

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 hexachlorobutadiene 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 hexachlorobutadiene.

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

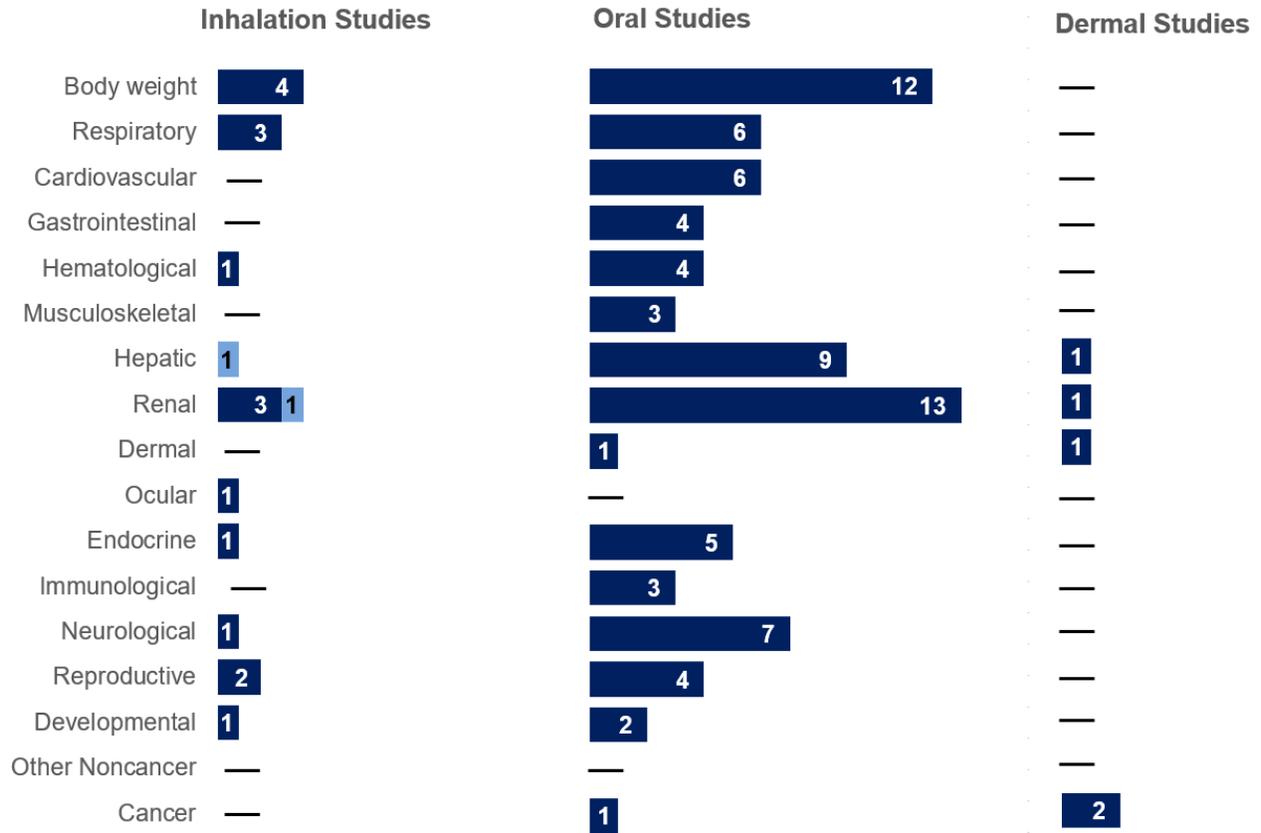
Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to hexachlorobutadiene that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of hexachlorobutadiene. The 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.

As illustrated in Figure 6-1, most of the data on the toxicity of hexachlorobutadiene come from studies in experimental animals. The most commonly examined endpoints were the kidney, body weight, and liver. Two human studies were identified examining potential liver and kidney effects; the exposure route for these studies is presumed to be inhalation. Hexachlorobutadiene toxicity has been evaluated in 24 inhalation, oral, or dermal exposure studies; approximately half of the animal studies were conducted by the oral exposure route.

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

Potential kidney, body weight, and liver effects were the most studied endpoints
 The majority of the studies examined oral exposure in **animals** (versus **humans**)



*Includes studies discussed in Chapter 2; the number of studies include those finding no effect. Many studies examined multiple endpoints.

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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.

Acute-Duration MRLs. Several studies have evaluated the acute toxicity of hexachlorobutadiene following inhalation exposure; however, the database was not considered adequate for derivation on an inhalation MRL due to the lack of repeated exposure studies examining the kidney. The overall database for hexachlorobutadiene suggests that the kidney is one of the most sensitive targets of toxicity. Two studies have examined the kidney, but neither study involved exposure for more than 2 days and the study identifying the lowest LOAEL was only for 4 hours. Additionally, repeated exposure studies examining a wide range of potential targets is needed to establish that the kidney is the most sensitive target and for derivation of an MRL. Three studies evaluated acute oral toxicity and were considered adequate for derivation of an oral MRL with the support of intermediate- and chronic-duration studies. Additional studies are needed to verify that the kidney is the most sensitive target of toxicity following acute-duration exposure.

Intermediate-Duration MRLs. The intermediate-duration inhalation database consists of a general toxicity study and a developmental toxicity study. Given the limited number of endpoints examined in both studies and the lack of study details provided for the general toxicity study, neither study was considered adequate for derivation of an MRL. Additional studies involving exposure durations of at least 13 weeks examining a wide variety of potential endpoints over a range of exposure concentrations are needed to identify the most sensitive targets of toxicity and establish concentration-response relationships that could be used to derive an MRL. A number of comprehensive intermediate-duration oral studies support the derivation of an intermediate-duration MRL. The principal study (NTP 1991) demonstrated a very steep dose-response curve; the incidence of renal lesions went from 1/10 at 0.2 mg/kg/day to 9/10 at 0.5 mg/kg/day. Thus, benchmark dose modeling could not be used to derive the MRL. Studies testing doses between 0.2 and 0.5 mg/kg/day would be useful for establishing dose-response relationships and decreasing the uncertainty in the MRL.

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Chronic-Duration MRLs. No chronic-duration inhalation studies were identified, and studies are needed for derivation of a chronic-duration inhalation MRL. One chronic-duration oral study was identified (Kociba et al. 1977). Although the study examined a wide range of effects at three dose levels, the insufficient reporting of the results, including lack of a description of the renal lesions and incidence data, precluded an independent assessment of the results and the use of the study as the basis of an MRL. An additional chronic oral study is needed for derivation of a chronic-duration oral MRL.

Health Effects.

Respiratory. Acute- and intermediate-duration inhalation studies suggest that hexachlorobutadiene is a respiratory irritant. However, none of the available inhalation studies included histological examination of the respiratory tract; these studies are needed to determine if the respiratory tract is a sensitive target and for comparison of the effect levels for respiratory and renal effects.

Renal. A number of studies have evaluated the renal toxicity of hexachlorobutadiene, particularly following intermediate-duration oral exposure. Available studies have examined potential effects on kidney weight, histology, and renal function. However, very few studies included both histological examination and measurement of renal function parameters; two studies reported histological and function alterations at the same dose level (Harleman and Seinen 1979; Jonker et al. 1993a) and a third study found histological alterations, but no alterations in urinary parameters (Kociba et al. 1977). Additional studies evaluating histology and urinary renal function parameters would be useful to understand the toxicity of hexachlorobutadiene and to assess whether renal function is affected at lower doses than those resulting in histological alterations.

Dermal. There are limited data on the dermal toxicity of hexachlorobutadiene. In a lethality study, hepatic, renal, and dermal effects were observed at the lowest dose tested. Additional studies are needed to establish the most sensitive endpoint following repeated exposure to lower doses.

Immunotoxicity. The potential of hexachlorobutadiene to impair immune function has not been evaluated following inhalation, oral, or dermal exposure, although studies have conducted histological examinations of immune tissues. An *in vitro* study did find inhibition of B or

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T lymphocyte mitogenesis. Whether similar effects would occur following *in vivo* exposure is not known and future studies should include examination of immune function.

Cancer. Information on the carcinogenic potential of hexachlorobutadiene is limited to a chronic oral and dermal studies and a dermal initiation/promotion study. The oral rat study (Kociba et al. 1977) reported increases in the total number of renal neoplasms. Additional studies in another species is needed to confirm these results and to decrease the uncertainty in the carcinogenicity assessment.

Epidemiology and Human Dosimetry Studies. There are limited epidemiology data available for hexachlorobutadiene. An occupational exposure study reported alterations in serum bile acids in chronically exposed workers (Driscoll et al. 1992), although interpretation of the results is limited by potential exposure to other hepatotoxic chemicals. A second study found some indications of altered renal function in residents living in homes with elevated hexachlorobutadiene levels (Staples et al. 2003). Experimental animal studies consistently demonstrated that the kidney is the most sensitive target of toxicity. Well-conducted epidemiological studies are needed to determine if similar patterns of damage occur in humans.

Biomarkers of Exposure and Effect. There is no single biological indicator of exposure to hexachlorobutadiene. Various tests of renal function and biochemical changes associated with renal damage may be measured to detect effects resulting from short-term, intermediate, and long-term exposure. Because similar effects can also occur following exposure to other substances, these tests are not specific for hexachlorobutadiene exposure. Although hexachlorobutadiene and its metabolites are excreted in urine, the metabolism of the compound has not been characterized in humans. Additional tests addressing the dose-response relationship between hexachlorobutadiene excretion in breath and the excretion of sulfur-containing metabolites in urine would prove valuable.

Absorption, Distribution, Metabolism, and Excretion. Data are available on the toxicokinetics of hexachlorobutadiene in animals by the oral route, but not in humans. There are no data in humans or animals on exposures to hexachlorobutadiene by the inhalation or dermal routes. Because of the key role of the liver in producing the metabolites that are responsible for the nephrotoxicity of this compound, knowledge of the toxicokinetics of inhalation and dermal exposures would be valuable. Oral studies reported the presence of the enzymes responsible for the glutathione conjugation reaction and the subsequent formation of derivatives in the liver, intestines, and kidney. It is not known at this time how

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hexachlorobutadiene is distributed and metabolized by inhalation and dermal routes. It is postulated that distribution and metabolism by these routes would be similar to that for the oral route.

Comparative Toxicokinetics. There are no data on metabolism of hexachlorobutadiene in humans. On the other hand, toxic metabolites and proposed mechanisms of renal toxicity have been evaluated in animals employing both *in vivo* and *in vitro* test systems (Dekant et al. 1990; Schnellmann et al. 1987). It is not known if similar metabolic pathways and metabolites occur in humans.

Children's Susceptibility. A study in rats found that weanlings were much more sensitive to the lethality of orally administered hexachlorobutadiene than adults (Kociba et al. 1977). However, a study examining renal toxicity did not find differences in the response to injected hexachlorobutadiene in rats aged 1–12 months (Zanetti et al. 2010). More information is needed to determine if children would be more susceptible to hexachlorobutadiene toxicity than adults or if there would be differences in target tissues.

Physical and Chemical Properties. The physical and chemical properties of hexachlorobutadiene are sufficient to make estimations on its fate in the environment. No data regarding the odor threshold of hexachlorobutadiene in water were located.

Production, Import/Export, Use, Release, and Disposal. Hexachlorobutadiene is not produced for commercial purposes in the United States; however, small amounts are imported from Germany. Hexachlorobutadiene is mainly produced as a byproduct of chlorinated hydrocarbon synthesis and is a primary component of "hex-wastes" (EPA 1982a). Its uses as a pesticide and fumigant have been discontinued. Hexachlorobutadiene is disposed chiefly by incineration, and to a lesser extent by deep well injection and landfill operations (EPA 1982a). More recent production and release data would be helpful in estimating human exposure to hexachlorobutadiene.

Environmental Fate. Much of the environmental fate information on hexachlorobutadiene consists of modeling based on its physical and chemical properties and its similarity to related compounds. Further studies that determine the extent to which hexachlorobutadiene volatilizes from surface waters and soils, and the effects of organic-carbon content on this process would be helpful. Studies that experimentally determine the specific reactions and rates that drive the degradation of hexachlorobutadiene in air, water, and soil would be valuable. Data are lacking on hexachlorobutadiene adsorption to soil or its

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biodegradation in this medium. More information on the fate of the compound in soil would be useful since this medium may be a pathway of exposure for populations living near emission sources.

Bioavailability from Environmental Media. Toxicity studies in animals indicate that absorption of hexachlorobutadiene through the gastrointestinal tract, respiratory tract, and skin can occur. Studies that identify the relationship between absorption and the matrix of soils, sediments, and foods would be useful in establishing whether or not absorption is significantly affected by such factors.

Food Chain Bioaccumulation. BCFs have been determined for algae, shellfish, and fish and exhibit a wide range (29–17,000) (EPA 1976a; Oliver and Niimi 1983; Pearson and McConnell 1975). This wide range may be explained, in part, by species differences in metabolism or differences in concentrations tested. Studies also indicate that hexachlorobutadiene preferentially accumulates in the livers of fish. Further studies that might explain the wide range of BCF values would be helpful. No information was located regarding the bioaccumulation of hexachlorobutadiene in plants or aquatic organisms. More information is needed to determine the importance of terrestrial/aquatic food chain bioaccumulation as a potential human exposure pathway.

Exposure Levels in Environmental Media. Data are available on the occurrence of hexachlorobutadiene in air, water, and foodstuff. The majority of the monitoring data on hexachlorobutadiene are outdated, and therefore, more recent information on the levels typically found in the environment would allow for more accurate estimation of human exposures, and could also serve to indicate time-dependent trends when compared with older data. No data were located regarding the occurrence of hexachlorobutadiene in groundwater or soil. Reliable monitoring data for the levels of hexachlorobutadiene in contaminated media at hazardous waste sites are also needed to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. Hexachlorobutadiene has been detected in human adipose tissues and blood (Bristol et al. 1982; Mes et al. 1985). However, biomonitoring data are limited and hexachlorobutadiene has not been included in the National Report on Human Exposure to Environmental Chemicals (CDC 2018). Studies that establish a correlation between exposure levels in environmental media and the resulting levels in human tissues and excreta would be valuable in predicting exposures and corresponding health risks in humans who live at or near hazardous waste sites and who are likely to be exposed to hexachlorobutadiene.

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Exposures of Children. No data specifically measuring exposure levels in children were located. General population monitoring studies should include an assessment on whether children may be exposed to higher levels than adults.

Analytical Methods. Hexachlorobutadiene can be measured in human blood and adipose tissue. No hexachlorobutadiene was detected in blood from controls or residents near a hazardous waste site (Bristol et al. 1982), indicating that the method was not sensitive enough to measure background levels of hexachlorobutadiene in the general population. It is likely that this method would be sensitive enough to measure levels at which biological effects occur. Hexachlorobutadiene was detected in adipose tissue of victims of accidental and nonaccidental deaths, with about twice as much in accident than nonaccident victims (Mes et al. 1985). This indicates that the gas chromatography/electron capture detection (GC/ECD) and GC/mass spectrometry (MS) method is sensitive enough to measure background levels of hexachlorobutadiene in the general population as well as levels at which biological effects occur.

Existing methods for analysis of air and water appear to be sufficiently sensitive, specific, and reliable to measure background levels in the environment. Matrix interference and contamination by co-eluting chemicals may limit the sensitivity and specificity of methods for analysis of hexachlorobutadiene in soil and solid waste. Development of analytical methods specific for hexachlorobutadiene could provide a rapid, inexpensive, and sensitive method for detecting hexachlorobutadiene in environmental samples.

6.3 ONGOING STUDIES

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