

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

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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

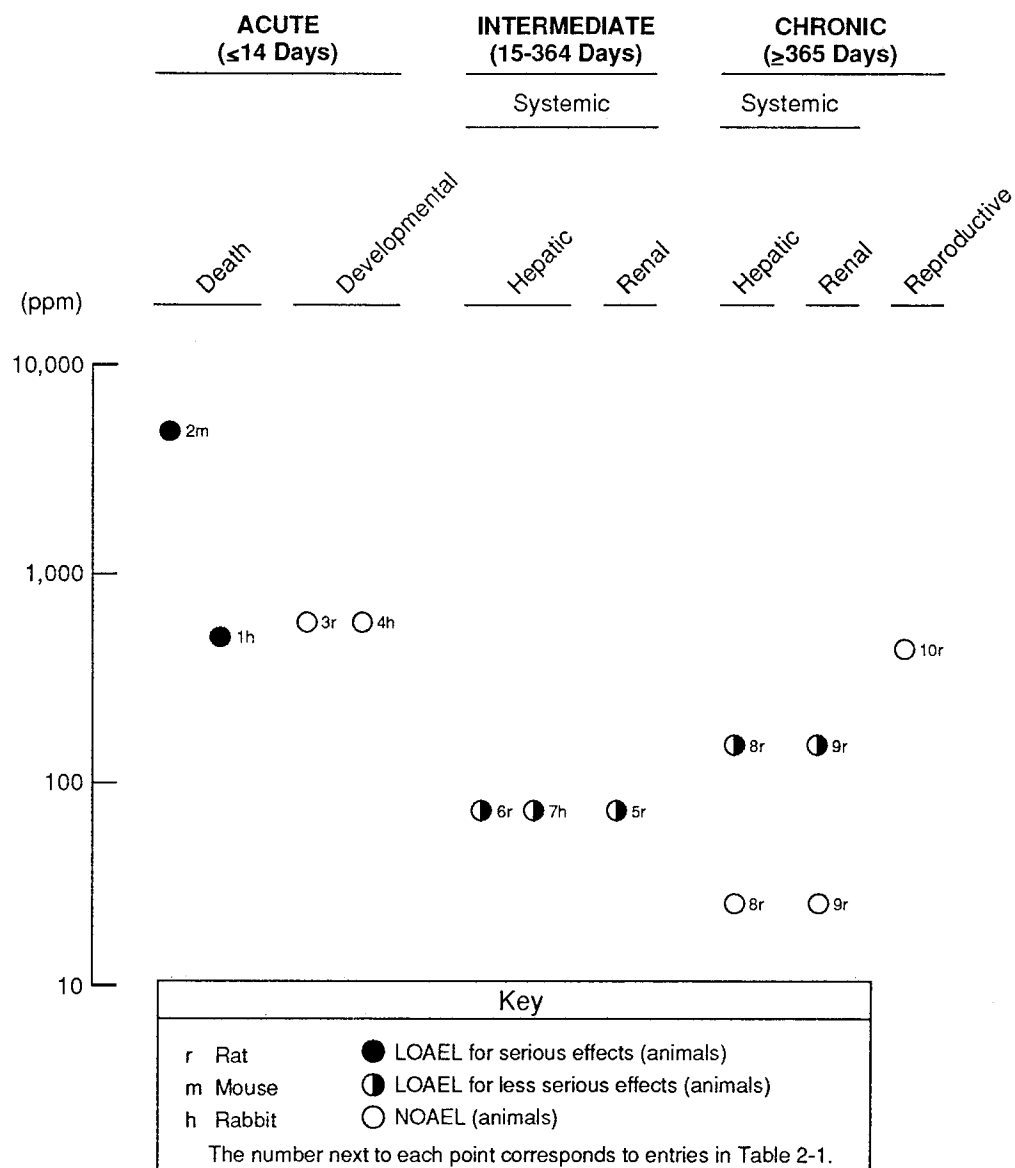


FIGURE 2-1. Levels of Significant Exposure to Chlorobenzene – Inhalation

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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.

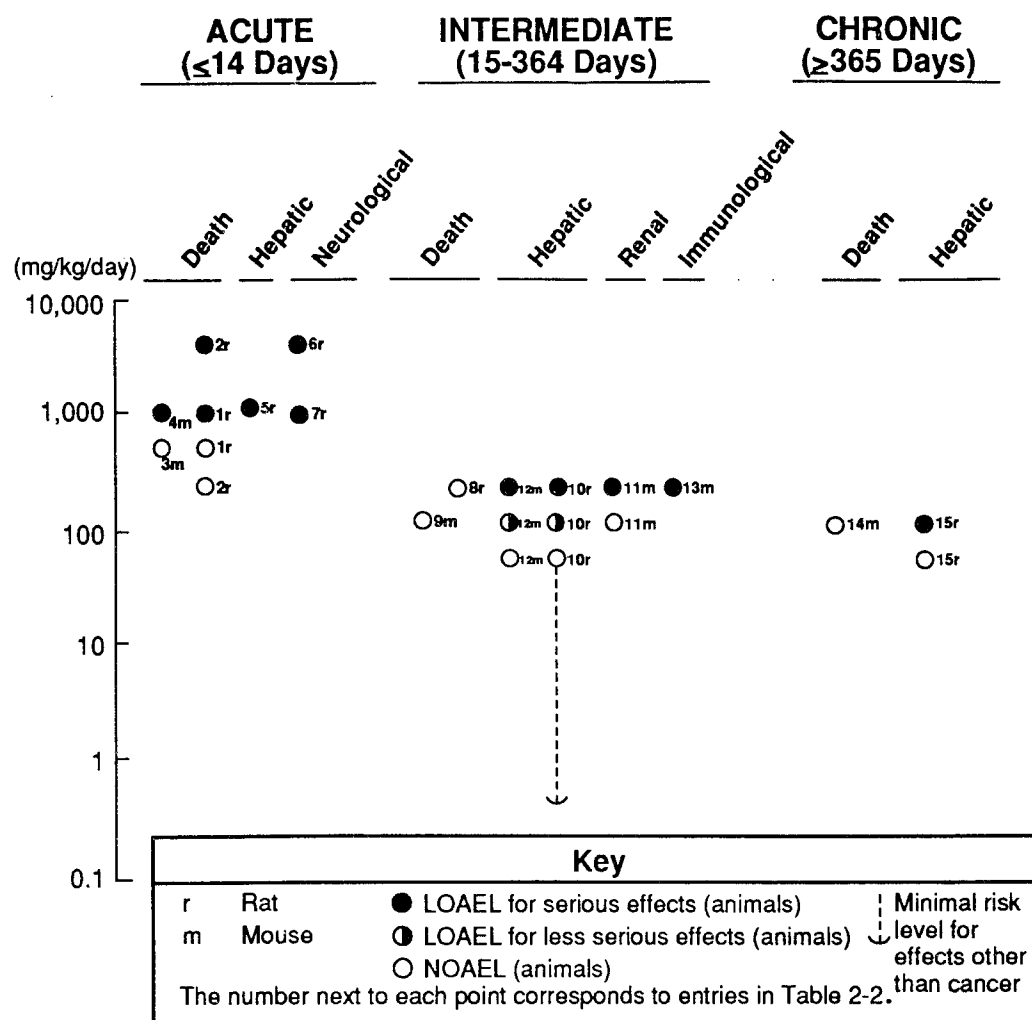


FIGURE 2-2. Levels of Significant Exposure to Chlorobenzene – Oral

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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 (Verschuieren 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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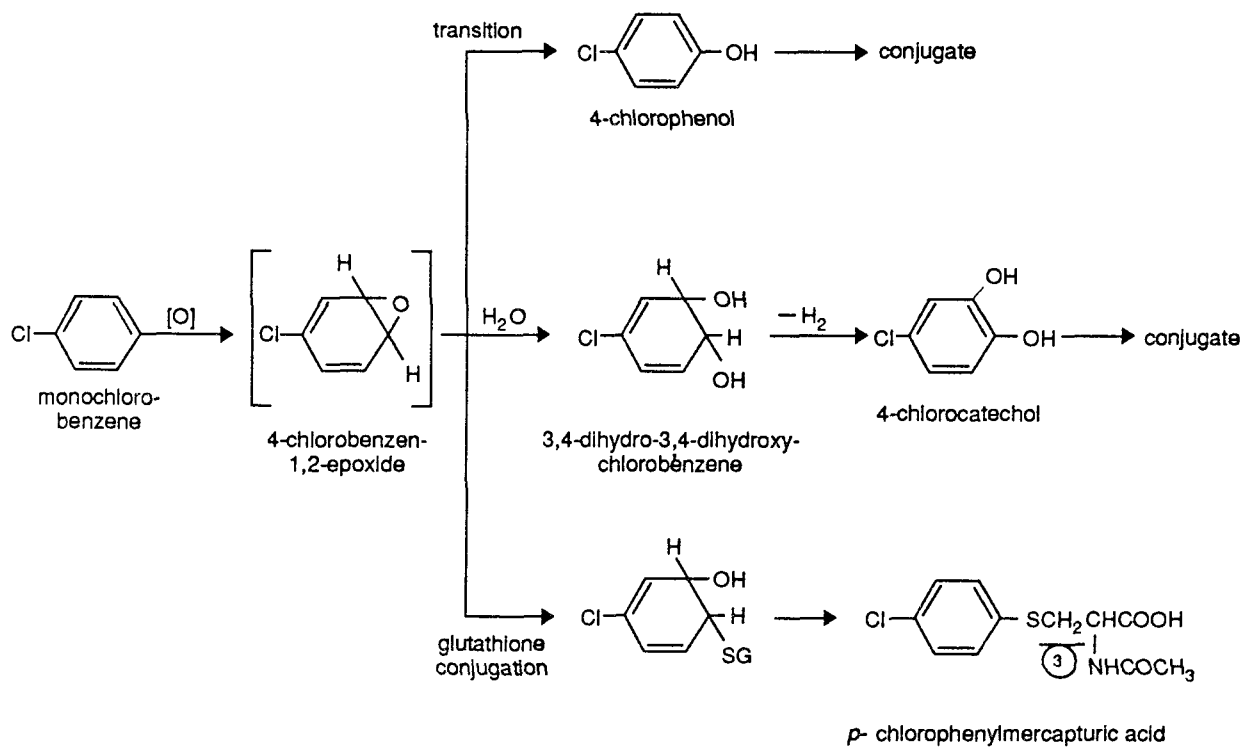


FIGURE 2-3. Metabolic Scheme for Chlorobenzene

Source: Adapted from Ogata and Shimada 1983.

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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

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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.

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	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

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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

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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

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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.

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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.