

GC = gas chromatography; MS = mass spectrometry; FID = flame ionization detector; µg = microgram; HSD = halide specific detector; L = liter; HRGC = high resolution gas chromatography; kg = kilogram.

6. ANALYTICAL METHODS

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect.

Excellent sensitive and selective methods are available for the qualitative and quantitative measurement of the parent compound, chlorobenzene after it is separated from its sample matrix. Methods need to be validated for chlorobenzene.

Further studies on the transfer analytes that have been purged or extracted from a biological or environmental sample quantitatively and in a narrow band to the capillary GC would better characterize exposure. Improvements in cryofocussing of VOC analytes for capillary GC determination of VOCs (Washall and Wampler 1988) should improve sensitivity for the determination of chlorobenzene.

Metabolites of chlorobenzene in biological materials cannot be determined in routine practice because of the lack of standard methods for measuring these metabolites. Further research on supercritical fluid (SCF) extraction holds great promise for meeting the goals of quantitative, rapid, easily performed, low cost, and safe procedures for the determination of nonpolar organic analytes such as chlorobenzene in biological samples.

Central nervous system, liver, and kidney injuries are characteristic biomarkers for effects of chlorobenzene intoxication. Since the effects are indicative of exposure to many other toxicants, methods are needed for more specific biomarkers.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Methods for determining the parent compound, chlorobenzene, in water, air, and waste samples with excellent selectivity and sensitivity are highly developed, thus the database in this area is good and undergoing constant improvement.

Means to measure organohalides such as chlorobenzene in situ in water and other environmental media could contribute to environmental studies of this compound.

Degradation products of chlorobenzene in environmental media are difficult to determine. This difficulty is not so much an analytical problem as it is a problem of knowing the fundamental environmental chemistry of these compounds in water, soil, air, and biological systems.

6. ANALYTICAL METHODS

6.3.2 On-going Studies

Research is ongoing to develop a "Master Analytical Scheme" for organic compounds in water (Michael et al. 1988), which includes chlorobenzene as an analyte. 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 semivolatile compounds and some compounds that are only "semi-soluble" in water, as well as volatile compounds (bp < 150°C).

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 chlorobenzene and other volatile organic compounds in blood. These methods use purge and trap and magnetic mass sector spectrometry which gives detection limits in the low parts per trillion range.

7. REGULATIONS AND ADVISORIES

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

7. REGULATIONS AND ADVISORIES

TABLE 7-1. Regulations and Guidelines Applicable to Chlorobenzene

Agency	Description	Value	Reference
<u>National</u>			
Regulations:			
a. Air:			
OSHA	PEL TWA	75 ppm (350 mg/m ³)	OSHA 1989 (29 CFR 1910.1000, Table Z-1-A)
b. Water:			
EPA ODW	Monitoring required for unregulated contaminants MCL (Proposed)	NA 0.1 mg/L	EPA 1987a, (40 CFR 141.40) EPA 1989c
EPA OWRS	General permits under NPDES	NA	40 CFR 122, (Appendix D, Table II)
	Criteria and Standards for the NPDES	NA	40 CFR 125
	General pretreatment regulations for existing and new sources of pollution	NA	40 CFR 403
	Hazardous substance	NA	EPA 1985b, (40 CFR 116)
	Reportable quantity	100 lb	40 CFR 117.3
c. Nonspecific media:			
EPA OERR	Reportable quantity	100 lb	EPA 1985b, (40 CFR 302.4)
EPA OSW	Hazardous waste constituent (Appendix VIII)	NA	EPA 1980b, (40 CFR 261)
	Groundwater monitoring list (Appendix IX)	NA	EPA 1987b, (40 CFR 264)
	Restriction on land disposal	NA	EPA 1988b, 1989c, (40 CFR 268)
EPA OTS	Preliminary assessment information rule	NA	EPA 1982d, (40 CFR 712)
	Health and safety data reporting rule	NA	EPA 1988c, (40 CFR 716.120)
	Final test rule	NA	EPA 1986e, (40 CFR 799.105)
	Toxic chemical release reporting	NA	EPA 1988c, (40 CFR 372)
Guidelines:			
a. Air:			
ACGIH	TLV TWA	75 ppm (350 mg/m ³)	ACGIH 1986
NIOSH	IDLH	2400 ppm	NIOSH 1985
b. Water:			
EPA ODW	MCLG (proposed)	0.1 mg/L	EPA 1989c
	Health advisories		
	1 day	2 mg/L	EPA 1987c
	10 days	2 mg/L	

7. REGULATIONS AND ADVISORIES

TABLE 7-1 - (Continued)

Agency	Description	Value	Reference
	Longer term		
	child	2 mg/L	
	adult	7 mg/L	
	Lifetime	100 mg/L	
EPA OWRS	Ambient water quality criteria Ingesting water and organisms	4.88×10^{-1} mg/L	EPA 1980b
c. Other:			
EPA	Carcinogenic classification Oral Rfd	Group D ^a 2×10^{-2} mg/kg/day	EPA 1987c IRIS 1989
	<u>State</u>		
Regulations:			
a. Air:	Acceptable ambient air concentration		NATICH 1988
	Connecticut	7000 $\mu\text{g}/\text{m}^3$ (8 hr)	
	Florida-Tampa	3500 $\mu\text{g}/\text{m}^3$ (8 hr)	
	Massachusetts	6.3 $\mu\text{g}/\text{m}^3$ (24 hr)	
	Nevada	8.333 $\mu\text{g}/\text{m}^3$ (8 hr)	
	New York	1167.0 $\mu\text{g}/\text{m}^3$ (1 yr)	
	North Carolina	2200 $\mu\text{g}/\text{m}^3$ (24 hr)	
	North Dakota	3500 $\mu\text{g}/\text{m}^3$ (8 hr)	
	Virginia	6000 $\mu\text{g}/\text{m}^3$ (24 hr)	
b. Water:	Drinking water		FSTRAC 1988
	Arizona	60 $\mu\text{g}/\text{L}$	
	California	30 $\mu\text{g}/\text{L}$	
	Kansas	60 $\mu\text{g}/\text{L}$	
	Maine	47 $\mu\text{g}/\text{L}$	
	Minnesota	60 $\mu\text{g}/\text{L}$	
	New Jersey	2 $\mu\text{g}/\text{L}$	
	Vermont	600 $\mu\text{g}/\text{L}$	
	Wisconsin	600 $\mu\text{g}/\text{L}$	

^a Group D: Not classifiable as to human carcinogenicity: Inadequate human and animal evidence of carcinogenicity.

OSHA = Occupational Safety and Health Administration; PEL = Permissible Exposure Limit; TWA = Time-Weighted Average; EPA = Environmental Protection Agency; ODW = Office of Drinking Water; NA = Not Applicable; MCL = Maximum Contaminant Level; OWRS = Office of Water Regulations and Standards; NPDES = National Pollutant Discharge Elimination System; 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; MCLG = Maximum Contaminant Level Goal; Rfd = Reference dose.

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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.

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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) (LC₅₀) -- 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) (LD₅₀) -- The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time(₅₀) (LT₅₀) -- 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.

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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 $\mu\text{g/L}$ for water, mg/kg/day for food, and $\mu\text{g/m}^3$ for air).

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

Reportable Quantity (RQ) -- The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are: (1) 1 lb or greater or (2) for selected substances, an amount established by

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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 (TD₅₀) -- 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

APPENDIX

PEER REVIEW

A peer review panel was assembled for chlorobenzene. The panel consisted of the following members: Dr. David Jollow, Professor in the Department of Pharmacology, Medical University of South Carolina, Charleston, South Carolina; Dr. Henry Peters, Professor in the Department of Neurology, University of Wisconsin Clinical Science Center, Madison, Wisconsin; Dr. Jay B. Silkworth, Research Scientist, Wadsworth Center Labs, New York Department of Health, Albany, New York; Dr. Frank Lu, Private Toxicology Consultant, Miami, Florida; Dr. James Pollard, Private Consultant, Las Vegas, Nevada. These experts collectively have knowledge of chlorobenzene'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.

A joint panel of scientists from ATSDR and EPA has 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 for the content of this profile lies with the Agency for Toxic Substances and Disease Registry.

