

CHAPTER 6. ADEQUACY OF THE DATABASE

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

Data needs are defined as substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.1 Information on Health Effects

Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to chlorobenzene that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of chlorobenzene. The number of human and animal studies examining each endpoint is indicated regardless of whether an effect was found and the quality of the study or studies.

6.2 Identification of Data Needs

Missing information in Figure 6-1 should not be interpreted as a “data need.” A data need, as defined in ATSDR’s *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

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Figure 6-1. Summary of Existing Health Effects Studies on Chlorobenzene By Route and Endpoint*

Potential body weight, liver, and kidney effects were the most studied endpoints

The majority of the studies examined inhalation or oral exposure in **animals**; limited data were identified for **humans** (counts represent studies examining endpoint)

| | Inhalation Studies | Oral Studies | Dermal Studies |
|------------------|--------------------|--------------|----------------|
| Body weight | 9 | 8 | — |
| Respiratory | — | — | — |
| Cardiovascular | — | — | — |
| Gastrointestinal | — | — | — |
| Hematological | 3 | 2 | — |
| Musculoskeletal | — | — | — |
| Hepatic | 6 | 1 6 | — |
| Renal | 4 | 6 | — |
| Dermal | — | — | — |
| Ocular | 2 | — | — |
| Endocrine | — | — | — |
| Immunological | — | 2 | — |
| Neurological | 2 2 | 1 | — |
| Reproductive | 1 | — | — |
| Developmental | 4 | 1 | — |
| Other Noncancer | — | — | — |
| Cancer | — | 1 | — |

*Includes studies discussed in Chapter 2; many studies examined more than one endpoint. The number of studies include those finding no effect. No dermal studies in humans or animals were located.

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Acute-Duration MRLs. No information is available on the health effects of acute-duration exposure of humans to chlorobenzene by any route of exposure. Limited studies that evaluated the health effects of acute-duration inhalation or oral exposure to chlorobenzene found adverse effects only at exposure levels that also caused lethality (Monsanto Co. 1977; NTP 1985; Rozenbaum et al. 1947; Shell Oil Co. 1991). Since data on health effects in humans are not available and animal data are mostly limited to lethality, data are not sufficient to derive acute-duration MRLs. Further studies would be useful to identify target tissues and threshold levels for health effects that may exist.

Intermediate-Duration MRLs. No studies are available in humans on the health effects of intermediate-duration exposure to chlorobenzene by any route. Available animal studies identify the nervous system, liver, and kidneys as targets of chlorobenzene toxicity. Oral data were considered adequate to derive an intermediate-duration oral MRL for chlorobenzene. Additional animal studies could be designed to provide useful information to serve as the basis for deriving an intermediate-duration inhalation MRL for chlorobenzene.

Chronic-Duration MRLs. Limited studies are available on the health effects in humans chronically exposed to chlorobenzene via inhalation and suggest that the 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 exposure. No information is available regarding health effects of chlorobenzene in animals following chronic-duration inhalation exposure. One 2-year oral toxicity and carcinogenicity study of rats gavaged with chlorobenzene at 60 or 120 mg/kg/day reported decreased survival and increased incidences of neoplastic liver lesions at 120 mg/kg/day in the absence of other signs of exposure-related adverse effects (NTP 1985). There were no signs of adverse effects in mice similarly treated at 30 or 60 mg/kg/day (males) or 60 or 120 mg/kg/day (females) (NTP 1985). No nonlethal or nonneoplastic effects were observed in rats or mice following chronic-duration oral exposures at doses resulting in adverse nonneoplastic effects in animals following intermediate-duration exposures. Results from intermediate-duration oral exposure to chlorobenzene indicate that dogs are more sensitive than rats or mice to chlorobenzene-induced adverse liver and kidney effects. The absence of chronic-duration oral data for dogs precludes derivation of a chronic-duration oral MRL for chlorobenzene. A well-designed chronic-duration oral study in dogs could potentially serve as the basis for deriving a chronic-duration oral MRL for chlorobenzene.

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Health Effects.

Hematological Effects. No data were located regarding the potential for chlorobenzene-induced renal effects in humans. Limited animal data are available. One study reported concentration-related effects on RBC parameters (primarily an increase in reticulocyte count) in rats and rabbits repeatedly exposed to chlorobenzene by inhalation (NIOSH 1977). Slight leukopenia and lymphocytosis were reported in mice repeatedly exposed by inhalation; however, limited details were included in the study report (Zub 1978). Additional studies could be designed to evaluate hematological effects in animals exposed to chlorobenzene.

Hepatic Effects. Available information regarding the potential for chlorobenzene-induced hepatic effects in humans is limited to a single case report (Babany et al. 1991; Reygagne et al. 1992). The liver was identified as a target of chlorobenzene toxicity in laboratory animals following inhalation or oral exposure (Monsanto Co. 1967a, 1967b; Nair et al. 1987; NTP 1985). No further animal studies are considered necessary.

Renal Effects. No data were located regarding the potential for chlorobenzene-induced renal effects in humans. The kidney was identified as a target of chlorobenzene toxicity in laboratory animals following inhalation or oral exposure (Monsanto Co. 1967a; Nair et al. 1987; NTP 1985). No further animal studies are considered necessary.

Immunotoxicity. No data were located regarding the potential immunotoxicity of chlorobenzene in humans. Histological examination of organs and tissues of the immunological system in orally-treated rats and mice resulted in some evidence for the immunotoxicity of chlorobenzene (NTP 1985). Immune function tests would provide a better assessment of potential immunotoxic effects.

Neurotoxicity. Limited data in humans indicate that exposure to chlorobenzene via inhalation and oral exposures can result in effects on the nervous system. Results from one acute-duration (30-minute exposure) inhalation study of rats and guinea pigs demonstrate the neurotoxicity of inhaled chlorobenzene at very high concentrations ($\geq 2,990$ ppm) (Shell Oil Co. 1991). Oral studies in animals could be designed to evaluate the potential neurotoxicity of chlorobenzene by this exposure route. However, it is not likely that oral exposure to chlorobenzene would cause neurological effects at environmentally-relevant exposure levels.

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Reproductive Toxicity. No studies were located regarding the potential reproductive toxicity of chlorobenzene in humans. In a 2-generation oral toxicity study of rats (Nair et al. 1987), chlorobenzene gavage exposure of parental males for 18–20 weeks at 450 mg/kg/day resulted in increased incidence of testicular germinal epithelial degeneration, but no evidence of impaired reproductive function. There was no evidence of adverse reproductive effects among chlorobenzene-treated parental females of either generation at doses as high as 450 mg/kg/day. Additional animal studies (including another animal species) could provide additional information regarding the potential for chlorobenzene-induced reproductive effects.

Developmental Toxicity. No data were located regarding the potential developmental toxicity of chlorobenzene in humans. Chlorobenzene did not affect the developing fetus following inhalation exposure of rats or rabbits (John et al. 1984) or oral exposure of rats (Monsanto Co. 1977). Additional studies, particularly in other species, could provide useful information for evaluating the potential of chlorobenzene to induce developmental effects in humans.

Cancer. No studies were found in humans regarding the carcinogenicity of chlorobenzene. Epidemiological studies would be useful to assess potential risk to people who may be occupationally exposed to chlorobenzene or people who live near hazardous waste sites where chlorobenzene may be present. There was no evidence for carcinogenicity in male or female mice or in female rats following oral exposure to chlorobenzene. However, an increased incidence of neoplastic liver nodules was observed in male rats. Based on available information from animal carcinogenicity studies and genotoxicity evaluations, EPA (IRIS 2003) assigned chlorobenzene to group D (not classifiable as to human carcinogenicity). An additional animal study could be designed to further assess the potential carcinogenicity of chlorobenzene. Although available human and animal data have not provided convincing evidence regarding the carcinogenicity of chlorobenzene, additional mechanistic studies should be designed to evaluate possible genotoxic mechanisms of carcinogenicity because chlorobenzene metabolism results in the formation of epoxides that can react with DNA, RNA, and proteins. Any *in vitro* assays should be performed using human microsomes due to interspecies differences in chlorobenzene metabolism.

Epidemiology 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

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occupational exposures in which the nervous system was identified as a target tissue following chronic inhalation of chlorobenzene. Reliable exposure data were not reported. Additional studies that provide quantitative exposure data would be useful in evaluating potential noncancer and cancer risk in humans exposed to chlorobenzene.

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 chlorobenzene vapor 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 located regarding 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.

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. Limited animal data 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. 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.

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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 of 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. Although existing studies regarding toxicokinetics of chlorobenzene in humans are limited, available data 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 PBPK modeling would be useful in determining the most suitable animal model for assessing human risk.

Children's Susceptibility. No data were located to suggest age-related differences in susceptibility to chlorobenzene toxicity. Studies are needed to assess the susceptibility of children to chlorobenzene toxicity and to evaluate potential differences in sensitive endpoints.

Physical and Chemical Properties. Physical and chemical properties of chlorobenzene have been adequately evaluated.

Production, Import/Export, 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.

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.

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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 water, groundwater, drinking water, and 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. There is also potential for inhalation exposure via vapor intrusion from soil and groundwater and during showering.

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 for measuring low levels of chlorobenzene in environmental media.

Exposure Levels in Humans. Chlorobenzene can be measured in blood, urine, and exhaled air. A survey of the general population (NHANES) did not find detectable levels of chlorobenzene in blood samples. Chlorobenzene is used in various occupational settings; however, there are limited biomonitoring data of populations potentially exposed to high levels of chlorobenzene. Additional studies are needed to evaluate occupational populations.

Exposures of Children. No data were located to suggest age-related differences in potential exposure to children. Studies are needed to evaluate potential exposure risks that are unique to children.

Analytical Methods. As noted previously, many environmental samples have undetectable levels of chlorobenzene. Additional studies to evaluate analytical methods with lower detection limits would be useful.

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6.3 Ongoing Studies

No ongoing studies were identified in the National Institutes of Health (NIH) RePORTER (2020) database.