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 chlorophenols 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 chlorophenols.

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

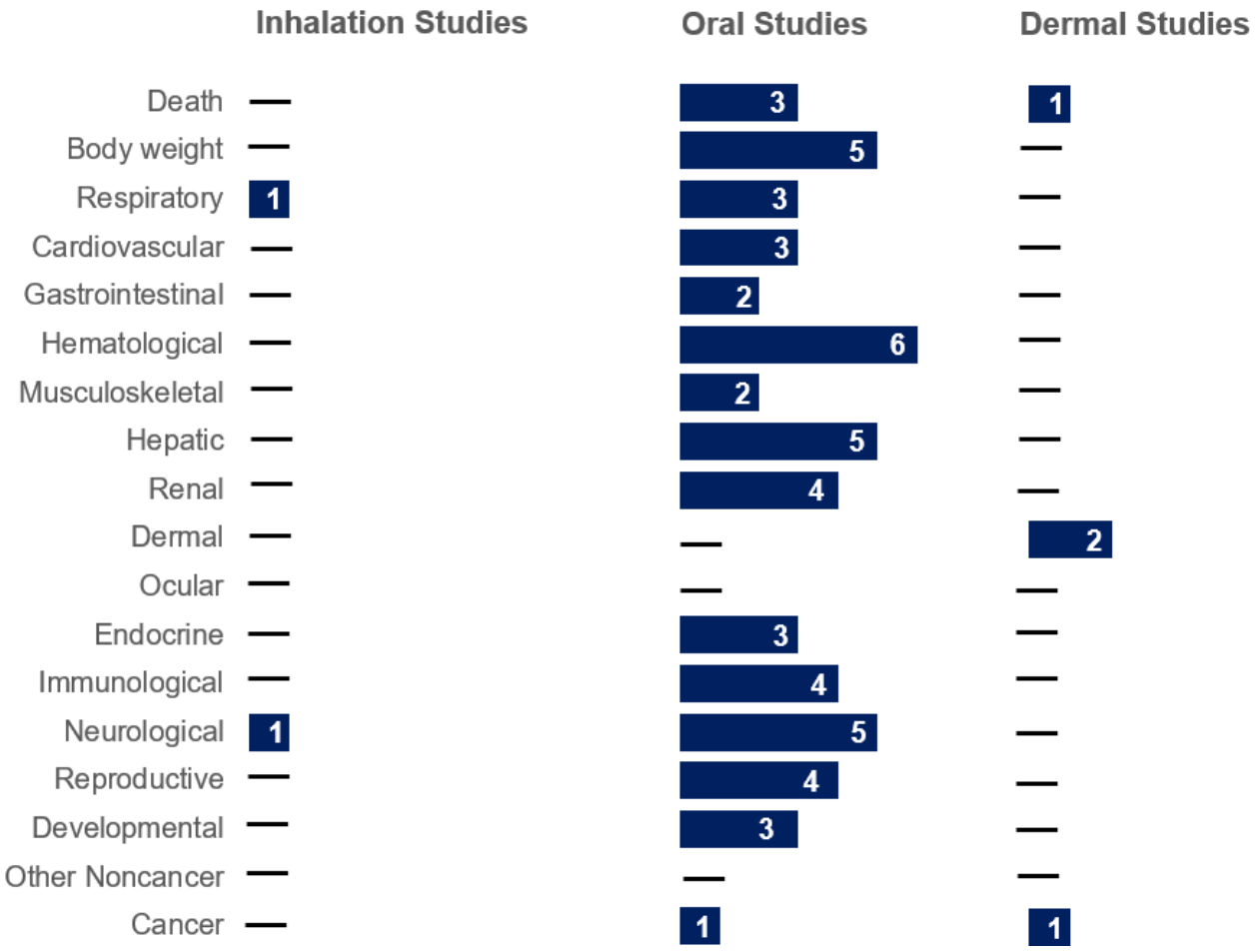
Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to chlorophenols that are discussed in Chapter 2 are summarized in Figures 6-1 (2-CP), 6-2 (4-CP), 6-3 (2,4-DCP), 6-4 (2,4,5-TCP), 6-5 (2,4,6-TCP), 6-6 (2,3,4,6-TeCP), and 6-7 (other chlorophenols). The purpose of these figures is to illustrate the information concerning the health effects of chlorophenols. 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.

The preponderance of data on the toxicity of chlorophenols come from oral studies in laboratory animals, as shown in Figures 6-1, 6-2, 6-3, 6-4, 6-5, 6-6, and 6-7. The most examined endpoints were body weight, neurological, hepatic, renal, hematological, and reproductive effects. There were two human case reports of dermal exposures to 2,4-DCP alone in which neurological effects and deaths were reported; these are included in the figures. The remaining human studies largely consisted of occupational cohort or case-control studies and population-based, cross-sectional studies. The former (n=18) were of populations exposed to multiple chlorophenols through inhalation and dermal routes; these studies primarily evaluated cancers and mortality. The population-based studies (n=24) used urinary chlorophenols, usually 2,4-DCP and 2,5-DCP and occasionally other compounds, to measure exposure, and evaluated associations with birth outcomes, obesity, blood pressure, thyroid levels, or reproductive endpoints.

Figure 6-1. Summary of Existing Health Effects Studies on 2-Chlorophenol By Route and Endpoint*

Potential hematological, neurological, body weight, and hepatic effects were the most studied endpoints

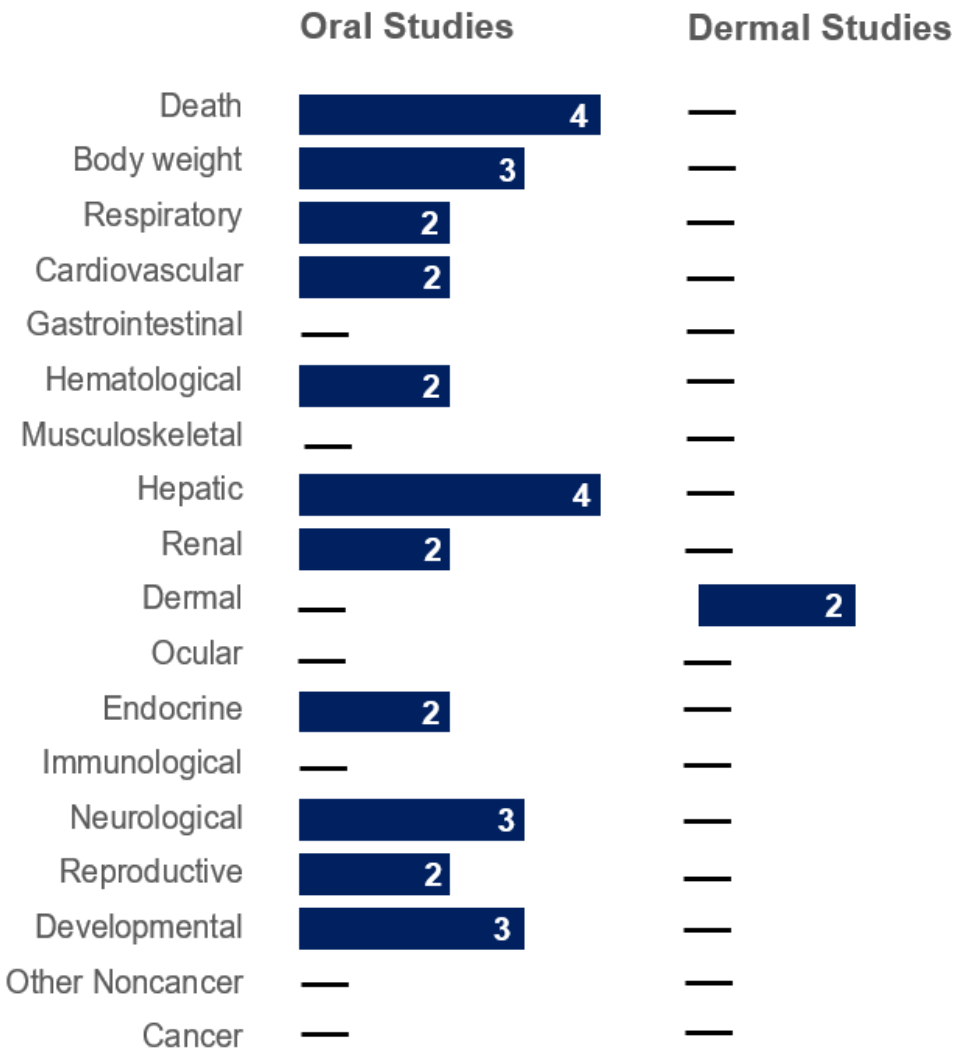
The majority of the studies examined oral exposure in **animals** (versus **humans**)



*Includes studies discussed in Chapter 2; the number of studies include those finding no effect. More than one endpoint may have been investigated in each study.

Figure 6-2. Summary of Existing Health Effects Studies on 4-Chlorophenol By Route and Endpoint*

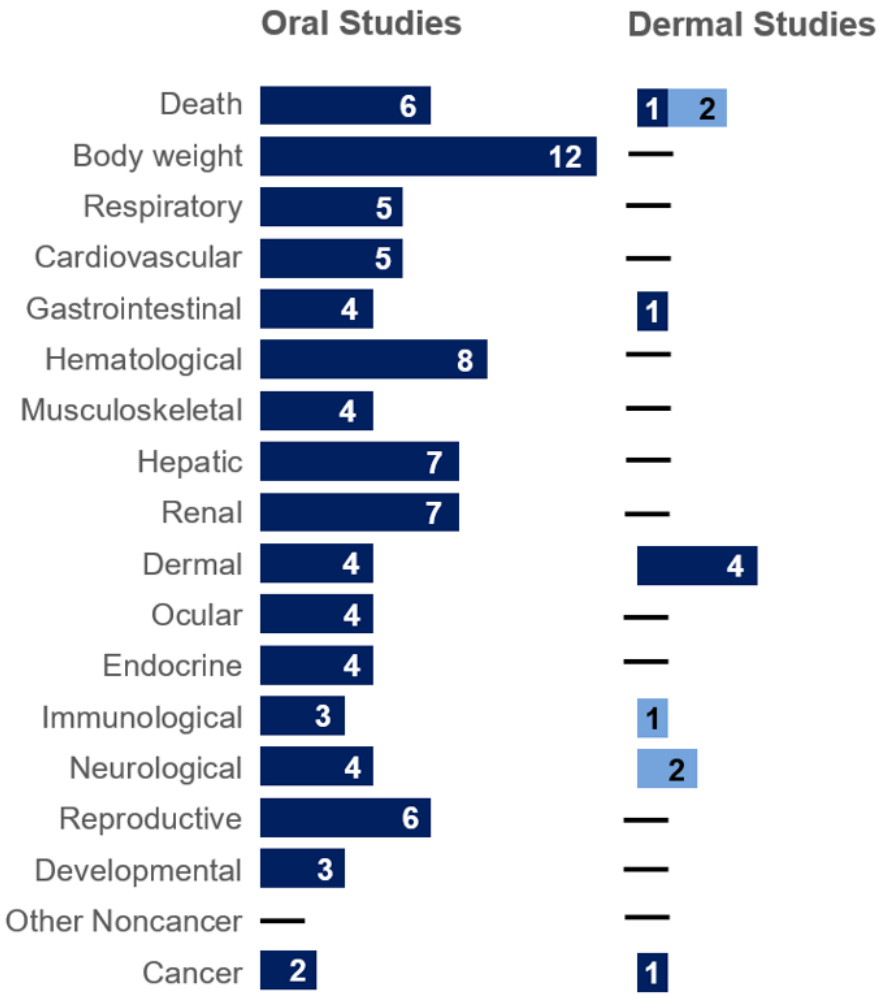
Potential mortality and hepatic effects were the most studied endpoints
The majority of the studies examined oral exposure in **animals** (versus **humans**)



*Includes studies discussed in Chapter 2; the number of studies include those finding no effect. More than one endpoint may have been investigated in each study. No inhalation studies in humans or animals were located.

Figure 6-3. Summary of Existing Health Effects Studies on 2,4-Dichlorophenol By Route and Endpoint*

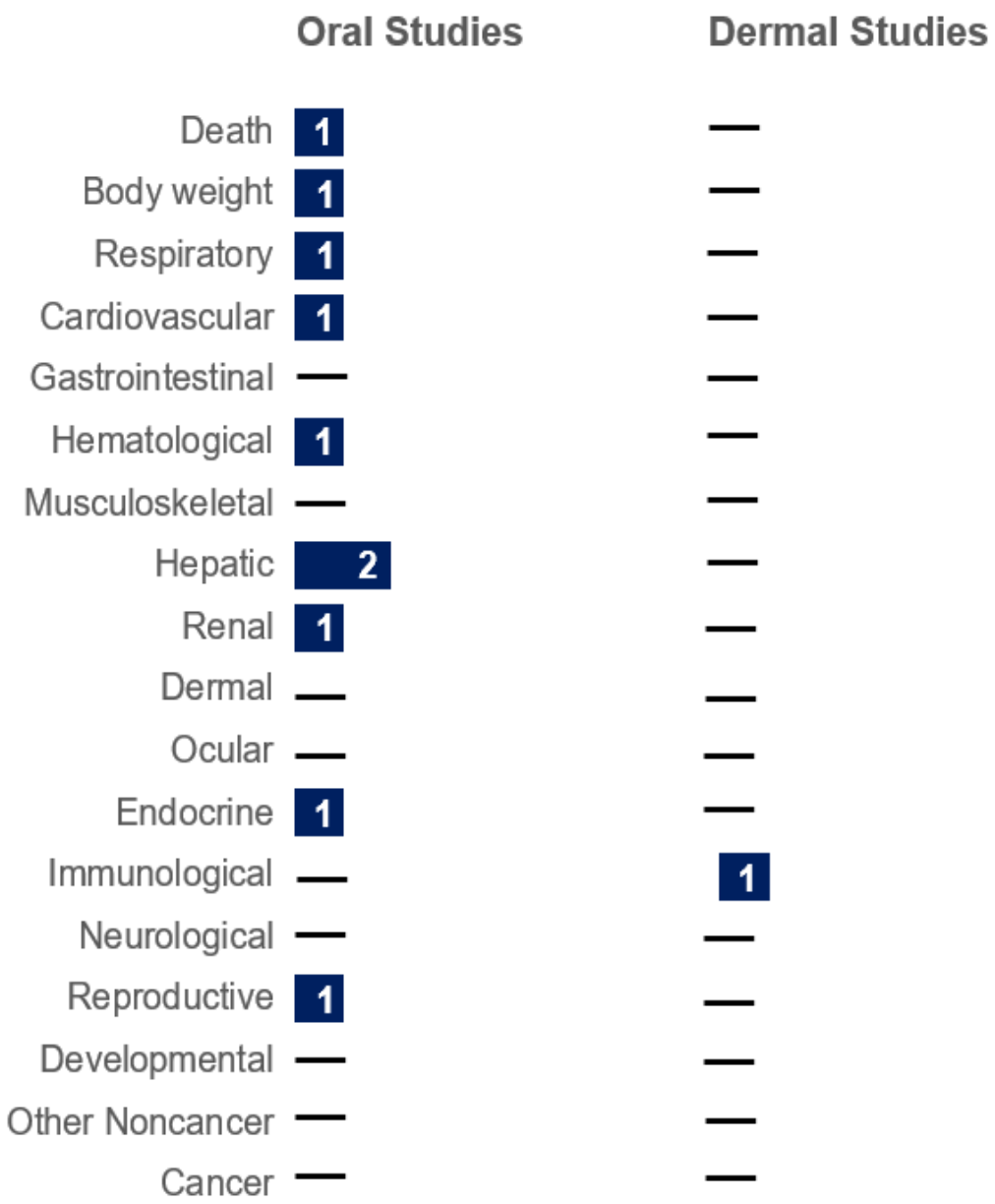
Potential mortality, body weight, hematological, and dermal were the most studied endpoints
The majority of the studies examined oral exposure in **animals** (versus **humans**)



*Includes studies discussed in Chapter 2; the number of studies include those finding no effect. More than one endpoint may have been investigated in each study. No inhalation studies in humans or animals were located.

Figure 6-4. Summary of Existing Health Effects Studies on 2,4,5-Trichlorophenol By Route and Endpoint*

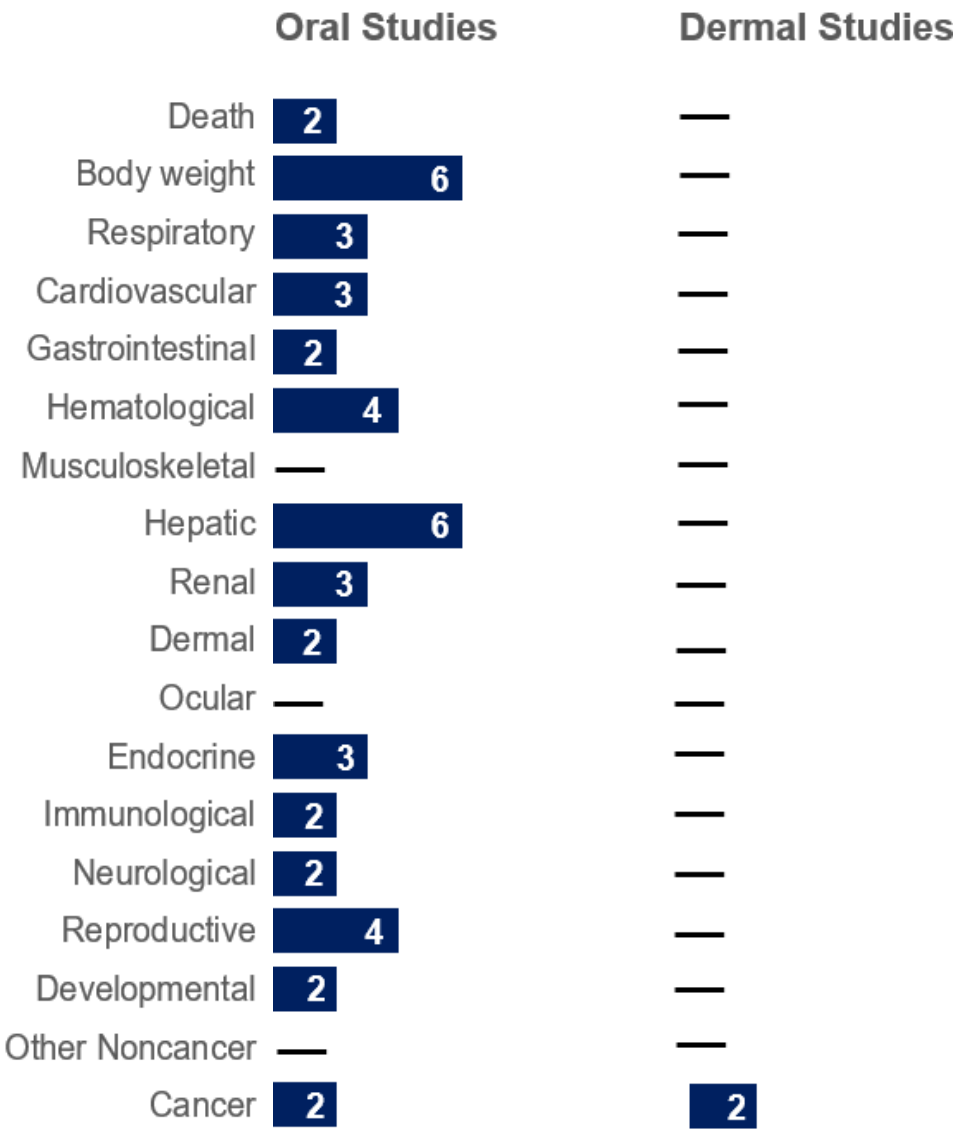
Potential hepatic effects were the most studied endpoints
The majority of the studies examined oral exposure in **animals** (versus **humans**)



*Includes studies discussed in Chapter 2; the number of studies include those finding no effect. More than one endpoint may have been investigated in each study. No inhalation studies in humans or animals were located.

Figure 6-5. Summary of Existing Health Effects Studies on 2,4,6-Trichlorophenol By Route and Endpoint*

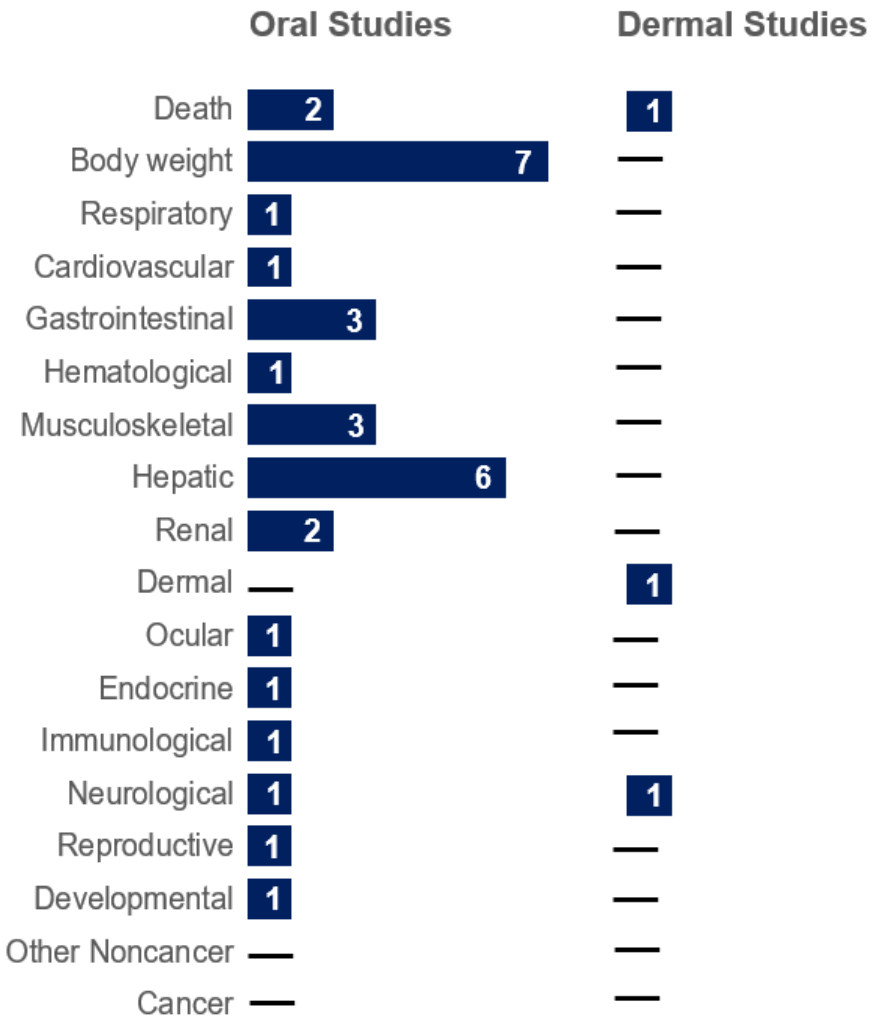
Potential body weight and hepatic effects were the most studied endpoints
The majority of the studies examined oral exposure in **animals** (versus **humans**)



*Includes studies discussed in Chapter 2; the number of studies include those finding no effect. More than one endpoint may have been investigated in each study. No inhalation studies in humans or animals were located.

Figure 6-6. Summary of Existing Health Effects Studies on 2,3,4,6-Tetrachlorophenol By Route and Endpoint*

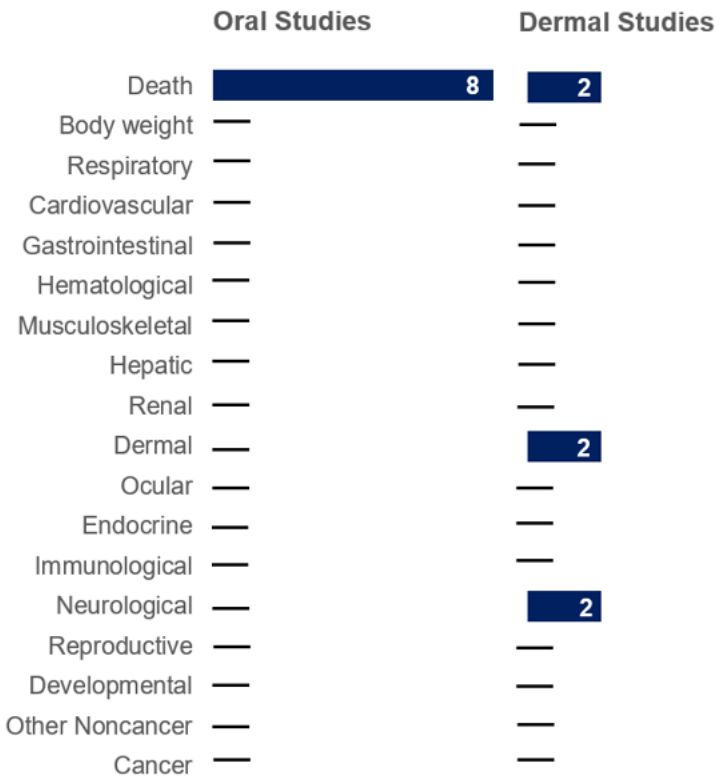
Potential body weight and hepatic effects were the most studied endpoints
The majority of the studies examined oral exposure in **animals** (versus **humans**)



*Includes studies discussed in Chapter 2; the number of studies include those finding no effect. More than one endpoint may have been investigated in each study. No inhalation studies in humans or animals were located.

Figure 6-7. Summary of Existing Health Effects Studies on Other Chlorophenols By Route and Endpoint*

Potential mortality, neurological, and dermal effects were the only 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. More than one endpoint may have been investigated in each study.

The latter studies included multiple chlorophenols, and their interpretation is further complicated by the fact that urinary chlorophenols may occur as a result of metabolism of other compounds such as chlorinated benzenes. The databases of studies in laboratory animals exposed by inhalation and dermal routes include small numbers of studies evaluating limited endpoints. Among animal studies of oral exposure shown in the figures, most studies examined effects of 2-CP, 4-CP, 2,4-DCP, 2,4,5-TCP, 2,4,6-TCP, or 2,3,4,6-TeCP. Only a single study was located on the health effects in animals of oral exposure to 2,3-, 2,5-, 3,4-, and 3,5-DCP (Borzelleca et al. 1985b) or 2,3,4,5- and 2,3,5,6-TeCP (Ahlborg and Larsson 1978).

6.2 IDENTIFICATION OF DATA NEEDS

Missing information in Figures 6-1, 6-2, 6-3, 6-4, 6-5, 6-6, and 6-7 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. No adequate acute-duration inhalation data were available for any of the chlorophenols discussed in this profile. The acute-duration oral data were considered adequate for derivation of MRLs for 2-CP and 2,3,4,6-TeCP. For 4-CP, available acute-duration data were not considered adequate because deaths were observed at the lowest LOAEL. Acute-duration oral data for 2,3-DCP, 2,5-DCP, 3,4-DCP, 3,5-DCP, 2,3,4,5-TeCP, and 2,3,5,6-TeCP were limited to acute lethality studies.

Intermediate-Duration MRLs. No adequate intermediate-duration inhalation data were available for any of the chlorophenols discussed in this profile. Studies in animals exposed by oral administration were considered adequate to derive intermediate-duration oral MRLs for 2-CP, 4-CP, 2,4-DCP, 2,4,5-TCP, 2,4,6-TCP, and 2,3,4,6-TeCP. There were no intermediate-duration oral studies for 2,3-DCP, 2,5-DCP, 3,4-DCP, 3,5-DCP, 2,3,4,5-TeCP, or 2,3,5,6-TeCP. Studies examining sensitive immunological endpoints following oral exposure to chlorophenols other than 2-CP, 2,4-DCP, and 2,4,6-TCP are needed to evaluate potential immunotoxicity of the other compounds.

Chronic-Duration MRLs. No adequate chronic-duration inhalation data were available for any of the chlorophenols discussed in this profile. In addition, there were no adequate chronic-duration oral data in

humans or animals for 4-CP, 2,4-DCP, 2,5-DCP, 3,4-DCP, 3,5-DCP, 2,4,5-TCP, 2,3,4,5-TeCP, 2,3,4,6-TeCP, or 2,3,5,6-TeCP. While a well-conducted chronic study of 2,4-DCP in rats and mice (NTP 1989) is available, this study did not examine sensitive measures of immunotoxicity, and identified effect levels higher than seen in the intermediate-duration study (Exon and Koller 1985; Exon et al. 1984), precluding its use for a chronic-duration oral MRL for 2,4-DCP.

Health Effects. Studies of health effects in humans exposed to chlorophenols are limited by the absence of specific, reliable biomarkers of exposure and by co-exposures to phenoxy herbicides and polychlorinated dibenzodioxins and furans in occupational and environmental settings. Furthermore, no repeated-exposure studies of animals exposed to chlorophenols by inhalation were located. Studies examining comprehensive endpoints in animals exposed by inhalation for acute, intermediate, and chronic durations would enable identification of target organs and exposure-response relationships for this exposure route; these are particularly important for the more volatile monochlorophenols. Finally, only acute lethality data are available for 2,3-DCP, 2,5-DCP, 3,4-DCP, 3,5-DCP, 2,3,4,5-TeCP, and 2,3,5,6-TeCP; thus, oral studies to identify target organs and establish exposure-response relationships for these compounds are needed.

Reproductive. Reproductive effects consisting of reduced numbers of implantations, litter sizes, and/or live births per litter have been observed in animals after oral exposure to 4-CP, 2,4-DCP, and 2,4,6-TCP (BSRC 2011; Exon and Koller 1985; Exon et al. 1984). Only 2,4-DCP has been tested in a multigeneration study examining comprehensive reproductive endpoints in exposed male and female animals (Aoyama et al. 2005); thus, multigeneration reproduction toxicity studies of other chlorophenols are needed.

Developmental. While results from animal studies showed minor effects occurring at doses that are maternally toxic (Blackburn et al. 1986; EPA 1987a, 1987b; Exon and Koller 1985; Rodwell et al. 1989), few developmental toxicity studies that included teratogenicity evaluations are available. Therefore, animal developmental toxicity studies that include evaluation of teratogenicity endpoints are needed. More epidemiological studies of developmental effects in humans exposed to chlorophenols would be beneficial as well.

Immunotoxicity. Only 2-CP, 2,4-DCP, and 2,4,6-TCP have been tested for sensitive measures of immune function (Exon and Koller 1982, 1983a, 1983b, 1985; Exon et al. 1984). Evidence of

effects on both cell-mediated and humoral immunity in rats exposed to 2,4-DCP suggests that additional chlorophenols may warrant testing.

Neurotoxicity. Available data on neurotoxicity of chlorophenols show serious effects including convulsions after acute- and intermediate-duration, oral, dermal, and intraperitoneal exposures in humans and animals (Borzelleca et al. 1985a, 1985b; Rhone-Poulenc 1991; Farquharson et al. 1958; Hasegawa et al. 2005; Kintz et al. 1992; Kobayashi et al. 1972; Phornchirasilp et al. 1989b; Shen et al. 1983; Spencer and Williams 1950; Wil Research Laboratories 1982). Although Borzelleca et al. (1985a, 1985b) reported a decrease in brain weight in mice exposed to 2-CP for 14 days, the authors reported few details of the experiment and results. No clinical signs or changes in brain weight, brain histology, and/or sciatic nerve histology were observed after acute- and intermediate-duration exposure of rats to 2-CP (Daniel et al. 1993; Hasegawa et al. 2005) or intermediate-duration exposure of rats or mice to 4-CP, 2,4-DCP, trichlorophenols, or tetrachlorophenols (Bercz et al. 1990; EPA 1986; Hasegawa et al. 2005; NCI 1979; NTP 1989). While inhibition of oxidative phosphorylation and cellular respiration are possible mechanisms for the clinical signs of neurotoxicity, studies to clarify the mechanism(s) may inform the dose-response assessment for these effects. There are no studies examining sensitive measures of neurotoxicity (e.g., functional observational battery, neurobehavioral changes); these studies are warranted based on the observed clinical signs. Finally, studies of 2-CP (Borzelleca et al. 1985b; Daniel et al. 1993) suggest that mice may be more sensitive to the neurological effects of chlorophenols than rats; further investigation of this possible species difference and its implications for extrapolation to humans would be beneficial.

Cancer. Apart from 2,4-DCP and 2,4,6-TCP, the chlorophenols discussed in this profile have not been adequately tested for potential carcinogenicity. Available chronic studies with rats and mice and predominantly negative results in studies of mutagenicity have indicated that 2,4,6-TCP may produce carcinogenicity in animal models through mechanisms other than direct gene mutation (Armstrong et al. 1993; Jansson and Jansson 1992; NCI 1979); however, candidate mode(s) of action have not been proposed. Additional animal and/or *in vitro* studies designed to evaluate potential key events in the mode(s) of action for 2,4,6-TCP carcinogenicity would be beneficial.

Epidemiology and Human Dosimetry Studies. Accurate human dosimetry studies may not be possible because environmental and occupational chlorophenols typically exist only in association with

other chlorinated organics, and urinary chlorophenol concentrations are not specific for chlorophenol exposure (see below). Consequently, it would be difficult to ascribe any observed health effect to a single chemical or a single group of compounds. Additional studies in workers, such as sawmill employees, who are exposed specifically to chlorophenols are needed. Careful monitoring of chlorophenol air concentrations and skin exposure combined with kinetic measures of urinary output for specific isomers may provide important data for human dosimetry and enable more reliable epidemiological studies.

Biomarkers of Exposure and Effect. Currently, no specific biomarkers for chlorophenol exposure or effect are available. The presence of chlorophenols or their metabolites in urine is not necessarily diagnostic for chlorophenol exposure because these compounds are also detectable in urine after exposure to other pesticides (Hill et al. 1989; Karapally et al. 1973; Shafik et al. 1973), dichlorobenzenes (Yoshida et al. 2002), and hexachlorocyclohexanes (Engst et al. 1976; Koransky et al. 1975). Research to identify specific biomarkers of chlorophenol exposure or effects would be useful to improve human epidemiological studies and/or medical surveillance of exposed populations.

Absorption, Distribution, Metabolism, and Excretion. Studies concerning the inhalation absorption and oral absorption of chlorophenols from different media (e.g., water, soil) and the effect of ionization on dermal absorption are needed for estimating exposure at a hazardous waste site. Available data on the toxicokinetics of chlorophenols are limited, but clearly establish the rapid and nearly complete absorption and rapid elimination of most chlorophenols after oral exposure. Data on the toxicokinetic behavior of the chlorophenols after inhalation exposure in humans or animals are lacking. Metabolism studies demonstrate that glucuronide and sulfate conjugates comprise the major portion of urinary chlorophenol metabolites. Semiquinone and quinone metabolites have been detected after oral exposure (Juhl et al. 1991; Phornchirasilp et al. 1989b); these compounds, while short-lived, are reactive and potentially toxic. Experiments to establish rate constants for the formation of both reactive intermediates and conjugates might provide data for the development of PBPK models. Finally, studies of differences in the rates of formation of reactive intermediates and conjugates after oral, inhalation, and dermal exposure, and/or in different species, would inform route- and species-specific differences in the toxic manifestations of chlorophenols.

Comparative Toxicokinetics. Toxicokinetic studies with chlorophenols have been conducted in humans, rats, rabbits, and dogs (Azouz et al. 1953; Bray et al. 1952a, 1952b; Exon and Koller 1982; Fenske et al. 1987; Hattula et al. 1981; Phornchirasilp et al. 1989a; Somani and Khalique 1982; Spencer and Williams 1950). Limited data suggest that mice may be more sensitive to the toxic effects of orally-

administered chlorophenols than rats; thus, toxicokinetic studies comparing metabolites and rates of elimination in mice and rats would be beneficial. Furthermore, the human fatalities seen after dermal and/or inhalation exposure to 2,4-DCP raise the question of whether humans may be more sensitive than rodents to the effects of this compound. Studies comparing human and rodent toxicokinetics of 2,4-DCP would provide data to inform this question.

Children's Susceptibility. There is inadequate experimental evidence to evaluate whether pharmacokinetics of chlorophenols are different in children. Higher chlorinated phenols (trichloro- and tetrachlorophenols) have been detected in human adipose tissue (Mussalo-Rauhamaa et al. 1989; Williams et al. 1984), suggesting that chlorophenols could be stored in maternal tissues. These studies did not examine whether mono- or dichlorophenols accumulate in adipose tissue; studies examining this issue would help to determine whether children have increased exposure from mobilization of contaminants stored in fat. Similarly, there are limited data showing detectable levels of 2,4-DCP 2,4,5-TCP and 2,4,6-TCP in breast milk (Ye et al. 2006), as well as measurable 2,5-DCP, but not 2,4-DCP in amniotic fluid (Philippat et al. 2013). These studies did not include analysis for other chlorophenols. There are no direct data on whether chlorophenols cross the placenta in humans or animals, but evidence of embryotoxicity in rats exposed to chlorophenols suggests that transplacental transfer may occur. In summary, the data on chlorophenol accumulation in human adipose tissue, breast milk, and amniotic fluid are incomplete, and there is a lack of data on transplacental transfer of chlorophenols. There is no experimental evidence to evaluate whether metabolism of chlorophenols or their mechanism of action may be different in children. Since the metabolic enzymes for detoxification exhibit age-dependent expression, there is a need for such data.

Physical and Chemical Properties. The physical and chemical properties of chlorophenols have been well studied, and reliable values for key parameters for most chlorophenols are available for use in environmental fate and transport models. Therefore, further studies of the physical and chemical properties of chlorophenols are not essential at the present time.

Production, Import/Export, Use, Release, and Disposal. Chlorophenols have a variety of different uses (Muller and Caillard 2011). 2,4-DCP is used as an intermediate in the production of herbicides and the manufacture of compounds used in mothproofing, antiseptics, and seed disinfectants. It is also used to produce miticides and wood preservatives. 4-CP is used as an intermediate in the production of acaricides, rodenticides, and dyes; it is used most commonly as a local antiseptic for dental procedures. 2-CP is used in the production of higher chlorinated phenols, dyestuffs, preservatives, and as

a disinfectant/bactericide/germicide. It is also used for extracting sulfur and nitrogen compounds from coal. 2,4,5-TCP is used as a fungicide/bactericide; an intermediate in the manufacture of herbicides, hide and leather processing; and as a disinfectant in swimming pool and sick-room related surfaces. Chlorophenols are potentially hazardous chemicals and are subject to a variety of regulations (see Chapter 7).

Data regarding the production methods for the chlorophenols are available; however, data regarding current production and import/export of the chlorophenols are extremely limited (Krijgsheld and van de Gen 1986; Muller and Caillard 2011). More complete and up-to-date production and import/export information would provide a better understanding of potential exposure in the United States. General disposal information for chlorophenols is adequately described in the literature. At low concentrations in aqueous media, microbial degradation followed by adsorption on activated charcoal is the common disposal method (WHO 1989).

Environmental Fate. The behavior of chlorophenols in solid and aqueous media depends on numerous physicochemical variables. These chemicals are partitioned to and transported in the air, soil, and water. The pH of soil and water is a major factor controlling their partitioning among the media, their mobility, and their ultimate fate in the environment. These processes are well characterized.

Atmospheric chlorophenols, primarily associated with production processes, are removed by free radical oxidation, photolysis, and both wet and dry deposition (Bunce and Nakai 1989; EPA 1982). More specific data regarding atmospheric dispersion and photochemical reaction rates are needed for occupational settings. Volatilization of the higher chlorinated phenols from water and soil is expected to be a slow process, but there were no experimental data located in the available literature. Experimental data are available pertaining to many of the transformations of chlorophenols in the environment including biodegradation in water, soil, and sediment and photodegradation in water. Confirmation of the estimated slow rate of volatilization in addition to data regarding the overall half-lives for chlorophenols in air are needed to estimate potential inhalation exposure near hazardous waste sites that contain chlorophenols. Data regarding the overall half-life in water and soil are needed to estimate potential oral and dermal exposure to chlorophenols.

Bioavailability from Environmental Media. The observation of systemic effects following inhalation, oral, and dermal exposure indicates that the chlorophenols are readily absorbed (see Chapter 3 for more details). Systematic studies of the bioavailability of the chlorophenols from different media

have not been completed. Because the compounds are relatively lipophilic and become adsorbed to soil and sediments, a study of the bioavailability of these compounds from soil relative to water following oral exposure would be useful.

Food Chain Bioaccumulation. Chlorophenols bioconcentrate in aquatic (fish) organisms to a limited extent, with the greatest bioaccumulation observed for the tetrachlorophenols (Carey et al. 1988). The extent of bioconcentration is limited by relatively rapid metabolism and excretion (Veith et al. 1980). Additional data on the bioaccumulation of chlorophenols within both aquatic and terrestrial organisms are needed.

Exposure Levels in Environmental Media. Reliable monitoring data for the levels of chlorophenols in contaminated media at hazardous waste sites are needed so that the information obtained on levels of chlorophenols in the environment can be used in combination with the known body burden of chlorophenols to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites. Few data are available concerning the levels of chlorophenols in ambient air or near known sources of atmospheric pollution. Limited monitoring data on chlorophenol levels in surface water are available. Additional monitoring for current data for better characterization of the ambient chlorophenol concentrations in air, surface water, groundwater, soils, and sediment are needed. These data are particularly needed in the vicinity of industrial and municipal chlorinated wastewater discharge points and hazardous waste sites, where individuals may be exposed by oral and/or dermal contact, such that estimates of human intake can be made. The presence or absence and any exposure levels of chlorophenols in food items is a data need.

Exposure Levels in Humans. This information is necessary for assessing the need to conduct health studies on these populations. Limited data regarding chlorophenol levels in urine in humans and adipose tissue are currently available. Toxicokinetic data on occupationally and environmentally exposed humans are needed to determine whether there are specific, reliable biomarkers of exposure. Because chlorophenols are metabolites of other chemicals, measurement of these compounds in biological samples (e.g., blood, urine) can provide an estimate of internal dose but may not provide information about the dose of chlorophenols to which individuals were exposed. This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. Exposure and body burden studies of chlorophenols conducted on children are limited; therefore, it is not known whether children are different from adults in their weight-adjusted

intake of chlorophenols, or if unique exposure pathways for children exist. In NHANES surveys of chlorophenol levels in urine (see Tables 5-8 through 5-15), the differences between concentrations in the urine of 6- to 11-year-old children and concentrations in the urine of adults were small. However, as noted earlier, chlorophenols in urine may reflect metabolism of other compounds rather than exposure to chlorophenols, so urine levels in populations without known chlorophenol exposures may not provide a reliable basis for this comparison. There is also little monitoring of chlorophenol levels in food (crops, fish), nor in environmental media, following application of herbicides and wood preservatives. Children whose parents work in manufacturing facilities that produce or use chlorophenols may also potentially be exposed to chlorophenols via parents' work clothes, skin, hair, tools, or other objects removed from the workplace; however, no studies exist on this means of exposure. A take-home exposure study may be warranted if such occupational exposure settings are identified. More complete information on levels of chlorophenols and their metabolites in breast milk will also help to determine the chlorophenols to which children may be exposed via breast milk ingestion.

Since children may be more susceptible to chlorophenols, it may be helpful to conduct studies aimed at identifying methods to prevent, mitigate, or limit exposure of children to chlorophenols.

6.3 ONGOING STUDIES

One ongoing study was identified in the National Institutes of Health (NIH) Research Portfolio Online Reporting Tools Expenditures and Results Tool (RePORTER 2022), as shown in Table 6-1.

Table 6-1. Ongoing Study of 2,4- and 2,5-Dichlorophenol

Investigator	Affiliation	Research description	Sponsor
Ana Katherine Rosen Vollmar	Yale University	The effect of phenol exposure on reproductive function and the urinary metabolome	NIEHS

NIEHS = National Institute of Environmental Health Sciences

Source: RePORTER 2022