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 pentachlorophenol 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 pentachlorophenol.

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

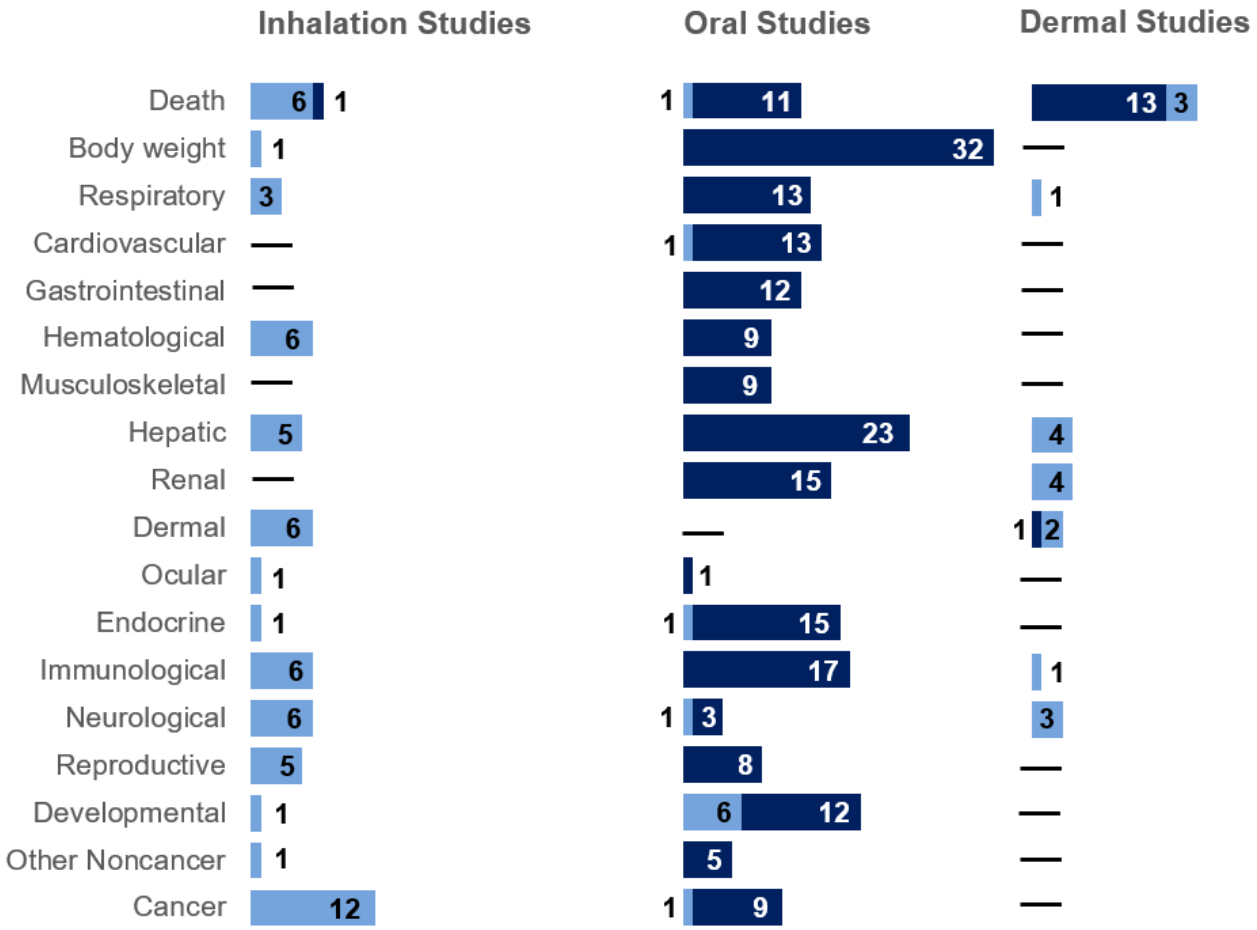
Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to pentachlorophenol that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of pentachlorophenol. The number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

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

Potential body weight, hepatic, and immunological 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.

Acute-Duration MRLs. Information regarding health effects in humans following acute inhalation exposure are limited to case reports of individuals exposed to pentachlorophenol dust (Gray et al. 1985; Hassan et al. 1985; Rugman and Cosstick 1990). A number of effects have been reported, but the case reports provided limited exposure information. Studies in animals are limited to a lethality study in rats (Hoben et al. 1976b). The acute inhalation database was not considered adequate for MRL derivation. Inhalation studies evaluating a range of potential health effects, including sensitive targets identified in oral exposure studies (liver and developmental endpoints) and neurotoxicity, which was found in human inhalation case reports, would be useful for identifying the critical targets following inhalation exposure and establishing concentration-response relationships. Although a small number of studies have evaluated the acute oral toxicity of pentachlorophenol, the database was considered adequate to derive an acute-duration oral MRL. Additionally, studies evaluating a wide range of endpoints would support the identification of developmental toxicity as the most sensitive endpoint.

Intermediate-Duration MRLs. No intermediate-duration inhalation studies were identified for humans or laboratory animals. Studies evaluating a wide range of potential endpoints, including liver and developmental endpoints, which were sensitive targets following oral exposure, are needed to identify the most sensitive targets of toxicity and establish concentration-response relationships. A number of studies in laboratory animals have evaluated the oral toxicity of pentachlorophenol following intermediate-duration exposure. These studies identified hepatotoxicity and developmental toxicity as the sensitive endpoints. An intermediate-duration oral MRL was not derived because an MRL based on the available data would have been higher than the acute-duration oral MRL.

Chronic-Duration MRLs. A number of epidemiological studies have evaluated the chronic toxicity of inhaled pentachlorophenol. The studies identified a number of targets of toxicity including respiratory, hepatic, hematological, dermal, and developmental effects. These studies could not be used to derive a chronic-duration inhalation MRL because the studies provided limited, if any, exposure information and frequently involved co-exposure to other chemicals. No chronic-duration inhalation laboratory animal studies were identified. Oral exposure studies in laboratory animal studies examining a wide range of endpoints including endpoints identified in epidemiological studies are needed to identify the most sensitive targets of exposure and establish concentration-response relationships. The available studies in rats, mice, and dogs were considered adequate for identifying a sensitive target of toxicity (liver) and for deriving a chronic-duration oral MRL. The intermediate-duration oral studies provide suggestive evidence that contaminants found in technical-grade pentachlorophenol may influence the hepatoxic effects observed at low doses. The chronic MRL is based on a dog study utilizing technical-grade

pentachlorophenol. Additional studies that compare the hepatotoxicity of pure pentachlorophenol to technical-grade pentachlorophenol would add support to the MRL.

Health Effects.

Immunological. Immunological effects have been observed in epidemiological studies (Colosio et al. 1993b; Daniel et al. 1995;Gerhard et al. 1991; McConnachie and Zahalsky 1991) and in laboratory animals exposed to technical-grade pentachlorophenol (Holsapple et al. 1987; Kerkvliet et al. 1982, 1985a, 1985b; NTP 1989; White and Anderson 1985). Most studies of pure pentachlorophenol did not find immunological effects (Kerkvliet et al. 1982, 1985a; NTP 1989), suggesting that the immune effects were due to the contaminants rather than pentachlorophenol. However, two studies of pure pentachlorophenol did find immune alteration (Blakley et al. 1998; Chen et al. 2013a). Additional immune studies comparing the effects observed following exposure to pure pentachlorophenol and technical-grade pentachlorophenol would be valuable in determining whether pentachlorophenol is an immunotoxicant.

Neurological. Overt signs of neurotoxicity have been reported in individuals presumably exposed to high level of pentachlorophenol (Chapman and Robson 1965; Gray et al. 1985; Haley 1977; Smith et al. 1996; Walls et al. 1998). Increases in subjective symptoms of neurotoxicity (Peper et al. 1999; Walls et al. 1998), impaired performance on neurobehavioral tests (Peper et al. 1999), and alterations in nerve conduction velocity (Cheng et al. 1993) have also been reported in epidemiological studies. A 6-month mouse study reported altered performance on neurobehavioral tests (NTP 1989), but these alterations were only observed in animals exposed to technical-grade pentachlorophenol; no effects were observed in mice exposed to commercial-grade pentachlorophenol or pure pentachlorophenol. Further studies are needed to determine whether the observed neurological effects are due to pentachlorophenol or to a contaminant.

Reproductive. Several laboratory animal studies have reported reproductive effects in animals exposed to technical-grade pentachlorophenol (Bernard et al. 2002) or pentachlorophenol of unknown purity (Beard and Rawlings 1998; Beard et al. 1997, 1999a, 1999b; Rawlings et al. 1998). Studies evaluating potential effects on reproductive function in animals exposed to pure pentachlorophenol and technical-grade pentachlorophenol are needed to evaluate whether observed effects are due to pentachlorophenol or contaminants.

Developmental. Developmental effects have been reported in several laboratory animal studies; these effects include increases in mortality, malformations/variations, and decreased growth. One study reported impaired development of the reproductive system (Bernard et al. 2002). Additional studies are needed to further evaluate possible effects on the reproductive system and to evaluate other possible functional impairments, such as impaired development of the nervous system or immune system.

Epidemiology and Human Dosimetry Studies. A number of studies have reported adverse health effects in humans following short- or long-term exposure to pentachlorophenol. The short-term data come from case reports involving home use of pentachlorophenol-containing products such as wood preservative or herbicides in the garden or a series of reports of newborn infants exposed to pentachlorophenol from diapers and linens treated with an antimildew agent. Long-term toxicity information comes from families living in log homes that were treated with pentachlorophenol and occupational exposure in agricultural and wood-treatment industries. Interpretation of these studies is limited by the lack of reliable information on exposure concentrations, exposure route, duration of exposure, possible concomitant exposure to other chemicals, and impurities present in technical-grade pentachlorophenol. Additional epidemiological studies that provide sufficient information for exposure characterization and examine a number of endpoints would be useful for establishing sensitive targets of toxicity in humans and dose-response relationship data.

Biomarkers of Exposure and Effect. Pentachlorophenol is primarily excreted in the urine as pentachlorophenol conjugates. Thus, measurement of pentachlorophenol in the urine is a useful biomarker of exposure. However, data that establish a quantitative relationship between levels in the urine and exposure levels are not available. Pentachlorophenol is also excreted in the urine as TCHQ and TCHQ conjugates. TCHQ level has potential use as an indicator of exposure to pentachlorophenol, although this biomarker is not specific for pentachlorophenol. Additional studies are needed to establish a relationship between exposure level and urinary concentration of TCHQ.

No pentachlorophenol-specific biomarkers of effect have been identified for pentachlorophenol. Development of sensitive biomarkers that are specific for pentachlorophenol effects would be useful in monitoring populations at high risk.

Absorption, Distribution, Metabolism, and Excretion. The absorption, distribution, metabolism, and excretion of pentachlorophenol have been investigated in humans and animals.

Estimates of absorption efficiency are available for short-term inhalation, oral, and dermal exposure. The distribution of pentachlorophenol following inhalation, oral, or dermal exposure has been characterized in acute-duration studies in animals. Long-term studies examining distribution would be useful to determine if there are any duration-related differences in distribution. The available data are adequate for developing metabolic pathways for pentachlorophenol. There are conflicting data on urinary metabolites in humans, with some studies reporting that pentachlorophenol is primarily excreted unchanged and other studies reporting that it is primarily excreted as pentachlorophenol conjugates. It appears that these differences may be due to the treatment of the urine, which could result in the hydrolysis of pentachlorophenol conjugates to pentachlorophenol. Studies are needed to verify the primary urinary metabolites. The elimination half-life has been estimated for several species; however, some studies based the elimination half-life estimates by only monitoring urinary excretion. Since approximately 10% of pentachlorophenol is excreted in the feces, these studies may underestimate the half-life. Two animal studies (Braun and Sauerhoff 1976; Braun et al. 1977) found an apparent difference in elimination kinetics between males and females. Additional studies examining potential sex-related differences would be useful.

Comparative Toxicokinetics. A series of studies conducted by Braun and associates (Braun and Sauerhoff 1976; Braun et al. 1977, 1979) suggest that there are toxicokinetic differences between humans, monkeys, and rats. The results of these studies suggest that the excretion of pentachlorophenol follows a linear, one-compartment model in humans and monkeys. In contrast, excretion in the rats was biphasic (two-compartment model). However, other pharmacological properties, such as maximum plasma concentration, absorption rate constant, volume of distribution, steady-state concentration, and the excretion of glucuronide conjugates, were similar for humans and rats, but not for humans and monkeys. These data suggest that the rat may be a better model for humans than the monkey. Additional studies are needed to further evaluate species differences in the toxicokinetic properties of pentachlorophenol and to identify the most appropriate model for humans.

Children's Susceptibility. Adverse effects on the nervous system, liver, kidneys, and respiratory system, and some deaths were associated with exposure of newborn children to pentachlorophenol in diapers and bedding, and suppression of the immune system was seen in older children exposed to pentachlorophenol. Oral exposure studies in animals provide evidence that pentachlorophenol is a developmental toxicant. Gestational exposure to pentachlorophenol has resulted in decreased fetal and neonatal survival, decreased fetal and neonatal body weight, and skeletal anomalies. The available data provide strong support that these effects are due to pentachlorophenol toxicity rather than due to

contaminant exposure. Laboratory animal studies examining potential differences in the toxicity of pentachlorophenol between juveniles and adult animals were not identified; these types of studies would provide valuable information on potential age-related differences.

Physical and Chemical Properties. The physical/chemical properties of pentachlorophenol are well characterized and allow the prediction of the environmental fate of the compound (see Chapter 4). Estimates of the distribution of pentachlorophenol in the environment based on available constants (e.g., water solubility, log K_{ow}, log K_{oc}, vapor pressure) are generally in good agreement with experimentally determined values. No additional studies are required at this time.

Production, Import/Export, Use, Release, and Disposal. Pentachlorophenol is currently being produced by two manufacturers (NPIRS 2019). Production volume and export data are available for 2011 from the Chemical data Reporting database (EPA 2014, 2017). In the past, pentachlorophenol was one of the most heavily used pesticides in the United States, but it is now regulated as a restricted use pesticide (EPA 1984a). The compound is found in all environmental media (air, soil, and water) as a result of its past widespread use. Disposal of pentachlorophenol is subject to EPA restrictions (EPA 1991, 1992).

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The TRI, which contains this information for 2018, became available in 2019. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

Environmental Fate. Information on environmental fate of pentachlorophenol is sufficient to permit a general idea of transport and transformation of the chemical in the environment. Additional data are needed on the mechanisms of degradation in the atmosphere and water; plant uptake and transformation; and extent of bioaccumulation.

Bioavailability from Environmental Media. Pentachlorophenol is readily and completely absorbed following inhalation (Casarett et al. 1969; Cline et al. 1989; EPA 1986b; Jones et al. 1986), oral (Braun et al. 1979; Uhl et al. 1986), and dermal exposure (EPA 1986b; Qiao et al. 1997; Wester et al. 1993). Using Rhesus monkeys, Wester et al. (1993) demonstrated the dermal absorption from pentachlorophenol-treated soil. It was also shown that when [^{14}C-UL]-pentachlorophenol in a soil-based mixture was applied occlusively or nonocclusively to a clipped 7.5-cm^2 abdominal site of 8- to 10-week-old female pigs, total radiolabel absorption was 29.08% under nonocclusive conditions and 100.72% under occlusive

conditions 408 hours after dosing (Qiao et al. 1997). Additional information on the bioavailability of pentachlorophenol adsorbed to soils would be helpful in assessing the relative importance of ingestion of contaminated soils as a potential route of human exposure. Additional information is also be useful on the desorption of the compound from soils when the soil pH is altered or when pentachlorophenol-contaminated soil comes into contact with cosolvents (such as alcohols or petroleum compounds), which may enhance desorption and/or increase the solubility of pentachlorophenol. Cline et al. (1989) detected elevated levels of pentachlorophenol in the urine of log-home residents. The study authors believed inhalation to be the most likely route of exposure. Additional information would help to correlate the presence of pentachlorophenol in contaminated air and the exposure via inhalation.

Food Chain Bioaccumulation. A data need exists for controlled bioconcentration experiments in fish as a function of pH of the water. The log K_{ow} of pentachlorophenol presented in Chapter 4 is 5.01, suggesting that pentachlorophenol is likely to bioaccumulate. However, the extent of bioaccumulation will depend on the pH of the medium since pentachlorophenol converts at higher pH levels to the more water-soluble pentachlorophenate anion. Pentachlorophenol is bioconcentrated by terrestrial and aquatic organisms (EPA 1986a; Makela et al. 1991; Smith et al. 1990). However, biomagnification of the compound in terrestrial and aquatic food chains has not been demonstrated as a result of the fairly rapid metabolism of the compound by exposed organisms (Niimi and Cho 1983).

Exposure Levels in Environmental Media. Pentachlorophenol has been detected in ambient air, surface water, drinking water, soils, and foods. Estimates of dietary intake of the compound have been made by the World Health Organization (WHO 1987), EPA (1978), and FDA (1989; Gunderson 1988). In a comparison of the 1986–1991 study to the 1982–1984 study, Gunderson (1995) observed a substantial reduction in the amount of pentachlorophenol in the estimated mean daily intake. Lewis et al. (1994) detected low levels of pentachlorophenol in air, dust, and soil in a nine-home (year of construction ranged from 1930 to 1989) pilot study to monitor the potential exposure of small children to pesticides in the residential environment. Further monitoring is would be useful for evaluating the risk of exposure from pentachlorophenol-treated wood in homes. Limited information is available regarding the levels of pentachlorophenol in air in the United States. More ambient monitoring data of air is required to estimate the exposure of the general population via inhalation of pentachlorophenol in the 1990s.

Contemporary monitoring studies demonstrating the presence or absence of pentachlorophenol in various sources of surface and drinking water are also needed.

Reliable monitoring data for the levels of pentachlorophenol in contaminated media at hazardous waste sites are needed so that the information obtained on levels of pentachlorophenol in the environment can be used in combination with the known body burden of pentachlorophenol to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. Pentachlorophenol has been measured in blood (NHANES III) (Ferreira et al. 1997), urine (Barbieri et al. 1995; Bevenue et al. 1967; CDC 2009, 2019; Colosio et al. 1993a; Ferreira et al. 1997; Hill et al. 1989, 1995; Thompson and Treble 1994, 1996; Treble and Thompson 1996), cerebrospinal fluid (Jorens et al. 1991), and tissues of humans (Bevenue et al. 1967). Quantitative data that correlate varying levels in the environment with levels in body fluids and health effects are not available. One study exists for residents of log homes treated with pentachlorophenol; levels in blood and urine were highly correlated with levels in indoor air (Lewis et al. 1994). Additional information on exposure levels for populations living near hazardous waste sites would be helpful. Information regarding the exposure levels for populations near pentachlorophenol-treated utility poles would be useful. This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. No monitoring studies have been performed to investigate the exposure to and the body burden of pentachlorophenol in children. No studies are available on the dermal absorption of pentachlorophenol in infants and toddlers due to activities such as crawling, which results in contact with the floor (carpet) and soil. Since pentachlorophenol is likely to be adsorbed to these materials, more information would allow the estimation of a child's exposure to pentachlorophenol to be more rigorously determined. A pilot study measured the amounts of pentachlorophenol in dust and soils that are found in areas where children may play, such as carpets and playgrounds (Lewis et al. 1994). As part of the FDA total diet study, mean daily intake of pentachlorophenol by 6- to 11-month-old infants, 2-year-old children, and 14- to 16-year-old males and females were determined (Gunderson 1995). Studies dealing with the weight-adjusted intake of pentachlorophenol by children would help in assessing the effects of pentachlorophenol in children. No studies are available on the amounts of pentachlorophenol present in the breast milk of women in the United States. The estimation of the amounts of pentachlorophenol in soil and house dust that are ingested by children needs to be determined. No information is available on the exposure of children to pentachlorophenol from the parent's body, work clothes, and other objects from work. Studies are required to identify childhood-specific means of decreasing exposure to pentachlorophenol.

6.3 ONGOING STUDIES

An ongoing study that was identified in the National Institutes of Health (NIH) RePORTER (2021) is summarized in Table 6-1.

Table 6-1. Ongoing Studies on Pentachlorophenol

Investigator	Affiliation	Research description	Sponsor
Antioine Snijders	University of California, Lawrence Berkeley Lab	Role of the gut microbiome in pesticide-induced effects on child neurodevelopment	NIEHS

NIEHS = National Institute of Environmental Health Sciences

Source: NIH RePORTER (2021)