

3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of pentachlorophenol. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration 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. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which

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major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary 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 in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in 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 or MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of pentachlorophenol are indicated in Table 3-1 and Figure 3-1. Because cancer effects could occur at lower exposure levels, Figure 3-1 also shows a range for the upper bound of estimated excess risks, ranging from a risk of 1 in 10,000 to 1 in 10,000,000 (10^{-4} to 10^{-7}), as developed by EPA.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for pentachlorophenol. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990a), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

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A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

Since humans are generally exposed to technical-grade pentachlorophenol, which usually contains such toxic impurities as polychlorinated dibenzo-*p*-dioxins and dibenzofurans (see Table 3-2), some of the effects observed in humans (or the severity and dose-response characteristics of the effects) may be related, at least in part, to the presence of the impurities. Animal studies with both technical-grade and purified pentachlorophenol have demonstrated that, within the ranges of doses tested, some of the toxic effects attributed to pentachlorophenol were actually due to the impurities. Because human exposure is generally to technical-grade pentachlorophenol and because ATSDR's intent is to protect human health, studies on both technical-grade and purified pentachlorophenol preparations are reviewed, and special reference is made to those adverse effects seen in humans that are believed to be a result of the contaminants.

3.2.1 Inhalation Exposure

Only limited data were available on the inhalation toxicity of pentachlorophenol in humans. Most of the information available for humans comes from cases of acute poisoning following home use of pentachlorophenol-containing products such as wood preservatives or herbicides in the garden (home and garden use of pentachlorophenol is no longer approved by EPA), and following occupational exposure in agricultural and wood-treatment industries. Many of these poisoning incidences involved inhalation and dermal exposure to pentachlorophenol. Below is a discussion of the case reports and studies in which inhalation is the primary route of exposure; the remaining studies are discussed in Section 3.2.3, Dermal Exposure. Exposure concentrations and duration, as well as information on other exposures and contaminants present in technical-grade pentachlorophenol, are often not available in these studies. Thus, no studies were considered suitable for presentation in a table describing significant levels of inhalation exposure to pentachlorophenol.

3.2.1.1 Death

Data on the lethality of pentachlorophenol in humans is limited to a case report of a man who died following 3 weeks of daily occupational exposure to pentachlorophenol dust (purity not reported) (Gray et al. 1985).

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Death has been reported in experimental animals following acute inhalation of sodium pentachlorophenate aerosol. The reported LC₅₀ (45 minutes) for rats is 14 mg/m³ (11.7 mg/kg) (Hoben et al. 1976b).

3.2.1.2 Systemic Effects

No studies were located regarding any systemic effects in animals after inhalation exposure to pentachlorophenol. No studies were located regarding cardiovascular, gastrointestinal, musculoskeletal, or renal effects in humans after inhalation exposure to pentachlorophenol. It should be noted that many of the systemic effects observed following occupational exposure which are discussed below resulted from uses of pentachlorophenol that are no longer accepted and that the pentachlorophenol used in these instances had a composition (e.g., presence of more impurities) different from the pentachlorophenol that is currently used.

Respiratory Effects. In humans, chronic high-dose occupational exposure to pentachlorophenol causes inflammation of the upper respiratory tract and bronchitis (Baader and Bauer 1951; Klemmer et al. 1980). The purity of pentachlorophenol in these cases was not specified, and inhalation of pentachlorophenol contaminants (chlorinated dibenzo-*p*-dioxins and dibenzofurans) and other compounds (such as dieldrin, chromium, fluorine, arsenic, copper, boron, and tin compounds) present in workplace air was likely and may have contributed to the respiratory response observed. Furthermore, the inflammation observed may have also been the result of physical irritation from the inhalation of particulate matter.

Hematological Effects. In a chronic occupational study, increased numbers of immature leukocytes and basophils were observed in workers exposed to technical-grade pentachlorophenol; however, these parameters were still within normal limits (Klemmer et al. 1980).

Hepatic Effects. In an epidemiology study of male and female pentachlorophenol-production workers, higher urinary excretion of coproporphyrins, compared with unexposed controls, was associated with workers with chloracne involved in the production of pentachlorophenol (Hryhorczuk et al. 1998). In another epidemiology study, Cheng et al. (1993) found elevated urinary porphyrin and delta-amino levulinic acid concentrations among male workers who produced technical-grade pentachlorophenol, but there were no differences in these parameters between the workers with chloracne and those without.

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Endocrine Effects. In a brief report, Gerhard et al. (1991) noted that elevated blood levels of pentachlorophenol (>25 µg/L) and/or lindane (>100 ng/L) were found in 22 of 90 women with histories of habitual abortion, unexplained infertility, menstrual disorders, or the onset of menopause. Exposure duration was 4.6–10 years, and exposure occurred via offgassing (from wooden ceiling and wall panels and from carpets and leather upholstery treated with wood preservatives) as well as via dermal contact with these treated materials. Pentachlorophenol blood levels were highest in the women with infertility (mean=73 µg/L) and lower in those with menstrual dysfunction (42 µg/L). Seventeen of the 22 women also exhibited adrenocortical insufficiency, and 6 of these women had thyroid dysfunction as assessed by measurement of thyroid stimulating hormone releasing hormone (no further details were provided). Conclusions cannot be drawn from these data because a control group was not used and statistical analyses were not performed. Gerhard et al. (1998) also examined several endocrine end points among 89 women with repeated miscarriages. An inverse correlation was found between triiodothyronine levels and pentachlorophenol levels. It should be noted that this is a preliminary study; study design limitations include lack of a matched control group, lack of control for other confounding factors, only 15% of the women had pentachlorophenol levels that were above the reference level of 25 µg/L, no information was provided on possible sources of exposure to pentachlorophenol, and elevated levels of other chlorinated hydrocarbons (e.g., PCBs, DDT) were also present in some of the women. In a third study by Gerhard et al. (1999) of a group of women with gynecological and/or endocrinological disorders, a decrease in triiodothyronine levels were found in women with elevated pentachlorophenol serum levels (median level of 3.59 µg/L); although the levels were lower than levels found in age-, geographical region-, and condition-matched controls, the mean and median triiodothyronine levels were within the normal range. An euthyroid goiter was also observed in 50% of these subjects as compared to 30% in the controls. Other statistically significant alterations in endocrine hormones included an increase in adrenocorticotrophic hormone (ACTH)-stimulated cortisol levels and decreases in follicle stimulating hormone, testosterone, hydroepiandrosterone, hydroepiandrosterone sulfate, 17-hydroxypregnenolone, and 17-hydroxyprogesterone levels. As with the triiodothyronine levels, the hormone levels were within the normal range. The source of pentachlorophenol was wood ceilings that were treated with wood preservatives; it is likely that these women were also exposed to other chemicals in the wood preservative.

No studies were located regarding endocrine effects in animals after inhalation exposure to pentachlorophenol.

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Dermal Effects. Occupationally-exposed workers at a wood-treatment plant exhibited a statistically significant increase in low-grade inflammation of skin and subcutaneous tissue, and severe eruptions of the skin. However, it is possible these symptoms resulted from exposure to contaminants in pentachlorophenol (chlorinated dibenzo-*p*-dioxins, dibenzofurans) and other materials such as dieldrin, chromium, fluorine, arsenic, copper, boron, and tin compounds (Baader and Bauer 1951; Klemmer et al. 1980). Hosenfeld et al. (1986) reported the presence of skin abnormalities (type not specified) in some residents of log homes treated with pentachlorophenol (purity not indicated).

Numerous occupational exposure studies have reported chloracne, characterized by extensive cysts and pus forming abscesses on the face, chest, abdomen, and proximal part of the extremities in sodium pentachlorophenate (Seghal and Ghorpade 1983) and pentachlorophenol (Cheng et al. 1993; Hryhorczuk et al. 1998; O'Malley et al. 1990) production workers. It is likely that these workers were also exposed to chlorinated dibenzo-*p*-dioxins and dibenzofurans, which are known to induce chloracne in humans.

Ocular Effects. Inflammation of the conjunctival membrane of the eyes was observed in workers exposed to technical-grade pentachlorophenol at a wood treatment plant (Klemmer et al. 1980).

3.2.1.3 Immunological and Lymphoreticular Effects

In an epidemiologic study, McConnachie and Zahalsky (1991) evaluated 18 lymphocyte phenotype frequencies, proliferative responses of peripheral lymphocytes to mitogens and allogenic stimulator lymphocytes, serum immunoglobulin levels, and autoantibody levels in 38 people ages 8–60 (21 males) and 9–60 (17 females) from 10 families who had been exposed to pentachlorophenol (purity not indicated) in their pentachlorophenol-treated log homes for periods of 1–13 years. Fifteen of the individuals were children ages 8–18. The mean serum concentration of pentachlorophenol in the individuals who still lived in log homes at the time of the study was 884 µg/L; this was higher than the mean of 420 µg/L found in another study of people living in log homes and a mean level of 40 µg/L reported for members of the general public with no known exposure to pentachlorophenol (Cline et al. 1989). Comparison of the pentachlorophenol-exposed individuals with controls indicated that the exposed individuals had activated T-cells, autoimmunity, immunosuppression, and B-cell dysregulation. T-cell activation was indicated by statistically-significant increases of more than 50% in the proportion of lymphocytes with T-cell activation markers, as detected by monoclonal antibodies, in pentachlorophenol-exposed individuals compared with controls. Autoantibodies were detected in 8 of 38 pentachlorophenol-exposed subjects, and there was increased expression of a monoclonal-antibody-detected marker

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associated with autoimmunity in the pentachlorophenol-exposed group. Functional immunosuppression was indicated by statistically-significant decreases of 24–41% in the proliferative response of peripheral lymphocytes of pentachlorophenol-exposed individuals, compared with controls, to three different mitogens and to allogeneic stimulation in mixed-lymphocyte culture. A statistically-significant increase in natural killer cell function was also reported in pentachlorophenol-exposed women compared with women of the control group. This study is limited by the absence of reported serum pentachlorophenol concentrations in members of the control group and the lack of control for potential confounders such as smoking, hypertension, and alcohol use. Gerhard et al. (1991) reported “immunological disorders” (no further details were given) in 15 of 22 women attending a clinic for reproductive and/or endocrinological disorders. The women were exposed to pentachlorophenol by the outgassing of wood products in the home.

No studies were located regarding immunological effects in animals after inhalation exposure to pentachlorophenol.

3.2.1.4 Neurological Effects

There are limited data on the neurotoxicity of inhaled pentachlorophenol in humans. Signs of central nervous system toxicity (lethargy and tachypnea) and cerebral edema with focal swelling of the myelin sheath was observed in a worker exposed to pentachlorophenol dust (Gray et al. 1985). It is likely that these effects were secondary to hyperthermia, which resulted from pentachlorophenol-induced uncoupling of oxidative phosphorylation.

A study by Peper et al. (1999) examined neurotoxicity in individuals exposed to wood preserving chemicals used to treat wood ceilings and wood paneling. An increase in subjective symptoms (increased fatigue, distractability, attenuated motivation, and depressed mood) and impaired performance on several objective tests of neurobehavioral performance (paired-associated learning with a distracting condition, verbal memory test with distraction, visual short term memory, and incidental learning of visual objects) were observed in 15 women with elevated pentachlorophenol (mean of 43.6 µg/L) and γ -hexachloro-cyclohexane (0.085 µg/L) blood levels, as compared to a sex-, age-, education-, and intelligence-matched control group. Additionally, the results of the reading speed, naming speed, paired associated learning, and visual short-term memory tests were significantly associated with pentachlorophenol blood levels. Although this study provides some suggestive evidence of the neurotoxic potential of pentachlorophenol,

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interpretation of the results is complicated by co-exposure to high levels of γ -hexachlorocyclohexane (lindane) and other solvents and the small number of subjects.

A reduction in median motor nerve conduction velocity was seen in male pentachlorophenol production workers, as compared to matched controls (Cheng et al. 1993). However, the reduction was only statistically significant in the subgroup of pentachlorophenol workers in the trichlorobenzene tank area where the highest levels of chlorinated dibenzo-*p*-dioxins (CDDs) were also found. In contrast, Triebeg et al. (1987) did not find significant alterations in motor or sensory nerve conduction velocities in the ulnar and/or median nerve in workers exposed to low levels (0.0003–0.18 mg/m³) of technical-grade pentachlorophenol.

In a case-control study of patients with Parkinson's disease, Seidler et al. (1996) found significant associations of Parkinson's disease with long-term (>15 years) exposure to wood paneling in the home, contact with wood preservatives in free time, and contact with wood preservatives at work. However, the association of Parkinson's disease with exposure to pentachlorophenol is uncertain because the patients were more likely than control subjects to have used organochlorines and alkylated phosphates/carbamates, and the patients reported more frequent exposure to heavy metals, solvents, exhaust fumes, and carbon monoxide than the control group.

No studies were located regarding neurological effects in animals following inhalation exposure to pentachlorophenol.

3.2.1.5 Reproductive Effects

In a brief report, Gerhard et al. (1991) noted that elevated blood levels of pentachlorophenol (>25 μ g/L) and/or lindane (>100 ng/L) were found in 22 of 90 women with histories of habitual abortion, unexplained infertility, menstrual disorders, or the onset of menopause. However, a causal relationship between pentachlorophenol exposure and the effects is uncertain because of concurrent exposures to other chemicals, the absence of matched controls, and lack of control for other confounding factors. Gerhard et al. (1999) also examined a group of 65 women with gynecological and/or endocrinological alterations and elevated serum pentachlorophenol levels (median level was 35.9 μ g/L). Statistically significant decreases in follicle stimulating hormone and testosterone levels were found, as compared to age-, geographical-, region-, and condition-matched controls. Although the hormone levels were lower than in the control group, they were within the normal range of values. The women were exposed to pentachlorophenol via

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outgassing of wood ceilings treated with wood preservatives. It is likely that the women were also exposed to other components of the wood preservatives.

No studies were located regarding reproductive effects in animals following inhalation exposure to pentachlorophenol.

3.2.1.6 Developmental Effects

Information on the developmental toxicity of pentachlorophenol in humans is limited to a study of male sawmill workers exposed to CDD-contaminated chlorophenate (a mixture of the sodium salts of pentachlorophenol and tetrachlorophenol) (Dimich-Ward et al. 1996). A significant correlation between presumed exposure to chlorophenate and an increased incidence of congenital eye cataracts were observed in the workers' children. Because there were no data on exposure level, exposure to chlorophenate was estimated by 10 experienced workers based on each cohort member's job title.

No studies were located regarding developmental effects in animals after inhalation exposure to pentachlorophenol.

3.2.1.7 Cancer

Case reports suggest a possible association between cancer (Hodgkin's disease, soft tissue sarcoma, and acute leukemia) and occupational exposure to technical-grade pentachlorophenol (Fingerhut et al. 1984; Greene et al. 1978; Roberts 1983). These studies are limited by confounding factors such as concurrent exposure to other potentially carcinogenic chemicals, small sample size, follow-up periods too short to detect an excess cancer risk, mortality due to competing causes of death, and brief exposure periods.

Several epidemiological studies found no association between inhalation of pentachlorophenol (purity not stated) in any form and cancer in humans (Gilbert et al. 1990; Jäppinen et al. 1989; Johnson et al. 1990; Robinson et al. 1985). For example, workers exposed to wood treating chemicals between the years of 1960 and 1981 were evaluated for health-related problems. Eighty-eight wood treaters having exposures of 0.33–26.3 years, with a median of 6.5 years, were compared to 58 matched controls. No adverse health effects or increased incidence of mortality from exposure were detected even though the urinary pentachlorophenol excretion levels were clearly increased (174 ppb versus 35 ppb) (Gilbert et al. 1990). However, IRIS (1999) indicated that the study of Gilbert et al. (1990) cannot be used as evidence of no

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effect of the exposures based on their evaluation of various aspects of the experimental design and conduct.

Johnson et al. (1990) found no association between soft tissue sarcoma and exposure to chlorophenols in a meta-analysis of deaths due to cancer in 15 cohort studies published 1979–1987. However, each of the individual studies had a low power to detect elevated risk estimates (Johnson et al. 1990). Because of the nature of the analysis performed by Johnson et al. (1990) (deaths due to cancer), their study excluded analysis of two studies, which had only incidence data, that found an association between exposure to technical-grade pentachlorophenol and soft tissue sarcoma (Eriksson et al. 1981; Hardell and Sandstrom 1979). In a recent study, in which all data collection and coding were blinded as to cases or controls, Eriksson et al. (1990) found an association between soft tissue sarcoma and high-grade exposure (1 week or more continuously or at least 1 month totally over the years) to technical-grade pentachlorophenol. Compared with the high-grade pentachlorophenol association, a slightly stronger association was found for chlorophenols exposure and a weaker association was found for exposure to phenoxyacetic acids. In a meta-analysis of four of their previous case-control studies, Hardell et al. (1995) found a significant association between soft tissue sarcoma and exposure to pentachlorophenol (purity not specified). An increase in the occurrence of soft tissue sarcoma was also found in workers reporting exposure to phenoxyacetic acids or chlorophenols. Hoppin et al. (1998) found a significant association in men aged 30–60 years between soft tissue sarcoma risk and ever having high-intensity chlorophenol exposure. However, their findings were also consistent with an association to some other component of cutting oils. Seventeen percent of the jobs rated as high intensity involved wood preservation, whereas 82% involved cutting oils. Due to the limited nature of the exposure information in this study, potential for dioxin exposure could not be evaluated.

Hardell et al. (1994) also reported a significant association, in men of various professions, between non-Hodgkin's lymphoma and high-grade exposure (1 week or more continuously or at least 1 month in total over the years) to pentachlorophenol (purity not specified). Compared with the high-grade pentachlorophenol association, a slightly stronger association was found for high-grade exposure to chlorophenols. Hertzman et al. (1997) reported a borderline positive association between an increasing incidence of non-Hodgkin's lymphoma and increasing chlorophenolate exposure among sawmill workers. The trend approached statistical significance.

Ramlow et al. (1996) reported a significant association between death from kidney cancer and increasing exposure to technical-grade pentachlorophenol but indicated that the finding must be considered

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preliminary because of the small number of cases, lack of control for confounders, and absence of information concerning other occupational exposures.

No studies were located regarding cancer in animals after inhalation exposure to pentachlorophenol.

3.2.2 Oral Exposure

Only two reports were found in the literature concerning adverse effects in humans of ingestion of pentachlorophenol (Cretney 1976; Haley 1977). However, pentachlorophenol (particularly the technical-grade) has been shown to affect several organ systems in experimental animals. Target organs or systems of oral pentachlorophenol-induced toxicity in experimental animals include liver, kidney, central nervous system, endocrine system, immune system, and reproductive system; the developing organism is also a sensitive target of pentachlorophenol toxicity. Hematologic, cardiovascular, and respiratory effects have also been noted following oral administration of pentachlorophenol in experimental animals. Oral administration of pentachlorophenol also produced developmental effects in animals and cancer in rats and mice.

Some of the effects of pentachlorophenol may be due, at least in part, to the uncoupling of oxidative phosphorylation by pentachlorophenol (see Section 3.5), which leads to hyperthermia and related effects. Some effects may also result from chlorinated dibenzo-*p*-dioxin and other impurities in technical-grade pentachlorophenol. The adverse effect of pure pentachlorophenol on thyroid homeostasis and the induction of oxidative deoxyribonucleic acid (DNA) damage by oral exposure to pentachlorophenol may also contribute to its spectrum of toxic effects.

3.2.2.1 Death

One case report that described a suicide from pentachlorophenol ingestion was found in the reviewed literature, but the amount of pentachlorophenol ingested was not specified (Cretney 1976). The lowest human lethal dose for pentachlorophenol (purity not specified) is estimated to be 1 gram (approximately 17.0 mg/kg) (Driesbach 1980).

Pentachlorophenol may cause death in experimental animals following ingestion. Death usually is a result of hyperthermia. There does not appear to be much difference in doses that cause death across species. The LD₅₀ values were 80–120 mg/kg in rats (St. Omer and Gadusek 1987) and 117–177 mg/kg

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in mice (Borzelleca et al. 1985; Renner et al. 1986). Preweaned and adult rats have been reported to have lower oral LD₅₀ values for technical-grade pentachlorophenol than juvenile rats (25–50 days old) (St. Omer and Gadusek 1987). The ranges of LD₅₀ values in preweaned, juvenile, and adult rats were 50–180, 220–230, and 80–120 mg/kg, respectively. The lethality of pentachlorophenol was greatly enhanced when it was administered in a fuel oil or corn oil vehicle (Deichmann et al. 1942). Absorption of chemicals such as pentachlorophenol that have substantial lipid solubility across skin and mucous membranes is increased by the presence of hydrocarbon or corn oil solvents. The greater toxicity of pentachlorophenol when dissolved in these vehicles may be due partly or entirely to more efficient absorption of pure pentachlorophenol.

Deaths were also seen in a 30-day oral range-finding study in mice (NTP 1989), a 28-day oral range-finding study in rats with highly purified pentachlorophenol (Chhabra et al. 1999; NTP 1999), and a 6-month oral study in mice (NTP 1989). At the highest dietary concentration tested (12,500 ppm) in the 30-day study in mice (NTP 1989), incidences of deaths were higher in animals fed pure pentachlorophenol (98.6% pure with <0.0002% chlorinated dibenzo-*p*-dioxins and dibenzofurans) and the purified EC-7 pentachlorophenol preparation (90% pure with <0.0002% chlorinated dibenzo-*p*-dioxins and dibenzofurans) than in animals fed technical-grade pentachlorophenol (90% pure with 0.18% chlorinated dibenzo-*p*-dioxins and dibenzofurans).

All reliable LD₅₀ values from acute duration studies and NOAELs/LOAELs for death in longer-duration studies are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.2.2 Systemic Effects

No studies were located regarding gastrointestinal, musculoskeletal, dermal, or ocular effects in humans or animals after oral exposure to pentachlorophenol.

The highest NOAEL values and all reliable LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

Respiratory Effects. The National Toxicology Program (NTP) conducted a 6-month dietary range-finding study (NTP 1989) with 3 different preparations of pentachlorophenol (technical-grade, Dowicide EC-7, and pure) in B6C3F₁ mice (see analysis in Table 3-2). Increased incidences of nasal mucosal metaplasia/goblet cell hyperplasia, compared with controls, were seen in female mice that received

Table 3-1. Levels of Significant Exposure to Pentachlorophenol - Oral

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
ACUTE EXPOSURE								
Death								
1	Rat	1x (GO, GW)				27 78 211	LD50-0.5% in fuel oil) (LD50-olive oil) (LD50-NaPCP in H2O)	Deichmann et al. 1942 tech NaPCP
2	Rat	1 x (G)				50	(LD50)	St. Omer and Gadusek 1987 tech
3	Mouse	1 x (G)				177 M 117 ^b F	(LD50) (LD50)	Borzelleca et al. 1985 pure (approx. 99%)
4	Mouse	1 x (GO)				129 ^b M 134 F	(LD50) (LD50)	Renner et al. 1986 pure (99%)
Systemic								
5	Mouse (B6C3F1)	up to 4 wk 7d/wk (F)	Hepatic		41 M		(incr liver wt, severe hepatocyte swelling, incr hepatic DNA content and DNA adducts)	Umemura et al. 1996 pure (98.6%)
Immunological/Lymphoreticular								
6	Mouse	14 d 7 d/wk (G)			10		(decr IgM antibody response)	Holsapple et al. 1987 tech
7	Mouse	14 d 7 d/wk (G)		100				Holsapple et al. 1987 tech (90% pure)

Table 3-1. Levels of Significant Exposure to Pentachlorophenol - Oral (continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
8	Mouse	1 x (G)		15	30 (decr IgM antibody response)		Kerkvliet et al. 1985a tech (86% pure)
9	Mouse	1 x (G)		120			Kerkvliet et al. 1985a pure (>99%)
10	Mouse	14 d 7 d/wk (G)		100			White and Anderson 1985 tech (91% pure)
11	Mouse	14 d 7 d/wk (G)			100 (inhibition of complement activity)		White and Anderson 1985 tech (90.4% pure)
Developmental							
12	Rat (Sprague-Dawley)	GD6-15 (GO)		30		80	(incr resorptions, decr fetal body weight, and incr soft tissue and skeletal malformations and variations) Argus 1993b tech (89% pure)
13	Rat	10 d Gd6-15 1 x/d (GO)		5		15	(fetal resorptions, subcutaneous edema, lumbar spurs) Schwetz et al. 1974 tech (88.4% pure)
14	Rat	10 d Gd6-15 1 x/d (GO)			5 ^c (delayed ossification of skull bones)	30	(42% decr fetal weight; increased male:female ratio) Schwetz et al. 1974 pure (97.5%)
15	Rabbit (New Zealand)	GD6-18 (GO)		30			Argus 1993a tech (88-89%)

Table 3-1. Levels of Significant Exposure to Pentachlorophenol - Oral (continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
INTERMEDIATE EXPOSURE							
Death							
16	Rat	1-3 mo 2x/wk (G)				300 (LD50)	Nishimura et al. 1980 tech NaPCP
17	Rat (Fischer- 344)	28d (F)				270 (death)	NTP 1999; Chhabra et al. 1999 pure (99%)
18	Mouse (B6C3F1)	30 d (F)				4428 M (death) 3561 ^b F (death)	NTP 1989 tech (90.4% pure)
19	Mouse (B6C3F1)	30 d (F)				1017 M (death) 848 ^b F (death)	NTP 1989 tech (90% pure)
20	Mouse (B6C3F1)	30 d (F)				650 M (death)	NTP 1989 pure (98.6%)

Table 3-1. Levels of Significant Exposure to Pentachlorophenol - Oral (continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
Systemic							
21	Rat (Sprague- Dawley)	P0: 70 days prematuring, and through gestation and lactation F1: postnatal day 28 and through gestation and lactation (GO)	Hepatic Bd Wt		10 (incr absolute and relative liver weight and hepatocellular hypertrophy)	30 (hepatocellular necrosis)	Argus 1997 not reported
22	Rat (Fischer- 344)	28 d 2x/wk (GO)	Hepatic Renal		2 M (incr relative wt)		Blakley et al. 1998 pure (>99%)
23	Rat	8 mo 7 d/wk (F)	Hepatic	6 M	36 M (centrilobular hepatocyte hypertrophy)		Kimbrough and Linder 1978 pure (>99%)
			Renal Bd Wt	45 F 6 M	36 M (10% decr bw)		

Table 3-1. Levels of Significant Exposure to Pentachlorophenol - Oral (continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
24	Rat	12 wk 7d/wk (F)	Hemato	2 M	4 M (incr and decr hemoglobin and decr RBC)		Knudsen et al. 1974 tech
			Hepatic	2 M	4 M (incr relative liver weight, centrilobular vacuolization)		
			Renal	4 F	8 F (decr calculi at corticomedullary junction)		
25	Rat	1-3 mo 2x/wk (G)	Hepatic		40 (incr liver weight; decr hepatic glycogen; incr serum lactate dehydrogenase, AST and ALT; hepatocellular swelling; vacuolization)		Nishimura et al. 1980 tech NaPCP
			Metab		40 (incr blood glucose)		
26	Rat (Fischer- 344)	28d (F)	Hepatic		20 F (incr absolute and relative liver wt)	40 (hepatocyte degeneration)	NTP 1999; Chhabra et al. 1999 pure (99%)
			Bd Wt		20 F (14% decr bw gain)	150 F (decr bw gain of 36% or more and wt loss)	
27	Rat	181 d 7d/wk (F)	Bd Wt	4	46 (15% decr maternal bw)		Welsh et al. 1987 pure (>99%)
28	Mouse	10-12 wk 7d/wk (F)	Hepatic		9 (hepatocellular swelling; nuclear swelling and vacuolization)	90 (multifocal necrosis)	Kerkvliet et al. 1982 pure (>99%)

Table 3-1. Levels of Significant Exposure to Pentachlorophenol - Oral (continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
29	Mouse	10-12 wk 7d/wk (F)	Hepatic		9 (hepatocyte swelling; nuclear swelling and vacuolization)	90 (multifocal necrosis)	Kerkvliet et al. 1982 tech (86% pure)
30	Mouse	6 wk 7d/wk (F)	Hepatic		47.1 (incr liver wt)		Kerkvliet et al. 1985a tech (86% pure)
			Other		47.1 (incr p-450 associated EROD activity)		
31	Mouse (B6C3F1)	6 mo (F)	Resp	209 F			NTP 1989 tech (90.4% pure)
			Hepatic			48 M (karyomegaly, cytomegaly, hepatocellular degen and necrosis, incr AHH activity and P450 levels, incr liver wt, incr liver porphyrins, incr serum ALT)	
			Bd Wt	376 M			
			Other		48 M (granular eosinophilic pigment in the urinary bladder, without inflammation)		

Table 3-1. Levels of Significant Exposure to Pentachlorophenol - Oral (continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
32	Mouse (B6C3F1)	6 mo (F)	Resp		64 F (nasal mucosal metaplasia/goblet cell hyperplasia)		NTP 1989 tech (90% pure)
			Hepatic			49 M (karyomegaly, cytomegaly, hepatocellular degen and necrosis)	
			Bd Wt Other	49 M	148 M (decr bw gain of 21%) 49 M (granular eosinophilic pigment in the urinary bladder, without inflammation)		
33	Mouse (B6C3F1)	6 mo (F)	Resp		67 F (nasal mucosal metaplasia/goblet cell hyperplasia)		NTP 1989 pure (98.6%)
			Hepatic			67 F (karyomegaly, cytomegaly, and hepatocellular degen and necrosis, incr relative liver wt, incr serum ALT)	
			Bd Wt Other	168 F	544 F (decr bw gain of 18%) 67 F (granular eosinophilic pigment in the urinary bladder, without inflammation)	381 M (decr bw gain of 30%)	
34	Mouse (B6C3F1)	30 d (F)	Hepatic	20 M		105 M (cytomegaly, karyomegaly, nuclear atypia, degen, or necrosis of the liver)	NTP 1989 tech (90.4%)
			Bd Wt	105 M		528 M (41% decr in bw gain)	

Table 3-1. Levels of Significant Exposure to Pentachlorophenol - Oral (continued)

Key to figure ^a	Species (Strain)	Exposure/Duration/Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
35	Mouse (B6C3F1)	30 d (F)	Hepatic	21 M		104 M (cytomegaly, karyomegaly, nuclear atypia, degen, or necrosis of the liver)	NTP 1989 tech (90% pure)
			Bd Wt		104 M	1017 M (86% decr in bw gain)	
36	Mouse (B6C3F1)	30 d (F)	Hepatic	23 M		101 M (cytomegaly, karyomegaly, nuclear atypia, degen, or necrosis of the liver)	NTP 1989 pure (98.6%)
			Bd Wt		101 M	604 M (80% decr in bw gain)	
37	Mouse (B6C3F1)	up to 4 wk 7d/wk (F)	Hepatic		41 M (incr liver wt, severe hepatocyte swelling, incr hepatic DNA content and DNA adducts)		Umemura et al. 1996 pure (98.6%)
38	Pig	30 d 7d/wk (C)	Hemato	5	10 (decreased white blood cell count)		Greichus et al. 1979 pure
			Hepatic	5	10 (increased liver weight; diffuse cloudy hepatocellular swelling)		
			Renal		10		
Immunological/Lymphoreticular							
39	Rat (Fischer- 344) (GO)	28 d 2x/wk			2 M (enhanced lymphocyte blastogenesis, suppressed antibody response against sheep RBC)		Blakley et al. 1998 pure (>99%)

Table 3-1. Levels of Significant Exposure to Pentachlorophenol - Oral (continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
40	Mouse	10-12 wk 7d/wk (F)			9	(enhanced susceptibility to tumor growth)	Kerkvliet et al. 1982 tech (86% pure)
41	Mouse	10-12 wk 7d/wk (F)		9	90.3	(enhanced susceptibility to tumor growth)	Kerkvliet et al. 1982 pure (>99%)
42	Mouse	6 wk 7d/wk (F)			1.9	(decr antibody response)	Kerkvliet et al. 1985a tech (86% pure)
43	Mouse	8 wk 7d/wk (F)			50.1	(reduction in lymphoproliferative response in mixed lymphocyte culture)	Kerkvliet et al. 1985b tech (86% pure)
44	Mouse (B6C3F1)	6 mo (F)			48 M	(decr immune response to sheep RBC injection)	NTP 1989 tech (90.4% pure)

Table 3-1. Levels of Significant Exposure to Pentachlorophenol - Oral (continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL		Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	
Reproductive						
45	Rat (Sprague-Dawley)	P0: 70 days pre-mating, and through gestation and lactation F1: postnatal day 28 and through gestation and lactation (GO)		10	30 (decr testicular spermatid count)	60 (decr fertility) Argus Research Laboratories, 1997 not reported
46	Rat (Fischer- 344)	28d (F)		150 M		270 M (min to marked germinal epithelial degen & lack of spermatozoa in the seminiferous tubules of the testes, considered secondary to the generalized poor condition of the high-dose rats) NTP 1999; Chhabra et al. 1999 pure (99%)
47	mink	3 wk pre-breeding thru weaning 1x/d (F)			1 ^d F (incr severity of cystic uteri, decr acceptance of 2nd mating, decr birth rate)	Beard et al. 1997 not reported

Table 3-1. Levels of Significant Exposure to Pentachlorophenol - Oral (continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL		Reference Chemical Form	
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)		Serious (mg/kg/day)
Developmental							
48	Rat (Sprague- Dawley)	P0: 70 days prematuring, and through gestation and lactation F1: postnatal day 28 and through gestation and lactation (GO)		4	10 (decr pup body weight)	60 (decr pup survival)	Argus 1997 not reported
49	Rat	10 week prematuring throughout gestation and lactation (F)				48 (decr litter size)	Exon and Koller 1982 tech (85.5% pure)
50	Rat	181 d 7d/wk (F)		4	14 (10% decr fetal bw)	46 (embryo lethality)	Welsh et al. 1987 pure (>99%)

Table 3-1. Levels of Significant Exposure to Pentachlorophenol - Oral (continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
CHRONIC EXPOSURE								
Systemic								
51	Rat (Fischer- 344)	52 wk (F)	Bd Wt			60	(decr bw gain of 24-35% at wk 52)	NTP 1997; Chhabra et al. 1999 pure (99%)
			Hepatic		60 M (basophilic foci, hepatodiaphragmatic nodules, chronic inflammation, and hepatocyte cystic degeneration)			
52	Rat (Fischer- 344)	105 wk (F)	Hepatic		10 M (hepatocyte cystic degen and hepatodiaphragmatic nodules)			NTP 1999; Chhabra et al. 1999 pure (99%)
			Bd Wt	20	30		(decr bw gain of 10-17%)	
53	Rat	22-24mo 7d/wk (F)	Hepatic	3 F	10 F (accumulation of brown pigment; elevated ALT)			Schwetz et al. 1978 tech (90% pure)
			Renal	3 F	10 F (accumulation of brown pigment in kidney tubules; increase in urine specific gravity)			
			Bd Wt	10 F	30 F (12% decr bw as compared to controls)			
54	mink	3 gen (F)	Endocr		1 ^e (statistically significant decr serum thyroxine and decr relative thyroid wt)			Beard and Rawlings 1998 not reported

Table 3-1. Levels of Significant Exposure to Pentachlorophenol - Oral (continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
Reproductive							
55	mink	3 gen (F)		1			Beard and Rawlings 1998 not reported
Cancer							
56	Rat (Fischer-344)	52 wk at 60; 105 wk at lower doses (F)				60 M (CEL, malignant mesothelioma and nasal squamous cell carcinoma)	NTP 1999; Chhabra et al. 1999 pure (99%)
57	Mouse	103 wk 1x/d (F)				17.5 (pheochromocytomas; hepatocellular carcinoma-CEL)	NTP 1989 tech (90% pure)

Table 3-1. Levels of Significant Exposure to Pentachlorophenol - Oral (continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
58	Mouse	103 wk 1x/d (F)				18 (hemangiosarcomas of the liver and spleen-CEL)	NTP 1989 tech (90% pure)

^aThe number corresponds to entries in Figure 3-1.

^bDifferences in levels of health effects and cancer effects between males and females are not indicated in Figure 3-1. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

^cUsed to derive an acute-duration oral Minimal Risk Level (MRL) of 0.005 mg/kg/day; dose divided by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

^dUsed to derive an intermediate-duration oral Minimal Risk Level (MRL) of 0.001 mg/kg/day; dose divided by an uncertainty factor of 1000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

^eUsed to derive a chronic-duration oral Minimal Risk Level (MRL) of 0.001 mg/kg/day; dose divided by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

Bd Wt = body weight; bw = body weight; CEL = cancer effect level; conc = concentration(s); d = day(s); decr = decrease; degen = degenerative;
 EC-7 = a mixture containing 90% pure pentachlorophenol; Endocr = endocrine; (F) = feed; F = female(s); (G) = gavage; Gd = gestation day; gen = generation(s);
 (GO) = gavage in oil; (GW) = gavage in water; IgM = immunoglobulin M; incr = increase; Ld = lactation day; LOAEL = lowest-observed-adverse-effect level;
 LD50 = lethal dose, 50% kill; M = males; min = minimal; mo = month(s); NaPCP = sodium pentachlorophenol; NOAEL = no-observed-adverse-effect level;
 RBC = red blood cell; Resp = respiratory; SGOT = serum glutamic oxaloacetic transferase; SGPT = serum glutamic pyruvic transaminase; tech = technical grade;
 TG-penta = technical grade pentachlorophenol; (w) = water; wk = week(s); wt = weight; x = times(s)

Figure 3-1. Levels of Significant Exposure to Pentachlorophenol - Oral
Acute (≤ 14 days)

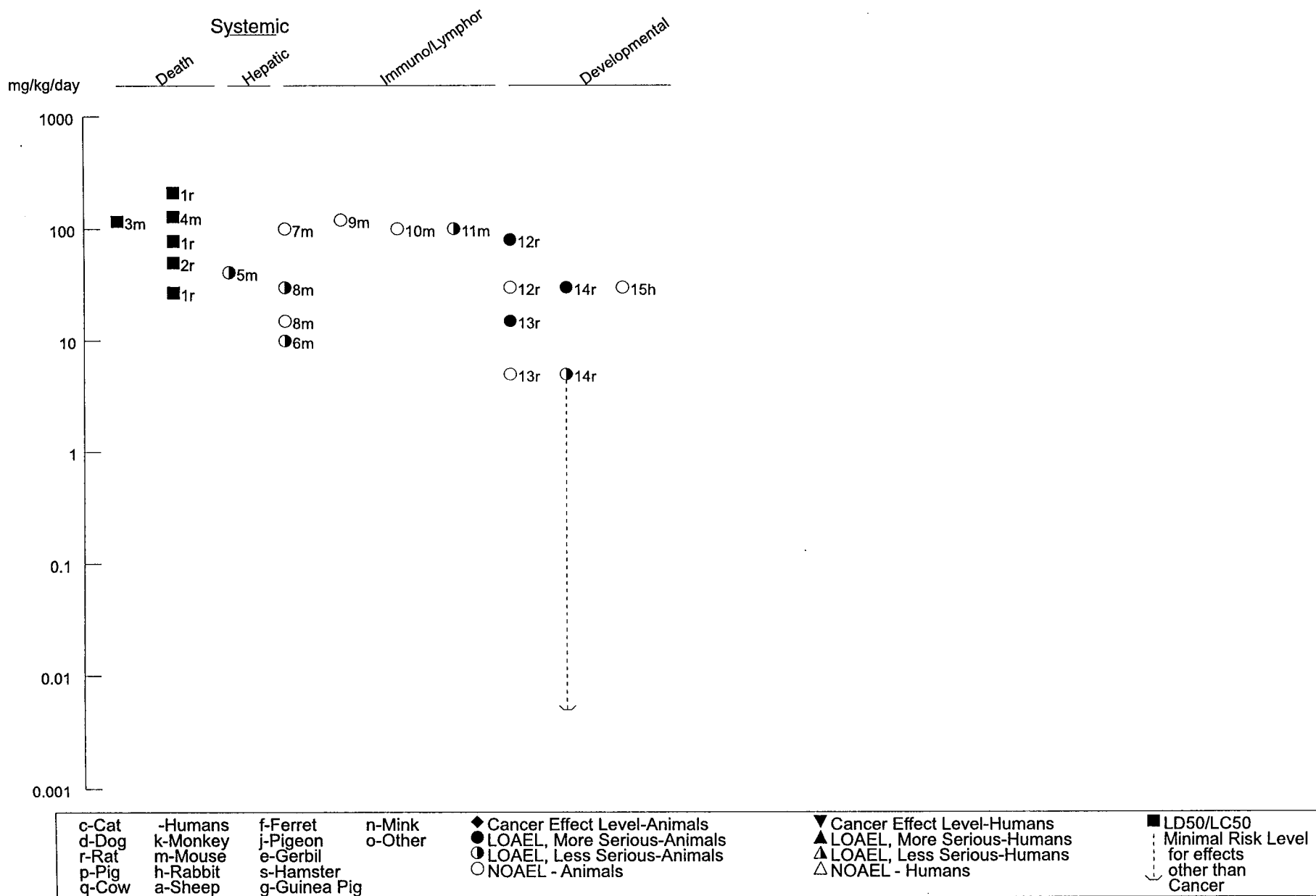
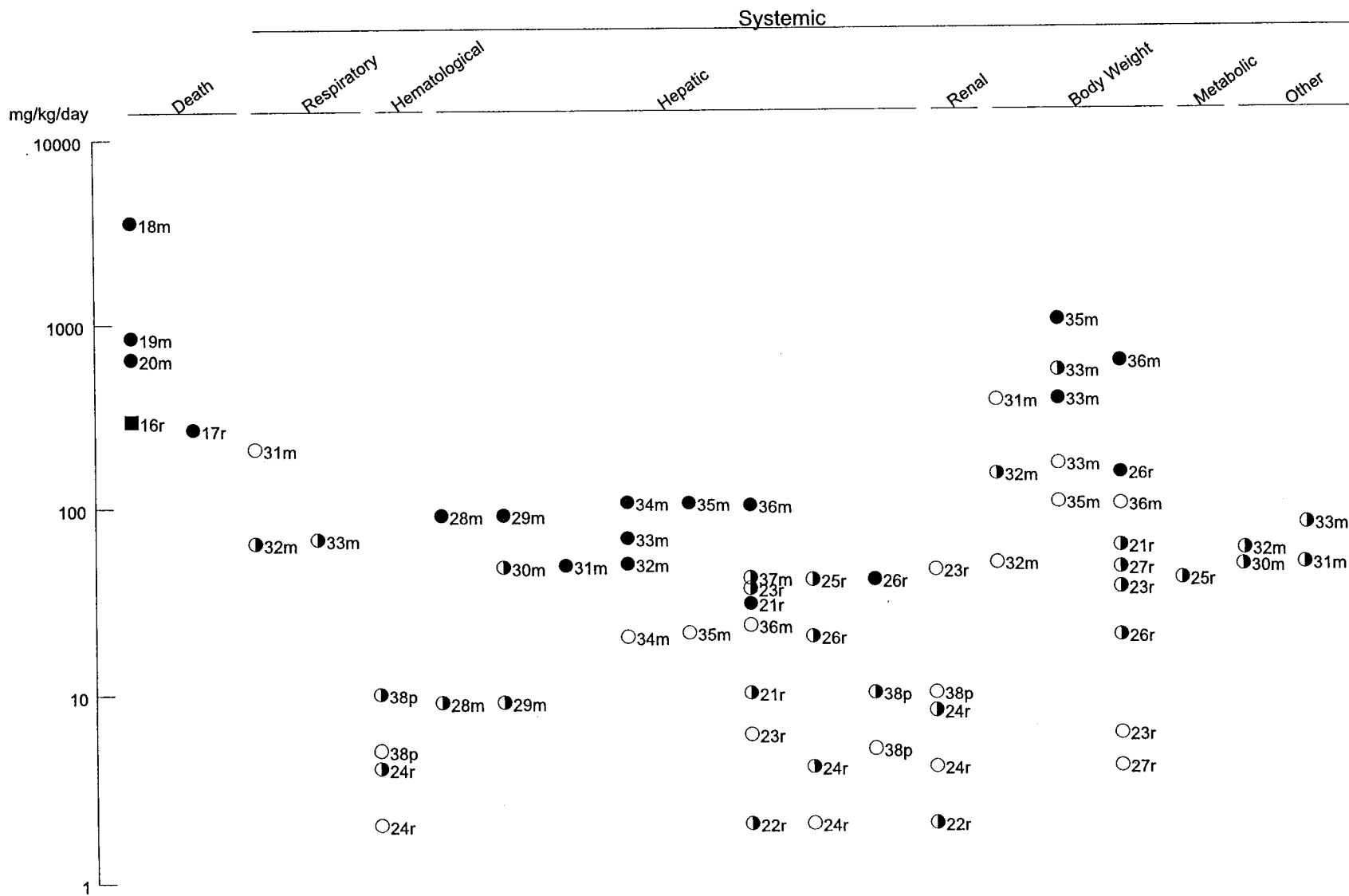


Figure 3-1. Levels of Significant Exposure to Pentachlorophenol - Oral (continued)
Intermediate (15-364 days)



c-Cat	-Humans	f-Ferret	n-Mink	◆ Cancer Effect Level-Animals	▼ Cancer Effect Level-Humans	■ LD50/LC50
d-Dog	k-Monkey	j-Pigeon	o-Other	● LOAEL, More Serious-Animals	▲ LOAEL, More Serious-Humans	⋮ Minimal Risk Level
r-Rat	m-Mouse	e-Gerbil		○ LOAEL, Less Serious-Animals	△ LOAEL, Less Serious-Humans	for effects other than Cancer
p-Pig	h-Rabbit	s-Hamster		○ NOAEL - Animals	△ NOAEL - Humans	
q-Cow	a-Sheep	g-Guinea Pig				

Figure 3-1. Levels of Significant Exposure to Pentachlorophenol - Oral (continued)
Intermediate (15-364 days)

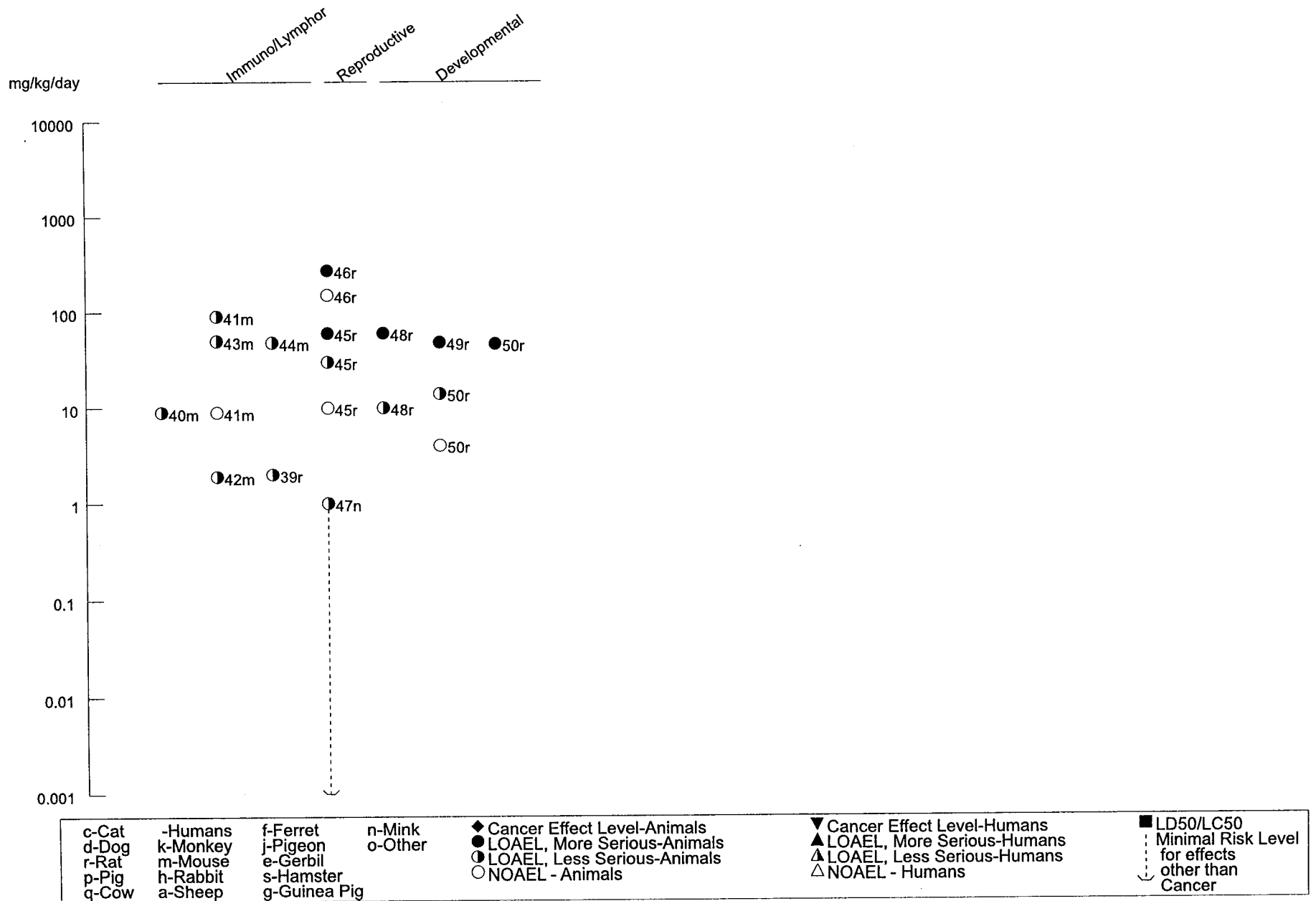
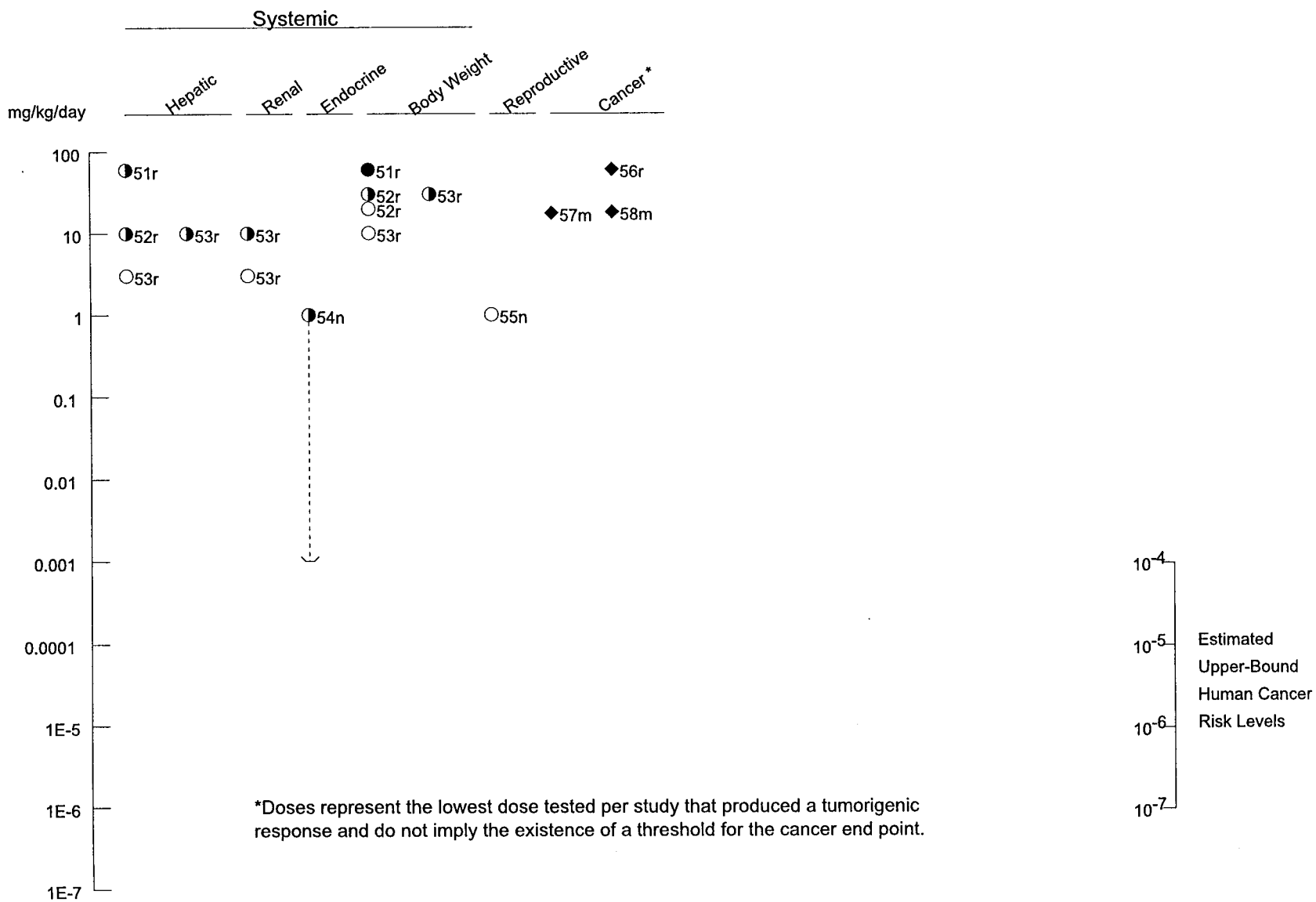


Figure 3-1. Levels of Significant Exposure to Pentachlorophenol - Oral (continued)

Chronic (≥365 days)



c-Cat	-Humans	f-Ferret	n-Mink	◆ Cancer Effect Level-Animals	▼ Cancer Effect Level-Humans	■ LD50/LC50
d-Dog	k-Monkey	j-Pigeon	o-Other	● LOAEL, More Serious-Animals	▲ LOAEL, More Serious-Humans	□ Minimal Risk Level
r-Rat	m-Mouse	e-Gerbil		○ LOAEL, Less Serious-Animals	△ LOAEL, Less Serious-Humans	⋯ for effects other than Cancer
p-Pig	h-Rabbit	s-Hamster		○ NOAEL - Animals	△ NOAEL - Humans	
q-Cow	a-Sheep	g-Guinea Pig				

Table 3-2. Results of Analyses of Impurities Present in the Pentachlorophenol Used in National Toxicology Program (NTP) Feeding Studies and the Types of Tumors They Induce^{a,b}

Impurity	Technical grade	Dowicide EC-7 ^c	Pure	Tumor type	Species
Dichlorophenol	–	–	–	No data	
Trichlorophenol ^d	100 ppm	70 ppm	100 ppm	Liver, leukemias ^e , lymphomas	Rat, mouse
Tetrachlorophenol	38,000 ppm	94,000 ppm	14,000 ppm	Not carcinogenic	Rat, mouse
Hexachlorobenzene	50 ppm	65 ppm	10 ppm	Liver	Rat, hamster, mouse
				Thyroid/ Parathyroid	Rat
				Adrenal	Rat
				Kidney	Rat
				Lymphosarcomas	Mouse
Tetrachlorodibenzodioxin	–	<0.04 ppm	<0.08 ppm	Liver, thyroid	Rat, mouse (both tumor types)
Hexachlorodibenzodioxin	10.1 ppm	0.19 ppm	<1 ppm	Liver	Rat, mouse
Heptachlorodibenzodioxin	296 ppm	0.53 ppm	–	No data	
Octachlorodibenzodioxin	1,386 ppm	0.69 ppm	<1 ppm	No data	
Pentachlorodibenzofuran	1.4 ppm	–	–	No data	
Hexachlorodibenzofuran	9.9 ppm	0.13 ppm	–	No data	
Heptachlorodibenzofuran	88 ppm	0.15 ppm	–	No data	
Octachlorodibenzofuran	43 ppm	–	–	No data	
Heptachlorohydroxydiphenyl ether	500 ppm ^f	–	100 ppm	No data	

Table 3-2. Results of Analyses of Impurities Present in the Pentachlorophenol Used in National Toxicology Program (NTP) Feeding Studies and the Types of Tumors They Induce^{a,b} (continued)

Impurity	Technical grade	Dowicide EC-7 ^c	Pure	Tumor type	Species
Octachlorohydroxydiphenyl ether	19,100 ppm	–	900 ppm	No data	
Nanochlorohydroxydiphenyl ether	35,600 ppm	–	2,100 ppm	No data	
Hexachlorohydroxydibenzofuran	1,600 ppm	–	1,100 ppm	No data	
Heptachlorohydroxydibenzofuran	4,700 ppm	–	2,200 ppm	No data	

^aSamples were dissolved in benzene, placed on a deactivated alumina column, and eluted with benzene. Further separation was carried out with a basic aluminum oxide column; elution was with methylene chloride in hexane. Identification was performed by gas chromatography with an SP2100 capillary column/mass spectrometry; quantitation was by comparison with spiked samples analyzed by gas chromatography with an SP1240 DA column.

^bDerived from NTP 1989

^cFour unidentified impurities with concentrations of 0.14, 0.057, 0.045, and 0.035 ppm were also detected.

^dIdentified as the 2,3,6-isomer; another isomer was believed to be present but was not identified.

^eData are for 2,4,6-isomer.

^fIncludes octachlorodiphenyl ether

– = not detected; EC-7 = Dow Company chemical name

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dietary doses of \$64 mg/kg/day EC-7 (90% pure) and \$67 mg/kg/day pure pentachlorophenol, but were not observed in the female mice exposed to 209 mg/kg/day technical-grade pentachlorophenol (which contains relatively high concentrations of chlorinated dibenzo-*p*-dioxins and dibenzofurans). The female mice appeared to be more sensitive to the nasal effects than the male mice. The LOAELs for nasal lesions were 148 and 381 mg/kg/day in the EC-7 and pure pentachlorophenol groups, respectively.

Cardiovascular Effects. One report describing effects of ingestion of pentachlorophenol in humans was found in the literature (Haley 1977). In this case, an adult male intentionally ingested an estimated 4–8 ounces of weed killer that contained 12% pentachlorophenol, 1.5% other chlorinated phenols, 82% aromatic hydrocarbons, and 4.5% inert ingredients. Clinical signs observed upon subsequent hospital admission included tachycardia. This effect is possibly the result of pentachlorophenol's ability to uncouple oxidative phosphorylation, leading to hyperthermia.

One early report described the occurrence of extensive vascular damage and heart failure in rats, rabbits, guinea pigs, and dogs following a single oral administration (dose not specified) of pentachlorophenol of unidentified purity (Deichmann et al. 1942).

Hematological Effects. No studies were located regarding hematological effects in humans after oral exposure to pentachlorophenol.

Various hematologic changes of questionable biological significance have been reported in animal studies. A depression in number of erythrocytes, a decrease in hemoglobin level, and a decrease in packed cell volume were observed in rats fed technical-grade pentachlorophenol for 90 days but not in those fed purified pentachlorophenol (Johnson et al. 1973). However, a decrease in white blood cell count was observed in pigs administered purified pentachlorophenol for 30 days (Greichus et al. 1979). Conflicting findings over time were reported in rats fed a purified pentachlorophenol preparation, which contained no tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD) and <0.03% of the other chlorinated dibenzo-*p*-dioxins, for 12 weeks (Knudsen et al. 1974). Increased hemoglobin and hematocrit were observed after 6 weeks of treatment, followed by a decrease in hemoglobin and erythrocytes at study termination.

Hepatic Effects. No studies were located regarding hepatic effects in humans after oral exposure to pentachlorophenol.

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The liver is a target organ for pentachlorophenol-induced toxicity in experimental animals. Evidence of biochemical (alterations in hepatic enzyme activities), and gross (increased liver weight), and histopathological (hypertrophy, vacuolization, hyperplasia, fibrosis, necrosis, and degeneration) effects is seen following acute, intermediate, and chronic oral exposure to pentachlorophenol in rodents. At low dosages, the observed liver effects are characteristic of enzyme induction. Increases in liver weight and hepatocellular hypertrophy and vacuolization have been observed in mice exposed to 41 mg/kg/day pure pentachlorophenol for 2 weeks (Umemura et al. 1996), in rats exposed to 1–40 mg/kg/day pure or technical-grade pentachlorophenol for an intermediate duration (Argus 1997/Bernard et al. 2001c; Blakley et al. 1998; Kimbrough and Linder 1978; Knudsen et al. 1974; Nishimura et al. 1982; NTP 1999), in mice exposed to 9 mg/kg/day pure or technical-grade pentachlorophenol for 4–12 weeks (Kerkvliet et al. 1982; Umemura et al. 1996), and in pigs exposed to 10 mg/kg/day pure pentachlorophenol for 30 days (Greichus et al. 1979).

The severity of the liver damage increased with increasing exposure concentrations. Intermediate-duration exposure to doses of 7–48 mg/kg/day pure or technical-grade pentachlorophenol resulted in necrosis, periportal fibrosis, and hepatocellular degeneration in rats (Argus 1997/Bernard et al. 2001c; Kimbrough and Linder 1978; NTP 1989) and multifocal necrosis and hepatocellular degeneration in mice exposed to 67–105 mg/kg/day pure or technical-grade pentachlorophenol (Kerkvliet et al. 1982; NTP 1989). Hepatocellular degeneration was observed in rats exposed to 10–60 mg/kg/day pure pentachlorophenol in the diet for 52 or 104 weeks (NTP 1999). The biochemical changes consisted of increases in the serum levels of alanine and aspartate aminotransferase at 40 and 67 mg/kg/day pure or technical-grade pentachlorophenol in rats (Nishimura et al. 1980) and mice (NTP 1989), respectively.

The results of the Kimbrough and Linder (1978) study suggests that the impurities found in technical-grade pentachlorophenol may influence its toxicity. The liver effects observed in this study included centrilobular hepatocyte hypertrophy at 1 mg/kg/day, periportal fibrosis at 7 mg/kg/day, and periportal fibrosis and bile duct proliferation at 48 mg/kg/day in rats exposed to technical-grade pentachlorophenol in the diet for 8 months. In contrast, minimal liver effects (centrilobular hepatocyte hypertrophy) were observed at the highest tested dose (32 mg/kg/day) of pure pentachlorophenol. It is possible that the tetrachlorophenol, hexachloro-*p*-dibenzodioxin, heptachloro-*p*-dibenzodioxin, octachloro-*p*-dibenzodioxin, hexachlorodibenzofuran, pentachlorodibenzofuran, and tetrachlorodibenzofuran present in the technical-grade pentachlorophenol influenced its hepatotoxicity. However, other studies that compared the hepatotoxicity of pure and technical-grade pentachlorophenol did not find differences in potency or the type of liver effects (Kerkvliet et al. 1982; NTP 1989).

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Renal Effects. No studies were located regarding renal effects in humans after oral exposure to pentachlorophenol.

There is evidence of mild-to-moderate renal toxicity in experimental animals as a result of long-term oral administration of pentachlorophenol. The most frequently reported toxic effects seen in kidneys of rodents include increased organ weight and altered enzyme levels. Histopathologic effects are rarely seen. The possibility that impurities in pentachlorophenol may be responsible for the adverse effects observed is likely. Furthermore, some of the data discussed below have many inconsistencies.

Purified pentachlorophenol (2 mg/kg/day, only dose tested, >99% pure with no detectable dioxin impurities) induced a small but significant increase in relative kidney weight in rats exposed twice weekly for 28 days (Blakley et al. 1998).

When similar doses of technical-grade and purified pentachlorophenol (>99% pure) were fed to rats for 8 months, the pure compound induced a slight, non-dose-related increase in kidney weight in males, whereas the technical-grade compound did not alter kidney weight in either sex (Kimbrough and Linder 1978). When similar doses of technical-grade and pure pentachlorophenol (no detectable chlorinated dibenzo-*p*-dioxins) were fed to rats for 3 months, increased kidney weight was reported at 10–30 mg/kg/day of the technical-grade preparation, but only at the 30 mg/kg/day dose of the pure pentachlorophenol (Johnson et al. 1973). In neither study were renal histopathological changes observed to accompany organ weight changes. Thus, the biological significance of these observations with regard to long-term toxicity is not known.

Increased kidney weight and urine specific gravity and a dose-related incidence of kidney discoloration were observed in rats fed 1–30 mg/kg/day of Dowicide EC-7 (a purified pentachlorophenol containing <0.0002% chlorinated dibenzo-*p*-dioxins and dibenzofurans) for 24 months (Schwetz et al. 1978). Pigmentation *per se* is not considered an adverse effect. Biochemical changes indicative of renal toxicity have also been reported in pentachlorophenol-treated animals. For example, after 15 days of oral exposure to purified pentachlorophenol at 10 or 15 mg/kg/day, young pigs exhibited statistically significant increased levels of blood urea nitrogen, but this effect was no longer significant after 30 days of treatment (Greichus et al. 1979). Proximal tubular alkaline phosphatase activity was decreased after 1 month of twice-weekly gavage doses (40–160 mg/kg/day) of 90% pure pentachlorophenol (sodium salt; impurities not identified) administered to rats, but this effect was no longer evident after 3 months of

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treatment (Nishimura et al. 1980). The biological significance of these apparently transient renal effects with regard to long-term toxicity is not known.

Endocrine Effects. No studies were located regarding endocrine effects in humans after oral exposure to pentachlorophenol.

Significant alterations in thyroid hormone levels have been observed in several intermediate- and chronic-duration animal studies. Oral gavage administration of pure pentachlorophenol to young adult female rats over a 28-day period at a dose of 30 mg/kg produced decreases in circulating and free concentrations of the thyroid hormones triiodothyronine and thyroxine in serum, a decrease in serum thyroid stimulating hormone, decreases in intrathyroidal levels of triiodothyronine and thyroxine, a decrease in the ratio of serum thyroxine to triiodothyronine, and a reduction in thyroidal hormone stores. Decreases in circulating and free thyroxine were also observed at 3 mg/kg/day. Technical-grade pentachlorophenol, tested only at a dose of 3 mg/kg, produced the same effects as 30 mg/kg of pure pentachlorophenol except the reduction in free T3 in serum (data for free serum T4 were not reported). Technical-grade pentachlorophenol, in addition, produced an increase in thyroid epithelial-cell height (Jekat et al. 1994). In a multigeneration study in mink, significant decreases in serum thyroxine levels were observed in the F1 males and the F2 males and females exposed to 1 mg/kg/day pentachlorophenol (purity not reported) (Beard and Rawlings 1998). A decrease in relative thyroid weight was also observed in the F2 female mink. This LOAEL of 1 mg/kg/day was used to derive a chronic-duration oral MRL of 0.001 mg/kg/day, as described in the footnote in Table 3-1.

Alterations in thyroid hormone levels were also observed in a series of studies in sheep. A significant decrease in thyroxine levels was observed in female sheep administered 2 mg/kg/day pure pentachlorophenol by gavage twice weekly for 36 days (Rawlings et al. 1998). Exposure of female sheep to 1 mg/kg/day pentachlorophenol (purity not reported) for 5 weeks pre-mating and throughout gestation and lactation, resulted in significant decreases in serum thyroxine levels in the mothers (Beard et al. 1999b), in the ram lambs that were also exposed for 20 weeks post weaning (Beard et al. 1999a), and in the ewe lambs also exposed for 67 weeks post weaning (Beard and Rawlings 1999). No alterations in thyroid stimulating hormone levels or the response to thyroid releasing hormone were observed in the female offspring. However, in response to thyroid stimulating hormone, there were reductions in the magnitude and duration of the thyroxine response and in the maximum triiodothyronine level and net triiodothyronine increase.

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There are limited data on the toxicity of pentachlorophenol to other endocrine tissues. A significant increase in mean serum insulin concentrations was seen in sheep receiving twice weekly gavage doses of 2 mg/kg/day (Rawlings et al. 1998). No alterations in cortisol levels were observed in ram lambs (Beard et al. 1999a).

Body Weight Effects. Significant (10%) decreases in body weight gain were observed in several studies where both technical-grade and pure pentachlorophenol were administered orally for intermediate or chronic durations to rats or mice (Chhabra et al. 1999; Kimbrough and Linder 1978; Nishimura et al. 1980; NTP 1989, 1999; Welsh et al. 1987). Suppression of body weight gain by oral administration of pentachlorophenol was also reported in maternal animals, fetuses, and neonates.

Metabolic Effects. There are limited data on the metabolic toxicity of pentachlorophenol. Nishimura et al. (1980) reported significant increases in blood glucose levels and decreases in hepatic glycogen levels in rats administered 40 mg/kg/day technical-grade sodium pentachlorophenate by gavage twice weekly for 1 to 3 months.

Other Systemic Effects. In the intermediate-duration studies conducted by NTP (1989), granular eosinophilic pigment was observed in the epithelial cells of the urinary bladder of rats exposed to technical-grade pentachlorophenol, EC-7 (90% pure), and pure pentachlorophenol; the increase in pigment was not accompanied by inflammation.

3.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans following oral exposure to pentachlorophenol.

Evidence for pentachlorophenol-induced alterations in immune function was obtained from studies conducted in experimental animals. The available data indicate that, at doses of 0.5–100 mg/kg/day, pentachlorophenol affects a wide range of immune functions, such as humoral and cellular immunity, susceptibility to tumor induction, and complement activity. Detailed studies in mice indicate that the majority of the immunotoxic effects of pentachlorophenol appear to be related to the level of impurities in the technical-grade product (e.g., polychlorinated dibenzo-*p*-dioxins and dibenzofurans) (Kerkvliet et al. 1982, 1985a; NTP 1989; White and Anderson 1985). However, a recent study in rats provides evidence that pure pentachlorophenol (>99% with no detectable dioxin impurities) can affect immune function

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(Blakley et al. 1998). Studies that compared effects of technical-grade to pure pentachlorophenol are reviewed below in an attempt to illustrate immunotoxic effects attributable to pentachlorophenol.

Female B6C3F₁ mice exposed daily to 10–100 mg/kg of technical-grade pentachlorophenol by gavage for 2 weeks exhibited a dose-related suppression of *in vivo* antibody response (IgM plaque-forming cells [PFC]) to sheep red blood cells (SRBC) when mice were immunized during exposure (Holsapple et al. 1987). This response was not seen following exposure to purified pentachlorophenol at a dose of 100 mg/kg. It was further observed that spleen cells from mice treated with technical-grade pentachlorophenol could still produce antibodies following *in vitro* immunization, indicating that the suppression seen following *in vivo* immunization was not due to a direct effect on antibody-forming cells.

Purified pentachlorophenol (>99% pure with no detectable dioxin impurities) administered to male F344 rats twice weekly for 28 days at a dose of 2 mg/kg/treatment significantly enhanced mitogen-induced T- and B-lymphocyte blastogenesis and significantly suppressed the antibody response against injected sheep red blood cells when the response was expressed per viable spleen cell (Blakley et al. 1998).

In 6-month dietary range-finding studies (NTP 1989) with 3 different preparations of pentachlorophenol (technical-grade, Dowicide EC-7, or pure) in B6C3F₁ mice (see Table 3-2), the antibody response to sheep red blood cell injection was decreased at doses of technical-grade pentachlorophenol \$48 mg/kg/day in males but was not affected in males by dosing with Dowicide EC-7 or pure pentachlorophenol. Antibody response data were not reported for females. In the same studies, significant increases in relative spleen weight were not seen in dosed females, but were seen in males at doses of 376 mg/kg/day technical-grade pentachlorophenol, \$49 mg/kg/day Dowicide EC-7, and \$225 mg/kg/day pure pentachlorophenol.

Effects of dietary administration of both technical-grade and purified pentachlorophenol for 10–12 weeks on the ability of male B6C3F₁ mice to resist syngeneic tumor growth, an indication of an organism's state of immunosurveillance, were studied (Kerkvliet et al. 1982). Technical-grade preparation induced a significant dose-independent enhancement of susceptibility to methylcholanthrene-induced sarcoma 1412 tumor growth, whereas the purified preparation had no effect on this parameter. In another test of immunocompetence, treated mice were studied for their ability to resist secondary tumor growth induced by Maloney sarcoma virus (MSV). After exposure to technical-grade pentachlorophenol, animals were inoculated with MSV, which resulted in transient subcutaneous injection-site tumors. Upon subsequent challenge with MSV-transformed tumor cells, a significant increase in mortality and secondary tumor

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susceptibility was seen in animals treated with technical-grade pentachlorophenol but not in animals administered purified pentachlorophenol. This result suggests a detrimental effect of components of the technical-grade pentachlorophenol on both primary and secondary T-cell-dependent cytotoxic immune response. An increase in secondary splenic tumors was seen in animals treated with both grades of pentachlorophenol at a dose of 25 mg/kg/day. This was interpreted as a more sensitive indicator of immunocompetence suppression by purified pentachlorophenol. In a third test designed to evaluate macrophage competence, resistance to encephalomyocarditis virus (EMCV) was also studied in mice treated with both grades of pentachlorophenol. No effect was seen on susceptibility of either group of animals to EMCV-induced mortality. The investigators concluded that immunomodulatory effects observed with pentachlorophenol were due primarily, but not exclusively, to contaminants present in the technical-grade preparation.

To further investigate the role of these impurities in immunotoxicity induced by technical-grade pentachlorophenol, the antibody (IgM) response to an SRBC challenge in C57BL/6 mice given single oral doses of both grades of pentachlorophenol was studied (Kerkvliet et al. 1985a). In agreement with results seen by Holsapple et al. (1987), technical-grade pentachlorophenol induced a dose-related suppression of this response at a dose of 30 mg/kg/day whereas purified pentachlorophenol did not. Co-administration of heptachloro-*p*-dibenzodioxin (HpCDD), one of the most prevalent chlorinated dibenzo-*p*-dioxin impurities in technical-grade pentachlorophenol, with pure pentachlorophenol resulted in an immunosuppressive response that was similar in magnitude to that seen with technical-grade pentachlorophenol or HpCDD alone. These results provide good evidence that impurities (particularly HpCDD) are responsible for some of the immunotoxic effects attributed to technical-grade pentachlorophenol. Results from the next series of experiments conducted by these investigators further supported this hypothesis. Technical-grade pentachlorophenol was fed to both C57BL/6 mice and DBA/2 mice for 6 weeks (Kerkvliet et al. 1985a). The former strain has a high-affinity aryl hydrocarbon (Ah) receptor and the latter a low-affinity Ah receptor. The ability of chlorinated dibenzo-*p*-dioxin and dibenzofuran congeners (that are present as impurities in pentachlorophenol) to bind to this receptor correlates with their toxicity and their ability to induce P₁-450 monooxygenase activity. Antibody response to SRBC was suppressed by 28% (p#0.01) and 72% (p#0.01) in the 2 groups of C57BL/6 mice with different levels of technical-grade pentachlorophenol, as opposed to 0 and 45% (p>0.01) in corresponding groups of D2 mice. Based on these results, the authors concluded that the immunosuppressive effect of technical-grade pentachlorophenol was probably mediated by contaminant chlorinated dibenzo-*p*-dioxins and dibenzofurans via interaction with the Ah receptor.

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In a study designed to evaluate effects of dietary exposure to technical-grade pentachlorophenol on T-cell, macrophage, and natural killer cell activity, C57BL/6 mice were administered technical-grade pentachlorophenol for 8 weeks prior to conducting a number of *in vitro* immunofunction tests (Kerkvliet et al. 1985b). They found that T-cell and macrophage-mediated (cell-mediated) immunocompetence is relatively resistant to perturbation by technical-grade pentachlorophenol. The only statistically significant change seen was a reduction in lymphoproliferative response in mixed lymphocyte culture. This finding contrasts with marked effects that technical-grade pentachlorophenol has on antibody-mediated immunity.

The complement component of the immune system in mice has also been found to be affected by exposure to technical-grade pentachlorophenol, but not Dowicide EC-7, a preparation of 90% pentachlorophenol that contains reduced levels of chlorinated dibenzo-*p*-dioxins and dibenzofurans (see Table 3-2) (White and Anderson 1985). In this study, technical-grade pentachlorophenol inhibited functional activity of all aspects of complement in a dose-dependent manner. This suppression was still seen up to 30 days after termination of treatment.

The highest NOAEL values and all LOAEL values from each reliable study for immunological effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.2.4 Neurological Effects

One report describing effects of ingestion of pentachlorophenol in humans was found in the literature (Haley 1977). In this case, an adult male intentionally ingested an estimated 4–8 ounces of weed killer that contained 12% pentachlorophenol, 1.5% other chlorinated phenols, 82% aromatic petroleums, and 4.5% inert ingredients. Clinical signs observed upon subsequent hospital admission included pyrexia, diaphoresis, hyperkinesia, muscle twitching, tremors, epigastric tenderness, leg pain, tachypnea, and tachycardia. These neurologic symptoms may be the result of pentachlorophenol's ability to uncouple oxidative phosphorylation (including the resultant increase in body temperature, tachycardia, and tachypnea) rather than a direct toxic effect of pentachlorophenol on the central or peripheral nervous systems.

Results from animal studies demonstrate that the central nervous system is adversely affected by pentachlorophenol, possibly as a result of hyperthermia induced by uncoupling of oxidative phosphorylation. At the neurochemical level, transient changes in activity of some brain enzymes and decreased glial

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glutathione levels were seen in rats administered technical-grade pentachlorophenol in drinking water for 14 weeks (Savolainen and Pekari 1979). These findings suggest another biochemical component to technical-grade pentachlorophenol neurotoxicity. The possibility and extent of the role of technical-grade contaminants in producing these effects are not known, although the study authors concluded that the neurochemical changes were most likely associated with the body burden of chlorophenols. Inhibition of the uptake of thyroxine into the cerebrospinal fluid, as demonstrated in rats following intraperitoneal injection of pentachlorophenol is another possible component of pentachlorophenol neurotoxicity.

Degenerative changes in 10% of the Types A and B fibers consisting of breaks in the myelin sheath of sciatic nerves and a variable loss of neurotubules, neurofilaments, and other axoplasmic components were observed in male rats administered 38 mg/kg/day pentachlorophenol (purity not reported) in drinking water for 90 days or 114 mg/kg/day for 120 days. Type C fibers were unaffected. These changes were more marked in the rats receiving the higher dose. No effects were observed in rats exposed to 11.4 mg/kg/day for 60 days or 38 mg/kg/day for 60 days. While these results suggest that pentachlorophenol can cause neurotoxic changes in the morphology of peripheral nerves, since the purity of the pentachlorophenol tested was not specified, it is not possible to determine whether these changes were due to pentachlorophenol itself or impurities present in technical-grade pentachlorophenol. Other limitations associated with this study include a lack of protocol details (e.g., number of animals per group) and a lack of quantitative incidence data (Villena et al. 1992).

The NTP (1989) conducted a 6-month dietary range-finding study with three different preparations of pentachlorophenol (technical-grade, Dowicide EC-7, or pure [see composition in Table 3-2]) in B6C3F₁ mice. Neurobehavioral studies were conducted during exposure weeks 5 and 26. No pentachlorophenol-related neurobehavioral effects were observed at 5 weeks except for animals administered technical-grade pentachlorophenol, which showed a dose-dependent decrease in motor activity and rotarod performance. In contrast, exposure to all 3 pentachlorophenol preparations caused dose-related increases in both motor activity and startle response in female mice at 26 weeks, whereas only technical-grade pentachlorophenol caused these effects in male mice. NTP (1989) did not provide actual dose-response data.

The LOAEL for neurological effects in rats following intermediate exposure is recorded in Table 3-1 and plotted in Figure 3-1.

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3.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to pentachlorophenol.

A number of animal studies have examined the reproductive toxicity of pentachlorophenol. The available data suggest that long-term exposure to pentachlorophenol can decrease fertility, although the mechanism does not appear to be through histological damage to reproductive tissue. In a two-generation study, decreased fertility (significant decreases in the number of rats mated and in the ratio of pregnant rats to the number of rats in cohabitation) was observed in the first generation of rats exposed to 60 mg/kg/day pentachlorophenol (purity not reported) administered by gavage (Argus 1997/Bernard et al. 2001c). No alterations in fertility were observed in the F1 generation exposed to 10 or 30 mg/kg/day or in the parental generation. The only other reproductive effects observed in this study were a significant decrease in testicular spermatid count, decreases in absolute testes weight and the ratio of testes weight to brain weight, and focal/multifocal mononuclear cell infiltrate in the epididymis in the F1 rats administered 30 or 60 mg/kg/day. However, no alterations in the average number of motile or nonmotile sperm, epididymal or testicular sperm counts, or sperm morphology were observed in either generation. No alterations in reproductive tissues were observed in the female rats. Significant increases in the average day of preputial separation and vaginal patency were observed in the F1 generation, suggesting that *in utero* exposure to pentachlorophenol disrupted the normal development of the reproductive system. No adverse reproductive effects were observed in another multigeneration study in which mink were fed a diet containing 1 mg/kg/day pentachlorophenol (purity not reported) (Beard and Rawlings 1998). A single-generation mink study also conducted by this group reported significant decreases in the proportion of mated females accepting a second mating and the proportion of mink that whelped, although no effect on the proportion of mink that accepted the first mating or the proportion of mink with visible implantation sites were found (Beard et al. 1997). In both studies, the minks were exposed to 1 mg/kg/day pentachlorophenol (purity not reported) in the diet for 3 weeks prior to mating. Additionally, no significant alterations in mating response, ovulation rate, follicle and corpus luteum size, gestation length, pregnancy rate, lambing rate, and lamb birth rate were observed in sheep exposed to 1 mg/kg/day pentachlorophenol in the diet for 5 weeks pre-mating and throughout the gestation and lactation periods (Beard et al. 1999b). No effect on fertility was observed in the offspring of these sheep, later mated to unexposed males (Beard and Rawlings 1999).

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Several reproductive toxicity and nonreproductive toxicity studies have reported histological alterations in reproductive tissues. The observed effects include focal degeneration of the seminiferous tubules and decreased sperm density in the epididymis body (but not in caput or cauda epididymis) in sheep exposed to 1 mg/kg/day pentachlorophenol (purity not reported) in the diet during gestation, lactation, and for 20-weeks postnatally (Beard et al. 1999a), minimal to marked germinal epithelial degeneration and lack of spermatozoa in the seminiferous tubules of rats exposed to 270 mg/kg/day pure pentachlorophenol in the diet for 28 days (effects may have been secondary to poor condition of animals) (Chhabra et al. 1999; NTP 1999), increased severity of cystic uterine glands in mink exposed to 1 mg/kg/day pentachlorophenol (purity not reported) prior to mating and during gestation and lactation periods (Beard et al. 1997), increased severity of oviductal intraepithelial cysts in sheep administered 2 mg/kg/day pure pentachlorophenol by gavage twice weekly for 43 days (Rawlings et al. 1998), and lymphocyte infiltration into the endometrium in sheep exposed to 1 mg/kg/day pentachlorophenol (purity not reported) in the diet for 5 weeks pre-mating and during the gestation and lactation periods (Beard et al. 1999b). No histological alterations in reproductive tissues were observed in male or female rats chronically exposed to 30 mg/kg/day pure pentachlorophenol in the diet for 2 years (Chhabra et al. 1999; NTP 1999). Additionally, no alterations in reproductive hormones (estradiol, testosterone, progesterone, follicle stimulating hormone, and/or luteinizing hormone levels) have been observed in mink (Beard et al. 1997) or sheep (Beard et al. 1999a). The LOAEL of 1 mg/kg/day for decreases in the proportion of females accepting a second mating and the number of mink that whelped and the increased severity of cystic uterine glands identified in the single-generation mink study was used to derive an intermediate-duration oral MRL of 0.001 mg/kg/day, as described in the footnote in Table 3-1.

3.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans after oral exposure to pentachlorophenol.

A number of animal studies have examined the developmental toxicity of pentachlorophenol and provide evidence that gestational exposure can result in fetal/neonatal mortality, malformation/variations, decreased growth, and possibly functional deficits in rats and sheep. No developmental effects have been observed in rabbits administered up to 30 mg/kg/day 88–89% pure pentachlorophenol by gavage on gestational days 6–18 (Argus 1993a/Bernard et al. 2001c). Significant increases in postimplantation resorptions or embryo lethality were observed in rats administered 30 mg/kg/day pure pentachlorophenol or 15 mg/kg/day technical-grade (88.4% pure) pentachlorophenol by gavage on gestational days

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6–15 (Schwetz et al. 1974), in rats administered 80 mg/kg/day 89% pure pentachlorophenol by gavage on gestational days 6–15 (Argus 1993b/Bernard et al. 2001b), and in the offspring of rats exposed to 46 mg/kg/day pure pentachlorophenol in the diet during mating and gestation (Welsh et al. 1987). A decrease in litter size and decreases in neonatal survival were observed in offspring of rats exposed for 77 days prior to gestation and throughout the gestation and lactation periods to 30 mg/kg/day 90.4% pure pentachlorophenol in the diet (Schwetz et al. 1978), in rats exposed to 48 mg/kg/day 85.5% pure pentachlorophenol in the diet for 10 weeks prior to mating and throughout gestation and lactation (Exon and Koller 1982), and in F1 and F2 rat pups exposed to 60 mg/kg/day pentachlorophenol (purity not specified) (Argus 1997/Bernard et al. 2001c). Schwetz et al. (1974) reported marked changes in the sex ratio of rats exposed to pentachlorophenol; the majority of surviving rats were males. The ratios were 3.6 and 4.9 in the rats administered 50 mg/kg/day technical-grade pentachlorophenol and 30 mg/kg/day pure pentachlorophenol, respectively, as compared to respective control values of 1.0 and 1.1. Other developmental toxicity studies have not found alterations in sex ratio (Argus 1993b/Bernard et al. 2001b, Argus 1997/Bernard et al. 2001c).

The occurrence of malformations and variations has been reported in a small number of studies. Soft tissue (subcutaneous edema) and skeletal (lumbar spurs) anomalies were observed in the offsprings of rats exposed by gavage 15 mg/kg/day of technical-grade (88.4%) pentachlorophenol (Schwetz et al. 1974) and skeletal (variations in vertebral, sternal, and pelvic ossification, increased rib pairs, delays in sternal forelimb and hindlimb ossification) and soft tissue (diaphragmatic hernia, slight to moderate dilation of the kidneys) malformations and variations have been observed in rat offspring administered 80 mg/kg/day, but not 30 mg/kg/day, 89% pure pentachlorophenol on gestational days 6–15 (Argus 1993b/Bernard et al. 2001b).

Decreases in growth have been reported in a number of developmental toxicity studies. Statistically significant decreases in fetal body weights were observed in the offspring of rats administered pure or technical-grade pentachlorophenol by gavage at doses of 30 mg/kg/day (Argus 1993b/Bernard et al. 2001b; Courtney et al. 1976; Larsen et al. 1975; Schwetz et al. 1974). Decreases in pup weight have been observed in the offspring of rats administered 14 mg/kg/day 99% pure pentachlorophenol in the diet (Welsh et al. 1987), rats in a two-generation study administered 10 mg/kg/day pentachlorophenol (purity not specified) in the diet (Argus 1997/Bernard et al. 2001c), and in sheep fed 1 mg/kg/day pentachlorophenol (purity not reported) in the diet (Beard et al. 1999b).

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There is some limited evidence that gestational/lactational exposure to pentachlorophenol may impair the development of the reproductive system. Significant increases in the average day of vaginal patency in F1 females exposed to 60 mg/kg/day and preputial separation in F1 males exposed to 60 mg/kg/day (Argus 1997/Bernard et al. 2001c). Decreased fertility was also observed in the F1 generation.

Schwetz et al. (1974) examined the differences in the developmental toxicity between pure and technical-grade pentachlorophenol. The pure pentachlorophenol was slightly more toxic than the technical-grade pentachlorophenol in terms of maternal body weight gain, fetal resorptions, fetal body weight, and occurrence of fetal anomalies. The study authors estimated that the maternal dose that would be lethal to one half of the embryos was 16 mg/kg/day pure pentachlorophenol versus 44 mg/kg/day for technical-grade pentachlorophenol.

In many of the oral developmental toxicity studies, decreases in maternal body weight were observed at the same doses as the developmental effects in rats (Argus 1993b/Bernard et al. 2001b; Courtney et al. 1976; Schwetz et al. 1974). However, in other rat studies (Argus 1997/Bernard et al. 2001c; Welsh et al. 1987), the LOAEL for maternal toxicity was higher than the LOAEL for developmental effects (decreased fetal or pup body weight), suggesting that developmental toxicity can occur in the absence of maternal toxicity.

The highest NOAEL values and all LOAEL values from each reliable study for developmental toxicity in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.2.7 Cancer

Lampi et al. (1992) demonstrated significantly elevated risk ratios, compared to reference populations, for non-Hodgkin's lymphoma and soft tissue sarcoma among people who consumed fish from a lake contaminated with tri-, tetra-, and penta-chlorophenols and drank water from wells nearby. For non-Hodgkin's lymphoma, there was a significant association with fish consumption. The population was not exposed to chlorinated dibenzodioxins or dibenzofurans.

Carcinogenicity of orally administered pentachlorophenol has been tested in at least four studies using rats and mice (Inns et al. 1969; NCI 1968; NTP 1989, 1999 [data also reported by Chhabra et al. 1999]; Schwetz et al. 1978). The purity of pentachlorophenol in these studies varied; this is an important factor to consider because pentachlorophenol, during its production, is usually contaminated with chlorinated

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dibenzo-*p*-dioxins, some of which are animal carcinogens. NTP (1989) tested both technical-grade pentachlorophenol (TG-Penta), a 90% pure composite mixture of 3 technical-grades of pentachlorophenol, and Dowicide EC-7, a mixture containing 90% pure pentachlorophenol and fewer chlorinated dibenzo-*p*-dioxin impurities than TG-Penta (see Table 3-2). NCI (1968) tested Dowicide EC-7 as well. Schwetz et al. (1978) tested Dowicide EC-7. NTP (1999) tested pure pentachlorophenol (approximately 99% with one impurity, tetrachlorophenol).

NCI administered Dowicide EC-7 (0 or 17 mg/kg/day) in the diet of weanling B6C3F₁ mice for 78 weeks (NCI 1968), while NTP (1989) administered Dowicide EC-7 (0, 18, 37, or 118 mg/kg/day) in the diet of B6C3F₁ mice for 103 weeks. No significant elevation in incidence of cancer occurred in the NCI study; however, in the NTP study, significant increases in incidence of tumors were observed. Male mice displayed significant dose-related increases in the incidence of adrenal medulla pheochromocytomas (benign and malignant) and hepatocellular adenomas and carcinomas. Female mice in the high-dose group displayed significant increases in incidences of hepatocellular adenoma and carcinoma, in pheochromocytomas (benign and malignant), and in hemangiosarcomas (spleen and liver). The differences between the two studies were that NCI tested for a shorter period of time, used fewer animals per group, had higher mortality in the dose group leaving fewer animals to be at risk of developing tumors, and used only one dose that was one-sixth of the highest dose used in the NTP study, and, therefore, was probably not the maximum tolerated dose.

NTP (1989) also tested TG-Penta, a composite mixture of three technical-grades of pentachlorophenol. This mixture contained a higher percentage of chlorinated dibenzo-*p*-dioxin contaminants than did the Dowicide EC-7 mixture (see Table 3-2). Groups of male and female B6C3F₁ mice were given diets that contained 0, 100, or 200 ppm TG-Penta (equivalent to 0, 18, or 35 mg/kg/day, respectively) or Dowicide EC-7 (as described above for 103 weeks). Survival was reduced in all groups, including controls, when compared to historical controls. Male mice displayed a significant increase over the male control incidence in tumors of the adrenal medulla (benign and malignant pheochromocytomas combined) and liver (adenomas and carcinomas combined). Treated female mice displayed a significant increase over female controls with regard to incidence of hemangiosarcomas of the spleen and liver. Chlorinated dibenzo-*p*-dioxins were found in the TG-Penta mixture at a concentration of 0.17%, but the mixture contained no 2,3,7,8-TCDD. Chlorinated dibenzo-*p*-dioxin exposure has been associated with an increased incidence of liver tumors in treated mice but not with pheochromocytomas or hemangiosarcomas (NCI/NTP 1980). Although this study is limited because of unusually low survival in the male

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TG-Penta control group, the occurrence of rare hemangiosarcomas was considered a carcinogenic response due to pentachlorophenol exposure.

In the NTP (1999) study, groups of male and female F344 rats were given diets that contained 0, 200, 400, or 600 ppm pentachlorophenol (approximately 99% pure with one impurity, tetrachlorophenol) in the diet (equivalent to doses of 0, 10, 20, or 30 mg/kg/day) for 105 weeks. A stop-exposure group was given a diet that contained 1,000 ppm pentachlorophenol for 52 weeks (equivalent to a dose of 60 mg/kg/day) followed by a control diet through 105 weeks. At 2 years, a significantly increased incidence of malignant mesothelioma originating from the tunica vaginalis was present in 60 mg/kg/day stop exposure group males compared with controls, and the incidence exceeded the historical control range. Nasal squamous cell carcinomas were present in one control male, three 10 mg/kg/day males, one 20 mg/kg/day male, and five 60 mg/kg/day males at 2 years, and the incidence in 1,000-ppm males exceeded the historical control range.

In an earlier study, Dovicide EC-7 was administered to rats at dietary levels of 0, 1, 3, 10, or 30 mg/kg/day in males and females for 22 months and 24 months, respectively (Schwetz et al. 1978). No significant increases in incidence of tumors were observed during this study. The study was limited, however because a small number of animals was tested, no data on survival were provided to evaluate if enough animals survived for a long enough period of time to develop tumors, and it is not known if the maximum tolerated dose was attained.

The NTP (1999) study in F344 rats showed some evidence that purified pentachlorophenol (approximately 99% with one impurity, tetrachlorophenol) is carcinogenic, producing mesotheliomas and nasal squamous cell carcinomas. The most convincing evidence that 90% pure pentachlorophenol is carcinogenic to mice following ingestion comes from the NTP (1989) bioassay. This study was generally well conducted, taking into account the lifetime of the study animal, that gross necropsy and histopathology were completed on all suitable animals, and that percentages of the maximum tolerated dose were administered to determine carcinogenic response. It is limited because the unusually low survival of males in the TG-Penta control group left fewer control animals at long-term risk of developing tumors.

EPA has classified pentachlorophenol as a Group B2 substance (probable human carcinogen) (IRIS 2001). A cancer potency factor of $0.12 \text{ (mg/kg/day)}^{-1}$ was calculated by IRIS (2001) based on the NTP (1989) data. This cancer potency factor translates to estimated upper-bound unit risk levels of 9×10^{-3} ,

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9×10^{-4} , 9×10^{-5} , 9×10^{-6} , and 9×10^{-7} mg/kg/day for cancer risks of 1 in 1,000, 1 in 10,000, 1 in 100,000, 1 in 1 million and 1 in 10 million respectively (see Figure 3-1).

The CELs for pentachlorophenol are recorded in Table 3-1 and plotted in Figure 3-1, and the estimated upper-bound human cancer risk levels are plotted in Figure 3-1.

3.2.3 Dermal Exposure

Data on the toxicity of pentachlorophenol in humans exposed via dermal contact come from a number of case reports and studies in individuals applying wood preservative products containing pentachlorophenol, using pesticides containing sodium pentachlorophenate, or children exposed to pentachlorophenol used in the laundering of diapers and bedding. The primary route of exposure is believed to be dermal contact, although inhalation exposure also occurred. Studies in which inhalation exposure was the primary route and dermal contact the secondary route are discussed in Section 3.2.1 Inhalation Exposure. No studies considered suitable for presentation in a table describing significant levels of dermal exposure to pentachlorophenol were found.

3.2.3.1 Death

In most instances, death in humans exposed to pentachlorophenol was a result of occupational exposure or use of pentachlorophenol-containing products in the home by individuals who did not employ proper precautionary measures. All of these reports are limited in that the possibility of concurrent exposure to other potentially toxic substances in technical-grade pentachlorophenol and concurrent exposure to other toxic substances (e.g., lindane, dieldrin) cannot be excluded, and because the pentachlorophenol exposure level and duration cannot be quantified because appropriate measurements were not taken at the time. Deaths were also seen in human infants exposed to pentachlorophenol used in the laundering of diapers and bedding. Though the primary route of exposure in all of these studies was believed to be dermal, the probability that inhalation exposure also occurred must be considered. It should be noted that occupational exposure to pentachlorophenol has been strictly limited not only by use patterns but by application procedures, and all household uses of pentachlorophenol have been banned. Therefore, exposure to pentachlorophenol resulting in death as described in this section is currently improbable, with the exception of hazardous waste workers involved in the clean up of pentachlorophenol-containing ponds or soils. It should also be noted that the deaths discussed below resulted from the use of

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formulations that likely had a different composition (e.g., presence of more impurities) than the pentachlorophenol that is currently used.

In a case report, nine infants in a small nursery for newborns exhibited an illness characterized by high fever, profuse sweating, increased respiratory rate, labored breathing, tachycardia, hepatomegaly, irritability followed by lethargy, metabolic acidosis, proteinuria, increased blood urea nitrogen, and pneumonia or bronchiolitis (Smith et al. 1996). Two of the infants died. At autopsy, both infants showed fatty metamorphosis of the liver and one showed fatty vacuolar changes in the renal tubules. The remaining infants recovered after exchange transfusions and transfer to another hospital. The clinical findings and deaths were attributed to the use of pentachlorophenol in a mixture of synthetic phenolic derivatives in the hospital laundry as an antimildew agent. Pentachlorophenol was found in freshly laundered diapers and in the serum and urine of the infants.

Five cases of fatal blood dyscrasias were reported. Reports followed exposures to technical-grade pentachlorophenol or pentachlorophenol of undefined purity for 1-month to 4-year periods—three as a result of industrial exposure and two from home use (Roberts 1963, 1981, 1990). The cause of death in all cases was reported to be either aplastic anemia or red blood cell aplasia. Clinical signs, chemistries, and postmortem findings revealed functional and degenerative changes in most organ systems. Deaths attributed to pentachlorophenol were also reported in a male working as a wood preserver for 1 week (Bergner et al. 1965), 5 herbicide sprayers exposed once (Gordon 1956), and nine sawmill workers exposed for 3–30 days (Menon 1958). Deaths reported by Gray et al. (1985), Bergner et al. (1965), and Menon (1958) were all due to hyperthermia that resulted from uncoupling of oxidative phosphorylation by pentachlorophenol. Manifestations of overexposure were chiefly those associated with hyperthermia: flushing, intense thirst, sweating, weakness, and occasionally, muscle spasms. Toxic effects seen in these fatalities will be discussed in sections dealing with specific organ toxicity. Hyperthermia is the major factor leading to death following fatal pentachlorophenol exposure in humans.

One report of death following dermal exposure in experimental animals was found in the reviewed literature (Deichmann et al. 1942). Eight out of 20 rabbits administered dermal applications of 4% pentachlorophenol (purity not indicated) in fuel oil for 6–61 weeks died of unspecified causes. The vehicle contained known toxic substances (e.g., polyaromatic hydrocarbons), which may have contributed to the lethal effects observed.

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3.2.3.2 Systemic Effects

Most of the literature reviewed concerning systemic effects of dermal exposure to pentachlorophenol in humans described case reports of individuals exposed either occupationally or in the home during misuse of pentachlorophenol-containing solutions as a result of failure to adhere to appropriate precautionary measures. The predominant route of exposure in such cases is dermal, but the possibility of some inhalation exposure cannot be ruled out. All of these reports are limited because the possibility of concurrent exposure to other potentially toxic substances in technical-grades of pentachlorophenol cannot be excluded, and because the pentachlorophenol exposure level and duration were not quantified. Some of the effects observed may be secondary to hyperthermia generated by uncoupling of oxidative phosphorylation (see Section 2.5).

No studies were located regarding cardiovascular, musculoskeletal, endocrine, or ocular effects in humans or respiratory, cardiovascular, gastrointestinal, musculoskeletal, hepatic, renal, endocrine, or ocular effects in animals after dermal exposure to pentachlorophenol.

Respiratory Effects. In a case report, nine infants in a small nursery for newborns exhibited increased respiratory rate and labored breathing from exposure to pentachlorophenol in a mixture of synthetic phenolic derivatives in diapers and linens from the hospital laundry (Smith et al. 1996). It is likely that these effects are secondary to hyperthermia rather than a direct effect on the respiratory tract.

Gastrointestinal Effects. Except for anecdotal reports of abdominal pain, nausea, and vomiting in humans occupationally exposed to pentachlorophenol of undefined purity (Gordon 1956; Menon 1958), no studies were located regarding gastrointestinal effects in humans or animals following dermal exposure to pentachlorophenol.

Hematological Effects. Incidents of fatal hematological disorders were found in case reports following exposure (level and duration not specified) to technical-grade pentachlorophenol or pentachlorophenol of undefined purity as a result of predominantly dermal exposure. Thirteen cases of aplastic anemia, pure red blood cell aplasia, or severe pancytopenia with abnormal marrow have been reported in individuals using pentachlorophenol-containing wood preservative products, eight of which resulted in death (Roberts 1981, 1990). Aplastic anemia was also diagnosed in an individual using pentachlorophenol in the renovation of an old home (Rugman and Cosstick 1990). A case of intravascular hemolysis was attributed to use of an insecticide containing pentachlorophenol (Hassan et al. 1985).

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Hepatic Effects. Most of the studies reviewed concerning hepatic effects of dermal exposure to pentachlorophenol in humans described case reports of individuals exposed either occupationally or in the home following the use of pentachlorophenol-containing solutions by individuals who did not employ appropriate precautionary measures. Information regarding pentachlorophenol-induced hepatic toxicity in humans following dermal exposure, discussed below, is subject to some doubt regarding the extent to which the adverse effects seen can be attributed to pure pentachlorophenol. Hepatic enlargement has been observed in herbicide sprayers (Gordon 1956), and in neonates exposed for a short time via contaminated diapers and bed linen in a hospital nursery (Armstrong et al. 1969; Robson et al. 1969; Smith et al. 1996). Autopsy findings in those affected individuals who died revealed fatty infiltration of the liver (in the neonates) and severe centrilobular congestion with hepatocellular fat accumulation (in the chemical worker). Centrilobular degeneration was also observed in a liver specimen from a worker who dipped wood in a preservative that contained 4.1% pentachlorophenol every day for 1 week (Bergner et al. 1965). In an epidemiologic study of male factory workers who brushed technical-grade pentachlorophenol onto wood strips, sometimes without gloves, serum biliary acid concentrations were elevated in the high-exposure group, but not the low-exposure group, compared with controls. Exposure was assessed by measurement of pentachlorophenol concentrations in plasma and urine (Colosio et al. 1993b). The presence of elevated concentrations of bile acids in serum is a sensitive indicator of liver dysfunction (Franco et al. 1986). Evidence of liver damage was seen in an epidemiologic study of adult males occupationally exposed to pentachlorophenol in wood-treatment plants or as farmers or pest control operators in Hawaii (Klemmer 1972). This evidence consisted of elevated levels of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) following chronic, predominantly dermal exposure to technical-grade pentachlorophenol or pentachlorophenol of undefined purity. Hyperthermia induced by pentachlorophenol may be a major factor leading to liver injury.

Renal Effects. Four reports were found that described renal toxic effects following dermal exposure to pentachlorophenol in humans. All involved either occupational exposure or accidental poisoning with the predominant route of exposure being dermal, but the possibility of inhalation exposure cannot be excluded. In one instance, a 3-year-old girl was exposed to pentachlorophenol of undefined composition via a pesticide-contaminated domestic water supply. Transient disruption of acid-base equilibrium and metabolic balance as evidenced by acidosis, aminoaciduria, and ketonuria suggested the occurrence of renal dysfunction in this child (Chapman and Robson 1965). In a case study of nine infants, metabolic acidosis, proteinuria, and increased blood urea nitrogen were found following exposure of the infants to pentachlorophenol of undefined composition in diapers and bedding at a hospital that used pentachlorophenol in the hospital laundry as an antimildew agent. Fatty vacuolar changes in the renal tubules were

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noted in one of the two infants that died (Smith et al. 1996). An autopsy conducted on a worker who dipped wood in a preservative that contained 4.1% pentachlorophenol every day for 1 week revealed mild renal tubular degeneration (Bergner et al. 1965). Finally, evidence for pentachlorophenol-induced impaired glomerular filtration and tubular function was reported in 18 workers employed at a wood-treatment facility (Begley et al. 1977). These findings consisted of depressed creatinine clearance and phosphorus reabsorption. Considerable improvement in these symptoms was seen following a 20-day absence from work. These data suggest that the renal toxicant effects of technical-grade pentachlorophenol are reversible. The extent to which contaminants of technical-grade pentachlorophenol are responsible for the effects discussed above is not known. Hyperthermia may also be a mechanism of renal injury in individuals that are acutely overexposed to pentachlorophenol.

Dermal Effects. Transient localized redness and pain subsequent to immersion of the hands in a 0.4% pentachlorophenol solution for 10 minutes were exhibited by an adult male (Bevenue et al. 1967). Two cases of pemphigus vulgaris and one of chronic urticaria (both examples of severe skin lesions) attributed to nonoccupational chronic pentachlorophenol exposure (i.e., via contact with wood treated with pentachlorophenol) have been described (Lambert et al. 1986). The dermal effects discussed above may have resulted from impurities present in the pentachlorophenol resulting from the manufacturing process.

Pentachlorophenol-induced toxic effects on the skin of experimental animals have also been reported. A single application of pentachlorophenol of unspecified purity (1,111 mg/kg in 95% ethyl alcohol or 150 mg/kg in pale paraffin oil) resulted in gross changes such as pronounced edema and inflammation leading to wrinkling, cracking, desquamation, and hair loss. Microscopic changes observed include widespread foci of atrophy and necrosis, thinning and disappearance of upper skin layers, and hyperkeratinization and hypertrophy of hair follicles (Deichmann et al. 1942). Single dermal applications of 250 mg/kg of a 10% aqueous solution of sodium pentachlorophenate of unspecified purity to rabbits did not result in dermal irritation. Repeated application of lower doses of pentachlorophenol (40 mg/kg in mineral oil) to rabbits for 21 days induced no irritation, whereas daily application of 10–50 mg/kg of a 4% solution of pentachlorophenol in fuel oil for 6–61 weeks resulted in pronounced dermal effects, and daily application of 63 mg/kg of an aqueous sodium pentachlorophenate solution for 32 days was without effect (Deichmann et al. 1942). No evidence of histologic changes in the epidermis or pilosebaceous unit were noted after application of 0.036 mg of sodium pentachlorophenate of unspecified purity to a 9 cm² area of the dorsal skin of hairless dogs once daily for 7 days. The toxic effects of dermal exposure to pentachlorophenol appear to be most severe following high-dose, acute exposure to pentachlorophenol in fuel oil.

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Acne was observed in rabbits following application of technical-grade pentachlorophenol to the ear, but was not observed following application of pure pentachlorophenol (Johnson et al. 1973), suggesting that the effects were due to contaminants rather than the pentachlorophenol.

3.2.3.3 Immunological and Lymphoreticular Effects

Two cases of pemphigus vulgaris and one of chronic urticaria (skin diseases with an immunologic etiology) have been attributed to nonoccupational exposure to pentachlorophenol (Lambert et al. 1986). Alterations in immune function were reported in patients who had been exposed for more than 6 months to pentachlorophenol-containing pesticides (composition not defined) (Daniel et al. 1995) and workers who brushed technical-grade pentachlorophenol onto wood strips (Colosio et al. 1993b).

No studies were located regarding immunological effects in animals following dermal exposure to pentachlorophenol.

3.2.3.4 Neurological Effects

Numerous signs of central nervous system toxicity have been reported in case reports of individuals exposed to high levels of pentachlorophenol via dermal contact and inhalation exposure. The observed effects include intermittent delirium and convulsions (Chapman and Robson 1965) and irritability (Robson et al. 1969; Smith et al. 1996). It is likely that these are effects secondary to hyperthermia due to pentachlorophenol-induced uncoupling of oxidative phosphorylation.

No studies were located regarding neurological effects in animals following dermal exposure to pentachlorophenol.

3.2.3.5 Reproductive Effects

No studies were located regarding reproductive effects in humans and animals following dermal exposure to pentachlorophenol.

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3.2.3.6 Developmental Effects

No studies were located regarding developmental effects in humans and animals following dermal exposure to pentachlorophenol.

3.2.3.7 Cancer

Epidemiological studies and case reports described in Section 3.2.1.7 (in which dermal exposure was also likely) provide evidence that exposure to pentachlorophenol may be associated with soft tissue sarcomas and non-Hodgkin's lymphoma in humans.

Only one study was located in which investigators topically administered pentachlorophenol to animals (Boutwell and Bosch 1959). These investigators applied a 20% solution of commercial grade pentachlorophenol in benzene to shaved dorsal skin of mice twice a week for 13 weeks. Mice were previously treated with a dose of 0.3% dimethylbenzanthracene (DMBA) in benzene to induce skin cancer. No increase in DMBA-induced skin tumors resulted from pentachlorophenol treatment. This study was designed to determine if pentachlorophenol was a tumor promoter and was therefore severely limited in its ability to detect a carcinogenic effect caused by pentachlorophenol because of administration of an insufficient dose over a short treatment period. However, based on results of this study, pentachlorophenol was inactive as a promotor of skin tumors in mice.

3.2.4 Other Routes of Exposure

Endocrine Effects. Studies in animals have shown that acute (single-dose, intraperitoneal injection) pentachlorophenol administration causes a marked, statistically significant decrease in serum total thyroxine levels in rats (van Raaij et al. 1991a). This decrease peaked 6–24 hours after administration, and thyroxine levels slowly returned to control values within 96 hours after administration. Further *in vitro* studies by these investigators revealed that the likely mechanism of action for this anti-thyroid effect was competition for serum protein thyroxine binding sites (van Raaij et al. 1991b).

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3.3 GENOTOXIC EFFECTS

Numerous *in vivo* and *in vitro* studies have assessed the genotoxic potential of pentachlorophenol, and the results of these studies are presented in Tables 3-3 and 3-4, respectively. Three studies examined the clastogenic activity of pentachlorophenol in workers primarily exposed via inhalation. A marginal increase in chromosomal aberrations was found in the lymphocytes of workers exposed to pentachlorophenol or its sodium salt (Bauchinger et al. 1982). In contrast, studies by Wyllie et al. (1982) and Ziemson et al. (1987) did not find significant increases in the occurrence of chromosomal aberrations in their studies of workers. The occurrence of sister chromatid exchange was not increased in the lymphocytes of workers (Bauchinger et al. 1982; Ziemson et al. 1987). No other human *in vivo* genotoxicity studies were located. An increase in DNA adduct formation was observed in the liver of mice orally exposed to pentachlorophenol (Sai-Kato et al. 1995; Umemura et al. 1996), but not in the kidney or spleen (Sai-Kato et al. 1995), and positive results were seen in a coat color spot test in mouse embryos treated transplacentally with pentachlorophenol (Fahrig et al. 1978). In other *in vivo* assays, no evidence of genotoxicity was observed; the assays included sex-linked recessive lethal mutations in *Drosophila melanogaster* (Fahrig 1974; Fahrig et al. 1978; Vogel and Chandler 1974), micronuclei formation in rats and mice (NTP 1999), and gene mutations and recombination in a mouse spot test (Fahrig and Steinkamp-Zucht 1996).

No alterations in the occurrence of gene mutations (Andersen et al. 1972; Donnelly et al. 1998; Lemma and Ames 1975; Markiewicz et al. 1996; Moriya et al. 1983; NTP 1999; Simmon et al. 1977; Waters et al. 1982) or DNA damage (Fahrig 1974; Waters et al. 1982) were observed in bacterial systems, with the exception of one study that reported positive activity in the rec assay using *Bacillus subtilis* (Waters et al. 1982). In yeast, pentachlorophenol induced gene mutations (Fahrig 1974; Fahrig et al. 1978) and genetic recombination (Fahrig et al. 1978; Waters et al. 1982). Weak clastogenic activity was observed in chromosomal aberration assays in human lymphocyte (Fahrig 1974) and in chromosomal aberration and sister chromatid exchange assays in Chinese hamster ovary cells (NTP 1999). No significant increases in the occurrence of DNA damage (adduct formation or single-strand breaks) were seen in mammalian cells (Dalhaus et al. 1996; Ehrlich 1990; Wang and Lin 1995).

A few studies were found regarding the genotoxic potential of pentachlorophenol metabolites. Tetrachloro-*p*-hydroquinone (TCHQ), (isomer not specified) but not tetrachlorocatechol, induced a dose-related and significant mutagenic response in Chinese hamster V-79 cells in the absence of exogenous metabolic activation (Jansson and Jansson 1991). The para isomer of TCHQ, but not the ortho isomer,

Table 3-3. Genotoxicity of Pentachlorophenol *In Vivo*

Species (test system)	End point	Results	Reference
<i>Drosophila melanogaster</i> spermatocytes	Sex-linked recessive lethal mutation	–	Fahrig 1974; Fahrig et al. 1978; Vogel and Chandler 1974
Human lymphocytes (occupational exposure)	Chromosomal aberrations	(+)	Bauchinger et al. 1982
Human lymphocytes (occupational exposure)	Chromosomal aberrations	–	Wyllie et al. 1982
Human lymphocytes (occupational exposure)	Chromosomal aberrations	–	Ziensen et al. 1987
Human lymphocytes (occupational exposure)	Sister chromatid exchange	–	Bauchinger et al. 1982
Human lymphocytes (occupational exposure)	Sister chromatid exchange	–	Ziensen et al. 1987
B6C3F1 mouse (oral exposure)	DNA adduct formation	+	Sai-Kato et al. 1995; Umemura et al. 1996
Mouse bone marrow (intraperitoneal exposure)	Micronuclei	–	NTP 1999
Rat bone marrow (intraperitoneal exposure)	Micronuclei	–	NTP 1999
Mouse embryonic cells (transplacental exposure)	Gene mutation	(+)	Fahrig et al. 1978
Mouse/spot test	Gene mutation	–	Fahrig and Steinkamp-Zucht 1996
Mouse/spot test	Recombination	–	Fahrig and Steinkamp-Zucht 1996

– = negative results; + = positive results; (+) = weakly positive results

Table 3-4. Genotoxicity of Pentachlorophenol and its Metabolites *In Vitro*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Pentachlorophenol				
Prokaryotic organisms:				
<i>Salmonella typhimurium</i>	Gene mutation	–	–	Donnelly et al. 1998; Markiewicz et al. 1996; Moriya et al. 1983; NTP 1999; Simmon et al. 1977; Waters et al. 1982
<i>S. typhimurium</i> /spot test	Gene mutation	NT	–	Andersen et al. 1972; Lemma and Ames 1975
<i>S. typhimurium</i> (mouse host-mediated assay)	Gene mutation	–	NT	Buselmaier et al. 1973
Invertebrate animal cells:				
<i>E. coli</i> /spot test	Gene mutation	NT	–	Moriya et al. 1983; Simmon et al. 1977; Waters et al. 1982
<i>Serratia marcescens</i> /spot test	DNA damage	NT	–	Fahrig 1974
<i>Bacillus subtilis</i> /rec- assay	DNA damage	NT	+	Waters et al. 1982
<i>E. coli</i> pol A	DNA damage	NT	–	Waters et al. 1982
Eukaryotic organisms:				
Fungi:				
<i>Saccharomyces cerevisiae</i> MP-1	Gene mutation	NT	+	Fahrig et al. 1978
<i>S. cerevisiae</i> aAeZ	Recombination	NT	+	Fahrig 1974
<i>S. cerevisiae</i> MP-1/intergenic recombination	Recombination	NT	–	Fahrig et al. 1978
<i>S. cerevisiae</i> MP-1/intergenic recombination	Recombination	NT	+	Fahrig et al. 1978
<i>S. cerevisiae</i>	Recombination	+	+	Waters et al. 1982

Table 3-4. Genotoxicity of Pentachlorophenol and its Metabolites *In Vitro* (continued)

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Mammalian cells:				
Human lymphocytes	Chromosomal aberrations	NT	(+)	Fahrig 1974
Chinese hamster ovary cells	Chromosomal aberrations	(+)	–	NTP 1999
Chinese hamster ovary cells	DNA damage	NT	–	Ehrlich 1990
Chinese hamster ovary cells	Sister chromatid exchange	–	(+)	NTP 1999
Chinese hamster V79 cells	DNA damage (8-OH-dG adduct)	NT	–	Dahlhaus et al. 1996
Chinese hamster V79 cells	DNA damage (single-strand breaks)	NT	–	Dahlhaus et al. 1996
Mouse embryonic fibroblast cells	DNA damage (single-strand breaks)	(+)	–	Wang and Lin 1995
Tetrachloro-o-benzoquinone				
Mammalian cells:				
Chinese hamster V79 cells	DNA damage (8-OH-dG adduct)	NT	+	Dahlhaus et al. 1996
Chinese hamster V79 cells	DNA damage (single-strand breaks)	NT	–	Dahlhaus et al. 1996
Tetrachloro-p-benzoquinone				
Mammalian cells:				
Chinese hamster V79 cells	DNA damage (8-OH-dG adduct)	NT	+	Dahlhaus et al. 1996
Chinese hamster V79 cells	DNA damage (single-strand breaks)	NT	+	Dahlhaus et al. 1996

Table 3-4. Genotoxicity of Pentachlorophenol and its Metabolites *In Vitro* (continued)

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Tetrachloro-o-hydroquinone				
Mammalian cells:				
Chinese hamster V79 cells	DNA damage (8-OH-dG adduct)	NT	–	Dahlhaus et al. 1996
Chinese hamster V79 cells	DNA damage (single-strand breaks)	NT	–	Dahlhaus et al. 1996
Tetrachloro-p-hydroquinone				
Mammalian cells:				
Chinese hamster ovary cells	DNA damage	NT	+	Ehrlich 1990
Chinese hamster V79 cells	DNA damage (8-OH-dG adduct)	NT	+	Dahlhaus et al. 1996
Chinese hamster V79 cells	DNA damage (single-strand breaks)	NT	+	Dahlhaus et al. 1996
Tetrachlorohydroquinone				
Mammalian cells:				
Chinese hamster V79 cells	Gene mutation	NT	+	Jansson and Jansson 1991

– = negative result; + = positive result; (+) = weakly positive result; DNA = deoxyribonucleic acid; 8-OH-dG = 8-hydroxydeoxyguanosine; NT = not tested

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induced DNA damage in Chinese hamster V79 cells as evidenced by DNA single-strand breaks and an increase in the amount of 8-hydroxydeoxyguanosine in DNA (Dahlhaus et al. 1996). In the same study, the para isomer of tetrachlorobenzoquinone produced DNA single-strand breaks and an increase in the amount of 8-hydroxydeoxyguanosine in DNA, whereas the ortho isomer of this compound produced an increase in the amount of 8-hydroxydeoxyguanosine in DNA but did not produce DNA single-strand breaks (Dahlhaus et al. 1996). TCHQ was also found to exert a severe cytotoxic effect and cause marked DNA damage (i.e., single-strand breaks and/or alkali-labile sites) in Chinese hamster ovary cells; the parent compound was weakly cytotoxic but not genotoxic at comparable levels (Ehrlich 1990).

3.4 TOXICOKINETICS

Pentachlorophenol is efficiently absorbed following inhalation, oral, and dermal exposure. Absorbed pentachlorophenol is distributed to the liver, lungs, kidneys, blood, fat tissues, and brain. The binding of pentachlorophenol to plasma proteins plays a significant role in the distribution of pentachlorophenol (Braun et al. 1977; Gómez-Catalán et al. 1991). Results from animal and human studies indicate that pentachlorophenol is not completely metabolized, as evidenced by a large portion of the administered dose being excreted in urine unchanged in all species studied. Pentachlorophenol binds extensively to plasma proteins as discussed in Section 3.4.2.2. Pentachlorophenol has a greater binding affinity for thyretin, a major thyroxine transport protein in the rat, than thyroxine itself (den Besten et al. 1991), and the binding of pentachlorophenol to thyretin is likely responsible for its adverse effect on thyroid homeostasis. The available human and animal data indicate that metabolism of pentachlorophenol does occur in the liver, and the major pathways are conjugation to form the glucuronide and oxidative dechlorination to form tetrachlorohydroquinone (TCHQ). However, recent studies in rats and mice following oral administration of pentachlorophenol (Lin et al. 1997; Waidyanatha et al. 1994, 1996) suggest that the metabolism of pentachlorophenol can also proceed through the quinols TCHQ and Cl₄CAT via microsomal cytochrome P 450 enzymes and that these quinols can be oxidized via semiquinone intermediates (tetrachloro-1,2-semiquinone [Cl₄-1,2-SQ] and tetrachloro-1,4-semiquinone [Cl₄-1,4-SQ]) into the corresponding quinones (tetrachloro-1,2-benzoquinone [Cl₄-1,2-BQ] and tetrachloro-1,4-benzoquinone [Cl₄-1,4-BQ]). Both the quinones and semiquinones are electrophilic and can bind to cellular macromolecules (Lin et al. 1997). Horseradish peroxidase catalyzed the oxidation of pentachlorophenol to Cl₄BQ *in vitro* via a phenoxyl radical intermediate (Samokyszyn et al. 1995). The study authors suggest that this is a potential *in vivo* metabolic step that could be catalyzed by mammalian peroxidases, including prostaglandin H synthase, myeloperoxidase, salivary peroxidase, lactoperoxidase, or uterine peroxidase.

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The primary route of pentachlorophenol elimination in all species studied, including humans, by all routes of exposure, is urine. Approximately 74 and 12% (total of 86%) of pentachlorophenol ingested by humans was eliminated as pentachlorophenol and its glucuronide conjugate, respectively (Braun et al. 1979). In rodents, from 60–83% of the administered oral dose is eliminated in the urine (Ahlborg et al. 1974; Braun et al. 1977; Larsen et al. 1972; Reigner et al. 1991); in monkeys, 45–75% of the administered oral dose is eliminated in the urine (Braun and Sauerhoff 1976) (see Section 3.4.4.2 for a discussion of the metabolites of pentachlorophenol excreted in each species). Fecal elimination of pentachlorophenol and its metabolites accounted for 4% of the administered oral dose in humans, 4–34% of the administered oral dose in rodents, and 4–17% in monkeys. Only trace amounts were eliminated in expired air. The pharmacokinetic profile of pentachlorophenol excretion following single doses is species- and possibly sex-dependent. Elimination was rapid and biphasic in rats (Braun et al. 1977; Reigner et al. 1991) and slow and first-order in monkeys and humans following oral exposure (Braun and Sauerhoff 1976; Braun et al. 1979). Enterohepatic circulation and plasma protein binding influence the elimination kinetics of pentachlorophenol, but no data are available to assess whether the elimination kinetics of pentachlorophenol are dependent on its concentration in blood.

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

There are limited data on the absorption of inhaled pentachlorophenol in humans. In an attempt to measure inhalation absorption of pentachlorophenol in humans, 2 volunteers were exposed to pentachlorophenol in an enclosed area for 45 minutes while they applied pentachlorophenol to wood with a brush (Casarett et al. 1969). Ambient pentachlorophenol concentrations in air were 0.230 and 0.432 ng/m³. The extent of pentachlorophenol absorption in these 2 subjects was calculated to be 88 and 76% of the total potential inhaled dose, based on measurements of respiratory rates during exposure, total urinary pentachlorophenol recovered for up to 1 week postexposure, and tidal volume estimates. These data indicate that pentachlorophenol is readily absorbed through the lungs of humans. These data are supported by the finding of increased plasma and urine pentachlorophenol levels in exposed workers (Casarett et al. 1969; Jones et al. 1986; Pekari et al. 1991) and in residents of log homes treated with pentachlorophenol (Cline et al. 1989; Hosenfeld et al. 1986).

Pulmonary absorption of pentachlorophenol in rats has been demonstrated to occur readily; 70–75% of radioactivity from a single 20-minute inhalation exposure (at a concentration calculated by the authors to

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be equivalent to 5.7 mg [^{14}C]-pentachlorophenol/kg) was recovered in urine, plasma, liver, and lung by 24 hours postexposure (Hoben et al. 1976c).

3.4.1.2 Oral Exposure

Results of studies in humans (Braun et al. 1979; Uhl et al. 1986) and animals (Ahlborg et al. 1974; Braun and Sauerhoff 1976; Braun et al. 1977; Meerman et al. 1983; Reigner et al. 1991) indicate that pentachlorophenol and its sodium salt are readily absorbed following oral administration. Oral absorption of pentachlorophenol (as the sodium salt in water) in humans was determined to be first order, with peak blood levels of 0.248 $\mu\text{g/mL}$ pentachlorophenol being achieved within 4 hours of ingestion of 0.1 mg sodium pentachlorophenate/kg by four healthy male volunteers (Braun et al. 1979). The average half-life of absorption was calculated to be approximately 1.3 hours, indicating that oral absorption of pentachlorophenol in humans is rapid.

Oral absorption of pentachlorophenol by rats and monkeys was compared following administration of single oral doses in corn oil of 10 mg [^{14}C]-pentachlorophenol/kg (monkeys) (Braun and Sauerhoff 1976) and 10 or 100 mg [^{14}C]-pentachlorophenol/kg (rats) (Braun et al. 1977). In both species, absorption through the gastrointestinal tract was rapid; females in both species exhibited faster absorption than males as evidenced by different rate constants of absorption. These rate constants were 1.95 hour^{-1} and 1.52 hour^{-1} for male and female rats, respectively, and 0.215 hour^{-1} and 0.383 hour^{-1} for male and female monkeys, respectively. The half-lives of absorption were 3.64 and 1.81 hours, for male and female monkeys, respectively. Peak blood levels of approximately 60 μg pentachlorophenol/g plasma were achieved in both sexes of rat within 4–6 hours, and peak plasma levels of 10–30 μg pentachlorophenol/g plasma were reached by 12–24 hours in both sexes of monkey. Absorption of pentachlorophenol through the gastrointestinal tract was extensive in both species following administration of a single dose of [^{14}C]-pentachlorophenol as evidenced by more than 90% recovery of radioactivity in urine, feces, expired air, tissues, and carcass.

Similar results were obtained in another study in rats using a lower dose (2.5 mg/kg) of pentachlorophenol (Reigner et al. 1991). Peak plasma concentrations (7.3 \pm 2.8 $\mu\text{g/mL}$) were achieved between 1.5 and 2 hours after administration. Absorption appeared to be first order and fit a one-compartment model in three of five animals tested. Half-life of absorption varied between 0.25 and 1.50 hours. Based on the results of this study, the authors concluded that pentachlorophenol is virtually completely absorbed after oral administration in rats. These same investigators studied the pharmacokinetics of pentachloro-

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phenol in B6C3F₁ mice following the administration of a single gavage dose of 15 mg/kg (Reigner et al. 1992b). Peak plasma concentrations (28 ± 7 $\mu\text{g/mL}$) were achieved between 1.5 and 2 hours after administration. Half-life of elimination from the blood averaged 5.8 ± 0.6 hours. Based on the results of this study, the study authors concluded that pentachlorophenol is virtually completely absorbed after oral administration in mice.

Absorption of pentachlorophenol (>99%) from the gastrointestinal tract of F344 rats after gavage doses of 9.5 or 38 mg/kg in an aqueous methylcellosolve vehicle was first order, with an absorption half-life of about 1.3 hours. The absorption rate of pentachlorophenol, determined after administration of 302 or 1,010 ppm concentrations in the diet (approximately 21 or 64 mg/kg), was comparable to that obtained from aqueous methylcellosolve gavage formulations, but the bioavailability of pentachlorophenol administered in the diet (52% at 302 ppm and 30% at 1,010 ppm) was markedly lower than the bioavailability of pentachlorophenol administered by gavage (100% at 9.5 mg/kg and 86% at 38 mg/kg). Following gavage administration of a single dose of 9.5 or 38 mg/kg pentachlorophenol to the male rats, peak plasma concentrations of pentachlorophenol appeared in 2–4 hours and the concentration was dose-dependent. In males administered pentachlorophenol in the diet for 5 days, diurnal variation was seen in the serum concentration of pentachlorophenol, with increases during the 12-hour dark period and decreases during the 12-hour light period (Yuan et al. 1994).

The extent of absorption of pentachlorophenol or sodium pentachlorophenate from the gastrointestinal tract was studied in rats allowed free access to drinking water that contained a 1.4 millimolar (mM) solution of sodium pentachlorophenate (288 mg/L) or food that contained 350 ppm pentachlorophenol or sodium pentachlorophenate (Meerman et al. 1983). Based on analysis of pentachlorophenol plasma concentrations over a 24-hour period and comparison with parameters obtained after intravenous administration, the study authors concluded that absorption of pentachlorophenol and sodium pentachlorophenate under these conditions was essentially complete.

3.4.1.3 Dermal Exposure

Using human abdominal skin (dermis and epidermis) obtained at autopsy, it has been demonstrated that 62% of pentachlorophenol in diesel oil solution penetrated skin *in vitro*, while only 16% of an aqueous solution of sodium pentachlorophenate penetrated skin (Hortsman et al. 1989). Thus, it appears that pentachlorophenol is absorbed to a much greater extent in an oily solution than in an aqueous solution following dermal exposure in humans. The only other available information on dermal absorption of

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pentachlorophenol and its salts by humans comes from occupational case studies in which elevated levels of pentachlorophenol have been detected in urine and plasma of workers who handle pentachlorophenol-treated wood and/or do not wear adequate personal protective gear when working in areas where pentachlorophenol is being sprayed (Jones et al. 1986). In addition, numerous case reports describe occurrence of severe toxicity and/or death in individuals whose exposure to pentachlorophenol is presumed to be predominantly via the dermal route (Gray et al. 1985; Robson et al. 1969; Smith et al. 1996; Wood et al. 1983).

Animal studies support the human findings that pentachlorophenol is absorbed across the skin. In a Rhesus monkey study, pentachlorophenol was well absorbed following percutaneous application in soil or in acetone (Wester et al. 1993). Under the conditions of this study ($0.7 \mu\text{g}/\text{cm}^2$ in soil and $0.8 \mu\text{g}/\text{cm}^2$ in acetone of ^{14}C -pentachlorophenol applied for 24 hours to abdominal skin), $24.4 \pm 6.4\%$ of the applied dose in soil and $29.2 \pm 5.8\%$ of the applied dose in acetone were absorbed. In an *in vivo* swine model, $40 \mu\text{g}/\text{cm}^2$ [^{14}C -UL]-pentachlorophenol was applied occlusively or nonocclusively in a soil-based mixture to a clipped abdominal site of 8–10-week-old female pigs (Qiao et al. 1997). By 408 hours after dosing, total radiolabel absorption was 29.08% under nonocclusive conditions and 100.72% under occlusive conditions. When antibiotics (neomycin sulfate, bacitracin, and polymyxin B) were codosed with occlusively applied [^{14}C -UL]-pentachlorophenol, total radiolabel absorption by 408 hours was 86.21%. The antibiotics were selected to provide a combined wide spectrum of antimicrobial and antifungal activity. If it assumed that the antibiotics had no direct effect on the dermal absorption of pentachlorophenol, then the inhibition of dermal absorption by the antibiotics suggests that degradation of pentachlorophenol by skin microorganisms may play a role in dermal absorption. The percentage of applied dose present in blood or plasma reached maxima at approximately 96 hours under occlusive conditions (with or without antibiotics) and 144 hours under nonocclusive conditions. These results indicate that pentachlorophenol is readily absorbed following dermal exposure and is bioavailable from soil.

3.4.2 Distribution

There are limited data on the distribution of pentachlorophenol in humans. The distribution of background levels of pentachlorophenol were measured in the urine and tissues collected during the autopsy of 21 humans (Grimm et al. 1981). The highest concentrations of pentachlorophenol were found in the liver ($0.067 \mu\text{g}/\text{g}$), kidneys ($0.043 \mu\text{g}/\text{g}$), brain ($0.047 \mu\text{g}/\text{g}$), spleen ($0.019 \mu\text{g}/\text{g}$), and body fat ($0.013 \mu\text{g}/\text{g}$). The median pentachlorophenol levels in the urine and blood were 0.0044 and $0.033 \mu\text{g}/\text{mL}$, respectively. Low levels of pentachlorophenol were found in human breast milk from West Germany

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(Gebefugi and Korte 1983) and Slovakia (Veningerova et al. 1996). The source of pentachlorophenol was not specified. It is possible that the pentachlorophenol in breast milk was not due to pentachlorophenol exposure, but rather to exposure to other industrial chemical (e.g., hexachlorobenzene, hexachlorocyclohexane), which are metabolized to pentachlorophenol. Since pentachlorophenol was detected in 64% of urine samples gathered from 1,000 human adults living in the United States (Hill et al. 1995), it is likely that pentachlorophenol is present in breast milk in U.S. citizens. Because pentachlorophenol is a metabolite of a number of environmental contaminants, it is not known if the pentachlorophenol present in the urine, breast milk, or tissues resulted from exposure to pentachlorophenol. The discussion of experimental animal studies follows.

3.4.2.1 Inhalation Exposure

Information regarding distribution of pentachlorophenol following inhalation exposure in animals is limited. Distribution of pentachlorophenol was evaluated following single and multiple (five) 20-minute inhalation exposures to concentrations calculated by the authors to be equivalent to a dose of 5.7 mg pentachlorophenol/kg body weight by measuring concentrations of pentachlorophenol in liver, lungs, blood, and urine only (Hoben et al. 1976c). Rapid distribution away from the site of exposure was apparent after a single exposure since only 1.8% of the administered dose was present in lungs immediately after exposure. By 24 hours postexposure, approximately 55% of the administered dose was recovered in urine, 7% in plasma, 9% in liver, and 0.7% in lung. These data indicate that pentachlorophenol was cleared rapidly, and only small amounts accumulated in the tissue samples studied. Repeated-exposure experiments support the observation that pentachlorophenol does not accumulate in rats following inhalation exposure. By 24 hours after the last (fifth) exposure, 70% of the administered dose was recovered in urine, 5% in plasma, 4% in liver, and 0.3% in lung. It is not clear from these data where pentachlorophenol was distributed immediately following exposure, but high levels in urine suggest that pentachlorophenol was cleared rapidly and did not reach an appreciable body burden following repeated exposure. Binding of pentachlorophenol to plasma proteins influences its distribution (see Section 3.4.2.2). Binding of pentachlorophenol to plasma proteins varies linearly with increasing dose following inhalation exposure (Hoben et al. 1976d). No studies were located regarding distribution of pentachlorophenol in animals following long-term inhalation exposure.

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3.4.2.2 Oral Exposure

Distribution studies in rats conducted 9 days after oral administration of a single dose of 10 mg [¹⁴C]-pentachlorophenol/kg body weight in corn oil demonstrated that the highest levels of radioactivity are found in liver and kidneys and lower levels are found in brain and fat tissue. Radioactivity was also detected in lungs, testes, ovaries, heart, and adrenal glands. Levels of radioactivity were uniformly higher in plasma and tissues of females as compared to males, though the distribution pattern was qualitatively the same (Braun et al. 1977). A similar distribution pattern was observed by Larsen et al. (1972) in rats 40 hours after gavage administration of 37–41 mg [¹⁴C]-pentachlorophenol/kg body weight in corn oil.

Larsen et al. (1975) administered a single oral dose of 60 mg/kg pentachloro[U-¹⁴C]phenol (99.54% radiochemical purity) to 14 rats on day 15 of gestation. Groups of 2 rats were sacrificed at 2, 4, 8, 12, 16, 24, and 32 hours after dosing, and the distribution of administered dose was determined in blood serum, placentas, and fetuses. Tissue distributions, expressed as the percentage of administered dose per gram tissue, were 0.88% in blood serum, 0.20% in placentas, and 0.05% in fetuses at 2 hours after dosing. Peak amounts occurred in serum at 8 hours (1.12%), in placentas at 12 hours (0.28%), and in fetuses at 12 hours (0.08%). By 32 hours after dosing, percentages of administered dose were 0.43% in serum, 0.08% in placentas, and 0.04% in fetuses. The chemical nature of the radioactivity present in serum, placentas, and fetuses was not investigated. Since the administered pentachlorophenol did not have 100% radiochemical purity, it is possible that some of the radioactive material distributed in the fetuses was due to radioactive impurities.

Following gavage administration of a single dose of 9.5 or 38 mg/kg pentachlorophenol (>99%) to male F344 rats, peak plasma concentrations of pentachlorophenol appeared in 2–4 hours and the concentration was dose dependent. In male F344 administered pentachlorophenol at 302 or 1,010 ppm concentrations in the diet (approximately 21 or 64 mg/kg) for 5 days, diurnal variation was seen in the serum concentration of pentachlorophenol, with increases during the 12-hour dark period and decreases during the 12-hour light period (Yuan et al. 1994).

At the end of the 2-year dietary bioassay of pentachlorophenol (approximately 99% with one impurity, tetrachlorophenol) in F-344 rats (NTP 1999), mean plasma concentrations of pentachlorophenol were approximately proportional to pentachlorophenol concentrations in the feed, and plasma concentrations in females were higher than those in males. Plasma concentration of pentachlorophenol were 24, 44, and

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67 µg/mL in females and 17, 36, and 53 µg/mL in males at dietary concentrations of 200, 400, and 600 ppm, respectively.

Distribution of [¹⁴C]-pentachlorophenol was measured in 2 monkeys 360 hours after oral administration of a single dose of 10 mg [¹⁴C]-pentachlorophenol/kg body weight. Approximately 11% of administered radiolabel was found in the body at the time of analysis; 80% of this activity was in the liver and in the large and small intestines. These data suggest that the monkey differs from the rat with regard to distribution of orally absorbed pentachlorophenol. There appears to be extensive biliary secretion and enterohepatic circulation of pentachlorophenol in the monkey as evidenced by the long half-life of pentachlorophenol in the body of monkeys and the fact that most of the radiolabel still present in the body 360 hours after administration was in the liver and large and small intestines (Braun and Sauerhoff 1976).

Binding of pentachlorophenol to plasma proteins plays a significant role in the distribution of pentachlorophenol. Tissue/plasma ratios and renal clearance rates following oral administration of pentachlorophenol were much lower than would be predicted, based on the octanol/water partition coefficient and glomerular filtration rate (Braun et al. 1977). This could be explained by extensive binding of pentachlorophenol to plasma proteins. The authors subsequently demonstrated using an *in vitro* diafiltration technique that 95% of pentachlorophenol in plasma is protein bound (Braun et al. 1977). In another experiment in rats, 97.1±2.0% of the administered dose of pentachlorophenol was found bound to plasma proteins as compared to plasma lipoproteins (Gómez-Catalán et al. 1991). Protein binding may result in lower levels being distributed to tissues (i.e., liver and kidney) for metabolism and excretion and increased retention in the body.

3.4.2.3 Dermal Exposure

The distribution of radiolabelled pentachlorophenol was examined in female pigs following occlusive application of 40 µg/cm² [¹⁴C-UL]-pentachlorophenol (Qiao et al. 1997). The distribution of radiolabel 17 days after dosing was as follows (highest to lowest): liver, lung, ovary, gall bladder, kidney, spleen, uterus, urinary bladder, heart, diaphragm, and brain. A large amount of the label was retained in the body, approximately 50–67% of the absorbed label was present in the tissues 17 days after exposure.

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3.4.2.4 Other Routes of Exposure

Distribution of radioactivity in mice following intraperitoneal and subcutaneous administration of single doses of [¹⁴C]-pentachlorophenol has been reported (Jakobson and Yllner 1971). Only 0.4–6% of the administered dose was found in tissues 96 hours after intraperitoneal injection of 14.8–37.2 mg [¹⁴C]-pentachlorophenol/kg body weight. The highest concentrations of radiolabel were found in the gall bladder, liver, stomach wall, and gastrointestinal contents, indicating the occurrence of biliary secretion of pentachlorophenol. Lesser amounts of radiolabel were found in the kidneys, heart, and brain. A similar distribution pattern was observed after subcutaneous administration of 50 mg [¹⁴C]-pentachlorophenol/kg body weight. The concentration of radiolabel in the liver remained high 1 week after dosing. These data are similar to those obtained after oral administration of pentachlorophenol.

Dose- and time-dependent uptake of pentachlorophenol (purity not stated) into the cerebrospinal fluid of rats was demonstrated following single intraperitoneal injections of pentachlorophenol into rats at doses up to 17 mg/kg. Since similar doses of pentachlorophenol also significantly decreased the uptake of radiolabeled T4 into cerebrospinal fluid, the study authors suggested that pentachlorophenol may interact with the T4 binding site of transthyretin and compete with T4 for uptake into cerebrospinal fluid (van Raaij et al. 1994). This is a plausible explanation since the affinity of pentachlorophenol for the T4 binding site on transthyretin is 2.5-fold greater than that of T4 itself (den Besten et al. 1991).

Based on plasma concentrations and clearance rates, the volume of distribution of pentachlorophenol was estimated to be relatively small and approximately correspond to the volume of distribution of albumin and volume of extracellular fluid following intravenous injection of a single dose of 2.5 mg/kg to rats (Reigner et al. 1991). Similar results were obtained in mice (Reigner et al. 1992b). Following intravenous administration of 5 mg/kg pentachlorophenol (>99% purity) into rats, plasma concentrations tended to be slightly higher in males than in females during the first 12 hours. The volume of distribution was 0.13±0.006 L/kg in males and 0.19±0.04 L/kg in females, but the difference was not statistically significant (Yuan et al. 1994).

Reigner et al. (1993) investigated the binding of radiolabeled pentachlorophenol to serum proteins *in vitro* using ultrafiltration. The percent unbound pentachlorophenol in serum was 1.37 in mice, 0.85 in rats, 0.67 in monkeys, 0.53 in humans, and 0.43 in cows. These percentages correlated inversely with the total protein levels in the same serum samples. Percent unbound pentachlorophenol also correlated inversely with serum albumin concentrations with the exception of the cow, which had a lower albumin

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concentration than humans. These data suggest that the distribution of pentachlorophenol may be restricted due to extensive plasma protein binding.

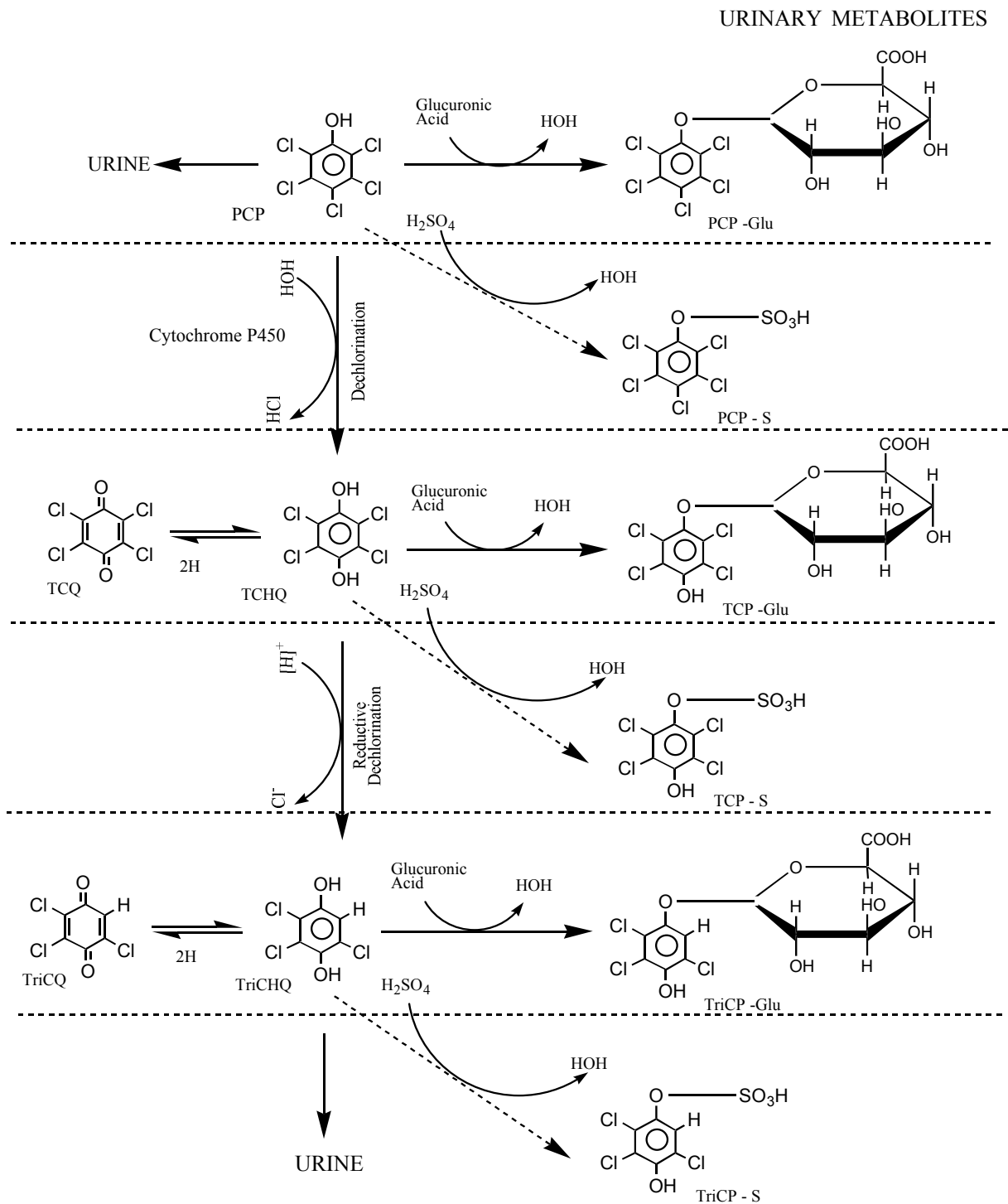
3.4.3 Metabolism

Results from animal and human studies indicate that pentachlorophenol is not extensively metabolized, as evidenced by a large portion of the administered dose being excreted in urine unchanged in all species studied. Extensive plasma protein binding of pentachlorophenol discussed in Section 3.3.2.2 may account for the low degree of metabolism because protein-bound material is not readily distributed to tissues. However, available human and animal data indicate that metabolism of pentachlorophenol does occur in the liver, and the major pathways are conjugation to form glucuronide and oxidative dechlorination to form TCHQ. A summary of possible metabolic pathways for pentachlorophenol is presented in Figure 3-2.

UDP-glucuronosyl transferase and sulfotransferases are involved in phase II metabolism of pentachlorophenol. Both of these enzymes are thought to be developmentally regulated (Leeder and Kearns 1997). Although the ontogeny of UDP-glucuronosyl transferase is isoform-specific, the adult level of activity seems to be achieved in humans by 6–18 months of age (Leeder and Kearns 1997). Ontogeny for the sulfotransferases seems to be more rapid than that for UDP-glucuronosyl transferase, and the activity for some isoforms of sulfotransferase may exceed adult levels during infancy and early childhood (Leeder and Kearns 1997).

Mehmood et al. (1996) has provided evidence that human cytochrome P450 3A4 may metabolize pentachlorophenol to TCHQ in phase I metabolism of pentachlorophenol; however, the initial purity of the pentachlorophenol used in this study was not indicated. In humans, this enzyme has low activity in the first month of life, with approach toward adult levels by 6–12 months of postnatal age; adult activity may be exceeded between 1–4 years of age and then activity progressively declines, reaching adult levels at the conclusion of puberty (Leeder and Kearns 1997). By Western immunoblotting using monoclonal antibodies to identify the different P 450 isozymes, pure pentachlorophenol (>99%) was identified as an inducer of cytochrome P450 3A7 in studies in cultured rat hepatocytes, quail hepatocytes, and human hepatoma (Hep G2) cells (Dubois et al. 1996). In humans, functional activity of cytochrome P450 3A7 in the fetus is approximately 30–75% of adult levels (Leeder and Kearns 1997).

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Figure 3-2. Proposed Metabolic Scheme for Pentachlorophenol

PCP = pentachlorophenol; PCP-Glu = pentachlorophenol- β -glucuronide; PCP-S = pentachlorophenylsulfate; TCHQ = tetrachloro-p-hydroquinone; TCP-Glu = tetrachlorophenol- β -glucuronide; TCP-S = tetrachlorophenylsulfate; TCQ = tetrachloroquinone; Tri CHQ = trichloro-p-hydroquinone; Tri CP-Glu = trichlorophenyl- β -glucuronide; Tri CP-S = trichlorophenylsulfate; Tri CQ = trichloro-p-quinone

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3.4.3.1 Inhalation Exposure

Ahlborg et al. (1974) analyzed urine from 2 workers employed as spraymen 24 hours after exposure to sodium pentachlorophenate that was presumably via the inhalation route. Both unchanged pentachlorophenol and TCHQ were identified (relative proportions were not specified), but no mention was made regarding the possible presence of glucuronide conjugates. Thus, at least oxidative dechlorination of pentachlorophenol occurs in humans exposed via inhalation. In rats, 70–75% of inhaled pentachlorophenol is excreted unchanged in urine following a single exposure (Hoben et al. 1976a).

3.4.3.2 Oral Exposure

Oral administration of small doses of pentachlorophenol (0.02–0.31 mg pentachlorophenol/kg) of 99% purity to volunteers resulted in excretion of unchanged pentachlorophenol (78% of administered dose) and pentachlorophenol glucuronide (12% of the administered dose) in urine and feces (Braun et al. 1979; Uhl et al. 1986). No TCHQ was identified.

Studies in rats indicate that both metabolic pathways described above were operative following oral administration of pentachlorophenol, but most of the administered dose was excreted unchanged (Ahlborg et al. 1974; Braun et al. 1977; Renner 1989; Renner and Hopfer 1990). The following urinary metabolites were recovered and identified by gas chromatography from female Sprague-Dawley rats dosed with pentachlorophenol (>99% pure) for 28 days: 2,3,4,5-tetrachlorophenol; 2,3,4,6-tetrachlorophenol; 2,3,5,6-tetrachlorophenol; tetrachlorocatechol (Cl₄CAT); trichloro-1,4-benzenediol; tetrachloro-1,4-benzenediol; tetrachlororesorcinol; trichlorohydroquinone; TCHQ; and traces of trichloro-1,4-benzoquinone and tetrachloro-1,4-benzoquinone. The major metabolite was TCHQ, which was excreted mainly as a glucuronide conjugate (Renner and Hopfer 1990). Based on the urinary metabolites identified, the study authors concluded that the main metabolic pathway for pentachlorophenol in the rat was pentachlorophenol to 2,3,5,6-tetrachlorophenol to TCHQ, with a minor pathway being pentachlorophenol to 2,3,4,6- and 2,3,4,5-tetrachlorophenol to trichlorohydroquinone. Pentachlorophenol (conjugated with glucuronic acid and unconjugated) and TCHQ (conjugated with glucuronic acid and unconjugated) were recovered from urine and quantified by high-performance liquid chromatography and confirmed by using capillary gas chromatography from female Sprague-Dawley rats dosed with pentachlorophenol (>99% pure) for 28 days (Renner and Hopfer 1990). Unconjugated pentachlorophenol accounted for 36–58% of pentachlorophenol recovered, and 10–19% of the TCHQ excreted was unconjugated. Concentrations of both pentachlorophenol and TCHQ in urine fell to negligible amounts

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within one week after cessation of treatment. The study authors concluded that conjugation of pentachlorophenol with glucuronide and the metabolism of pentachlorophenol to TCHQ in rats results in more rapid excretion than in species that excrete unchanged pentachlorophenol (e.g., monkey) (see discussion below).

In other studies in rats, 48% of the 100 mg [¹⁴C]-pentachlorophenol/kg administered orally to rats was recovered as unchanged pentachlorophenol in urine, 10% was TCHQ, and 6% was pentachlorophenol-glucuronide. No TCHQ-glucuronide was detected (Braun et al. 1977). Similar results were obtained in rats and mice when a single dose of 25 mg [¹⁴C]-pentachlorophenol was administered by gavage, except that TCHQ conjugates (not positively identified as glucuronides) were identified in urine (Ahlborg et al. 1974). These investigators found that 41–43% of the administered radiolabel was recovered in the urine as unchanged pentachlorophenol in rats and mice, 5% as TCHQ in rats, and 24% as TCHQ in mice. An unspecified proportion of radioactivity was found in urine as conjugated pentachlorophenol and TCHQ, but it could not be determined whether these were glucuronide conjugates. Other investigators have reported results in rats that differ from those of Braun et al. (1977). Approximately 60% of a 2.5 mg/kg dose of pentachlorophenol was recovered in the urine of Sprague-Dawley rats after 72 hours, mostly as conjugated pentachlorophenol and TCHQ, with only 5.3±0.2% of the dose recovered as unchanged pentachlorophenol (Reigner et al. 1991). Treatment of urine with sulfuric acid indicated that sulfate conjugates of pentachlorophenol and TCHQ accounted for about 90% of conjugated pentachlorophenol and TCHQ (glucuronide conjugates reported by Braun et al. [1977]). Metabolites and unchanged pentachlorophenol in feces accounted for 10% of the administered dose.

It has been demonstrated that the monkey differs from the rat and mouse in that virtually all radioactivity recovered in urine following oral administration of 10 mg [¹⁴C]-pentachlorophenol/kg was associated with pentachlorophenol; no TCHQ or glucuronide conjugates were identified (Braun and Sauerhoff 1976). These data suggest that pentachlorophenol is not metabolized to any great degree by the monkey.

Binding of pentachlorophenol to specific components of liver cells or differential distribution of pentachlorophenol to different cellular organelles can affect its metabolic fate or that of other xenobiotics and ultimately regulate the manifestation of toxic effects. Arrhenius et al. (1977) administered a single dose of gas-chromatographically pure pentachlorophenol (40 mg/kg) by stomach tube to rats, killed them 16 hours later, separated subcellular fractions, and determined that the relative concentration of pentachlorophenol in microsomes was 6 times greater than in mitochondria. Since maximum effects on inhibition of microsomal detoxification processes (requiring electron transport from flavin to cytochrome)

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occur at a pentachlorophenol concentration (100 μM) that is 4 times greater than the concentration of pentachlorophenol required to cause maximum inhibition of oxidative phosphorylation in mitochondria (25 μM), Arrhenius et al. (1977) suggested that inhibition of mitochondrial oxidative phosphorylation and inhibition of microsomal detoxification by pentachlorophenol might be equally important. The possibility that the presence of pentachlorophenol in microsomes allows this substance to inhibit its own metabolism provides a possible explanation for the relative lack of pentachlorophenol metabolism seen in all species studied. Another possible explanation is that extensive plasma binding of pentachlorophenol limits distribution of pentachlorophenol to the liver for subsequent biotransformation. In either case, any perturbation that increases the level of free circulating pentachlorophenol may result in enhanced toxicity as well as an increased rate of biotransformation and elimination. For individuals living in close proximity to areas of potentially high pentachlorophenol exposure, concomitant exposure to chemicals or intentional ingestion of drugs that compete with pentachlorophenol for protein binding may enhance pentachlorophenol-induced toxicity.

3.4.3.3 Dermal Exposure

No studies were located regarding metabolism in humans or animals after dermal exposure to pentachlorophenol.

3.4.3.4 Other Routes of Exposure

Results of studies in rats and mice indicate that metabolism of pentachlorophenol following intraperitoneal injection is similar to that observed following oral exposure (Ahlborg et al. 1978; Jakobson and Yllner 1971). *In vitro* studies in both human and rat liver homogenates clearly demonstrate that pentachlorophenol is converted to TCHQ (Juhl et al. 1985). Using a genetic construct in which human cytochrome P450 3A4 is expressed in *Saccharomyces cerevisiae* strain AH22, Mehmood et al. (1996) demonstrated that human cytochrome P450 3A4 may metabolize pentachlorophenol to TCHQ; however, the initial purity of the pentachlorophenol used in this study was not indicated. By Western immunoblotting using monoclonal antibodies to identify the different P 450 isozymes, pure pentachlorophenol (>99%) was identified as an inducer of cytochrome P450 3A7 in studies in cultured rat hepatocytes, quail hepatocytes, and human hepatoma (Hep G2) cells (Dubois et al. 1996).

Since studies with rat liver microsomes using ^{19}F nuclear magnetic resonance have demonstrated the cytochrome P450-dependent oxidation of pentafluorophenol to tetrafluorobenzoquinone (den Besten et al.

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1993), it can be speculated that cytochrome P450 may also catalyze the oxidation of pentachlorophenol to tetrachlorobenzoquinone.

Horseradish peroxidase catalyzed the oxidation of pentachlorophenol to Cl₄BQ *in vitro* via a phenoxyl radical intermediate (Samokyszyn et al. 1995). The study authors suggest that this is a potential *in vivo* metabolic step that could be catalyzed by mammalian peroxidases, including prostaglandin H synthase, myeloperoxidase, salivary peroxidase, lactoperoxidase, or uterine peroxidase.

The rate of pentachlorophenol-glucuronide conjugation in human liver microsomes is reported to be one-third of that found in rat liver microsomes (Lilienblum 1985), although phenobarbital-enhanced dechlorination of pentachlorophenol, phenobarbital, and 3-methylcholanthrene (another microsomal enzyme inducer) had little effect on the conjugation reaction in rat liver microsomes (Ahlborg et al. 1978). This indicated that the extent of glucuronide conjugation was governed by factors other than phenobarbital- and 3-methylcholanthrene-inducible microsomal enzyme activity.

It has been proposed that accumulation of pentachlorophenol by lipid-containing tissues seen *in vitro* is due to conjugation with fatty acids (Leighty and Fentiman 1982). These investigators reported that pentachlorophenol conjugated with palmitic acid in an *in vitro* rat liver coenzyme A fortified microsomal system. This ester is also found in human fat (Ansari et al. 1985). The mechanism by which the palmitoyl-pentachlorophenol is formed in human fat has yet to be determined. The presence of this ester in human fat demonstrates that xenobiotics such as pentachlorophenol can be made more lipophilic and stored in the fat of humans rather than excreted by the kidneys, thereby providing a potential reservoir of toxin that could be released at a later time.

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

The available information regarding pentachlorophenol excretion following inhalation exposure in humans comes predominantly from occupational case studies. Data obtained by Bevenue et al. (1967) from measuring urinary levels of pentachlorophenol in residents of Honolulu (some with a history of occupational exposure to pentachlorophenol) indicated that elimination was biphasic, with urinary pentachlorophenol levels decreasing approximately 35% per day in the first 2 days. Urinary levels of pentachlorophenol measured in wood-treatment workers prior to, during, and after vacation implied a urinary

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half-life of elimination of 19–20 days following inhalation exposure (Begley et al. 1977). A 10-day half-life of pentachlorophenol excretion in urine was estimated from urinary levels of pentachlorophenol measured in a tannery worker 1 day after the last day of work-related pentachlorophenol exposure and during a subsequent holiday period (Barbieri et al. 1995). The results of studies conducted by Casarett et al. (1969) in occupationally exposed humans suggest that pentachlorophenol excretion kinetics differ between single high-level and chronic low-level exposure. Urinary half-lives of approximately 10 hours were displayed by 2 subjects following a 45-minute inhalation exposure resulting from painting household materials in an enclosed area, whereas urine pentachlorophenol levels in exposed workers decreased only by 60–80% when the workers were absent from work for up to 18 days. The authors hypothesized that slower elimination of pentachlorophenol in the chronic situation may be the result of the establishment of an equilibrium between lung, plasma proteins, urine, and tissue depots.

A group of 7 sawmill workers (6 males and 1 female) exposed to a sodium chlorophenolate wood-preserving product containing 3% pentachlorophenol were monitored for serum and urinary concentrations of pentachlorophenol (as well as other chlorophenols) throughout a wood-treatment season of approximately 7 months and an additional 171 days after the termination of exposure for the season (Pekari et al. 1991). Maximal pentachlorophenol urine concentrations after the period of exposure were 0.2–0.9 $\mu\text{mol/L}$. Approximately 76% of the pentachlorophenol in urine was conjugated. The elimination rate constant in these workers using a one-compartment model was $0.044 \pm 0.018/\text{day}$ with a corresponding half-life of 16 days for pentachlorophenol. The minimal urinary clearance for pentachlorophenol was 0.2 mL/minute and varied with urine flow. The study authors noted that the relatively high concentrations of pentachlorophenol found in the serum (23%) as compared to the low percentage of pentachlorophenol in the technical product (3%) indicates that pentachlorophenol accumulates in the serum, in accordance with its relatively long half-time (16 days as compared to 18 hours and 4.2 days for tri- and tetrachlorophenol, respectively). Breathing zone measurements of concentration of airborne contamination compared to quantitative urine measurements would greatly improve the quality of the study.

Excretion of pentachlorophenol following inhalation exposure in animals has not been well documented. The elimination half-life of pentachlorophenol following a single 20-minute inhalation exposure to 5.7 mg [^{14}C]-pentachlorophenol/kg was 24 hours (Hoben et al. 1976c). Pentachlorophenol does not undergo appreciable biotransformation as most of the inhaled dose was found to be eliminated unchanged in the urine. The authors of this study also reported that repeated (five) exposures increased urinary output of pentachlorophenol. These results are not inconsistent with those of Casarett et al. (1969).

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Elimination of many toxicants from high body burdens follows first-order kinetics initially, but the pattern of elimination becomes much more complex as lower body burdens are attained. Accumulation with repeated exposure will occur if rate of absorption exceeds rate of elimination, irrespective of excretion kinetics or tissue storage.

3.4.4.2 Oral Exposure

Studies investigating excretion of pentachlorophenol by humans following ingestion of 0.016–0.31 mg pentachlorophenol/kg have yielded conflicting results. Uhl et al. (1986) found that pentachlorophenol was excreted slowly, displaying an elimination half-life in both blood and urine of 14 days and a renal clearance of 0.07 mL/minute following ingestion of 0.016–0.31 mg pentachlorophenol/kg in ethanol by volunteers. The authors concluded that slow elimination could be attributed to extensive plasma protein binding and tubular reabsorption.

When Braun et al. (1979) studied excretion kinetics of pentachlorophenol (as the sodium salt) in volunteers who ingested 0.1 mg pentachlorophenol/kg, they found that the half-life of elimination was 30.2 hours from plasma and 33.1 hours from urine for pentachlorophenol, and 12.7 hours from urine for the glucuronide conjugate. Approximately 74% of the administered dose was eliminated in urine as pentachlorophenol and 12% as pentachlorophenol-glucuronide within 168 hours postingestion, and 4% was recovered as pentachlorophenol and pentachlorophenol-glucuronide in feces. These investigators concluded that pentachlorophenol elimination in humans followed first-order kinetics with enterohepatic recirculation following oral exposure. One possible explanation for the different half-lives observed in the Uhl et al. (1986) and the Braun et al. (1979) studies is the different dosing procedures employed. Subjects in the Uhl et al. (1986) study were reported to have ingested pentachlorophenol "without restriction of diet," while Braun et al. (1979) reported that "food was withheld 8 hours before and 1 hour after ingestion of the dose." Dispersion in gut contents may have slowed absorption in the Uhl et al. (1986) subjects, while absorption of the full dose occurred over a much shorter interval in the Braun et al. (1979) subjects, thus accounting for the different half-lives observed. Other explanations for the differences observed between the two studies include the fact that sodium pentachlorophenate was used for the Braun et al. (1979) study and pentachlorophenol in ethanol was used for the Uhl et al. (1986) study, and the vehicle used in the Uhl et al. (1986) study (ethanol) may have altered the solubility of pentachlorophenol.

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Elimination of pentachlorophenol in rats following oral exposure was shown to be rapid and biphasic, with urine being the major route of excretion (Braun et al. 1977). The authors of this study reported that within 8–9 days, 80% of the radioactivity from the single oral administration of 10 mg [¹⁴C]-pentachlorophenol/kg to rats was recovered in urine and 19% in feces; 64% was detected in urine and 34% in feces following single oral administration of 100 mg [¹⁴C]-pentachlorophenol/kg. Elimination half-lives were 17 and 13 hours for the first phase and 40 and 30 hours for the second phase in low-dose males and females, respectively. Ninety percent of the radioactivity was eliminated in the first phase. High-dose males exhibited elimination half-lives of 13 and 121 hours for the first and second phases, respectively. High-dose females exhibited first-order kinetics with a half-life of 27 hours. No explanation was offered for the difference in kinetics seen in high-dose females. These data indicate that: (1) the rate of elimination in the slow phase only and the relative distribution of radioactivity in feces varied linearly with increasing dose, (2) females eliminated pentachlorophenol faster than males, and (3) plasma binding and hepatic retention could account for the prolonged second phase of elimination.

Different results were reported in rats administered single doses of 37–41 mg [¹⁴C]-pentachlorophenol/kg (Larsen et al. 1972). While the half-lives of rapid phases of elimination were comparable, Larsen et al. (1972) reported a half-life of 102 days for the second phase. However, these data are questionable because Larsen et al. (1972) did not obtain 100% recovery in urine and assumed that fecal excretion was constant. Therefore, they only reported a total fecal excretion value after 10 days.

Results similar to those obtained by Braun et al. (1977) were reported by Reigner et al. (1991, 1992b) with respect to urinary and fecal elimination of pentachlorophenol following single-dose exposure in rats and mice. In the Reigner et al. studies, 8–10% of the administered dose (2.5 and 15 mg/kg, respectively, for rats and mice) of pentachlorophenol was recovered in the feces. Therefore, biliary excretion must play some role in elimination of pentachlorophenol.

Elimination of pentachlorophenol by monkeys was slow and followed first-order kinetics. Braun and Sauerhoff (1976) orally administered single doses of 10 mg [¹⁴C]-pentachlorophenol/kg to monkeys and monitored excretion of radioactivity for up to 360 hours after administration. They found that 10–20% of administered radioactivity was steadily excreted in the feces, attesting to a relatively high degree of biliary secretion. Urinary pentachlorophenol accounted for 70–80% of the administered radiolabel. The half-life of elimination was 40.8 hours in males and 92.4 hours in females. The long half-life was attributed to enterohepatic circulation with subsequent biliary secretion.

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The role of enterohepatic circulation and biliary secretion in pentachlorophenol elimination in monkeys was further investigated by measuring the relative extent of excretion of pentachlorophenol in urine, feces, and bile before and after administration of cholestyramine, a substance that binds phenols (Ballhorn et al. 1981; Rozman et al. 1982). The cholestyramine was administered in the diet 24 hours after pentachlorophenol exposure. At 30 mg/kg/day, control excretion was 92.3% in urine and 7.7% in feces. Following cholestyramine administration, excretion was 12.1% renal and 86.9% fecal. At 50 mg/kg/day, control excretion was 79.9% renal and 20.1% fecal. Following cholestyramine administration, excretion was 15.4% renal and 84.6% fecal. Total excretion was also increased by cholestyramine administration. Total recovery of administered dose over a 6-day period increased from 26 to 45% at the low dose and from 15 to 31% at the high dose (Ballhorn et al. 1981).

In a follow-up study, cholestyramine treatment reduced urinary excretion of pentachlorophenol from 35 to 5% of the administered dose and increased fecal excretion from 3 to 54% of the administered dose. The increase in fecal excretion induced by cholestyramine exceeded the decrease in urinary excretion. Total excretion increased by 40%. Seventy percent was excreted in bile during the control period, and 52% was excreted in bile after cholestyramine treatment (Rozman et al. 1982), suggesting that cholestyramine treatment also enhanced the excretion of pentachlorophenol across the intestinal wall.

The following conclusions can be drawn from these studies:

- In untreated monkeys, oral absorption of pentachlorophenol was followed by elimination via bile into the duodenum, reabsorption in the small intestine, and enterohepatic circulation and excretion, predominantly via the kidney.
- Cholestyramine, which binds phenols, interrupted enterohepatic circulation by binding pentachlorophenol and/or its metabolites, resulting in predominantly fecal excretion.
- Total excretion was increased after cholestyramine treatment, suggesting that it reduced the half-life of pentachlorophenol in the monkey by enhancing its elimination from the body.
- Cholestyramine increased elimination of pentachlorophenol by sequestering it from enterohepatic circulation and increasing its excretion across the intestinal wall.

3.4.4.3 Dermal Exposure

No studies were located regarding excretion in humans after dermal exposure to pentachlorophenol.

In an *in vivo* swine model, 40 µg/cm² [¹⁴C-UL]-pentachlorophenol was applied occlusively or nonocclusively in a soil-based mixture to a clipped abdominal site of 8–10-week-old female pigs (Qiao et

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al. 1997). As an additional dosing protocol, antibiotics (neomycin sulfate, bacitracin, and polymyxin B, selected to provide a combined wide spectrum of antimicrobial and antifungal activity) were codosed with occlusively-applied [^{14}C -UL]-pentachlorophenol to determine if inhibition of dermal microbial activity would influence absorption and disposition. Only one-third to one-half of the absorbed dose was almost equally excreted through urinary and fecal routes at constant rates over the 408-hour study period. In general, both the urinary and fecal excretion rates were faster for occlusive than for nonocclusive conditions. At 408 hours, the excretion data indicated that occlusion significantly increased the urinary (4x) and fecal (2.5x) excretion. Codosing of antibiotics with occlusive pentachlorophenol application significantly decreased urinary and fecal excretion. Based on the excretion curves, the urinary excretion rates were 0.35, 1.29, and 0.65% dose/day for nonocclusive, occlusive, and occlusive-antibiotic conditions, respectively, and the fecal excretion rates were 0.47, 1.24, and 0.82% dose/day for nonocclusive, occlusive, and occlusive-antibiotic conditions, respectively.

3.4.4.4 Other Routes of Exposure

Kinetics of elimination of pentachlorophenol in rats following a single intravenous injection (Reigner et al. 1991) differ from those reported by Braun et al. (1977) following oral exposure. In the Reigner et al. (1991) study, the clearance rate of pentachlorophenol from plasma was 0.026 ± 0.003 L/hour/kg. Elimination of pentachlorophenol from plasma was biphasic and fit a two-compartment model, with the half-life for the first phase being 0.67 ± 0.46 hours and the half-life for the second phase being 7.11 ± 0.87 hours. Most of the pentachlorophenol was eliminated during the second phase. However, routes of excretion and main metabolites recovered in urine and feces were similar to those seen by these same investigators after oral administration (Reigner et al. 1991). The study authors proposed that specificity of the analytical methodology is one possible explanation for the difference in elimination kinetics seen between their study and the study by Braun et al. (1977), who, instead of taking multiple blood samples from the same animal, killed two animals at different times to get the kinetic profile. Use of pooled data such as this may have provided inaccurate data for modeling.

Following intravenous administration of 5 mg/kg pentachlorophenol (>99% purity) into rats, the estimated mean terminal elimination half-life of pentachlorophenol was 5.6 ± 0.37 hours in males and 9.5 ± 4.2 hours in females, but the difference was not significant (Yuan et al. 1994).

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3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen et al. 1987; Andersen and Krishnan 1994). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) is adequately described, however, this simplification is desirable because data are often unavailable for

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many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-3 shows a conceptualized representation of a PBPK model.

No PBPK modeling studies were located for pentachlorophenol.

3.5 MECHANISMS OF ACTION

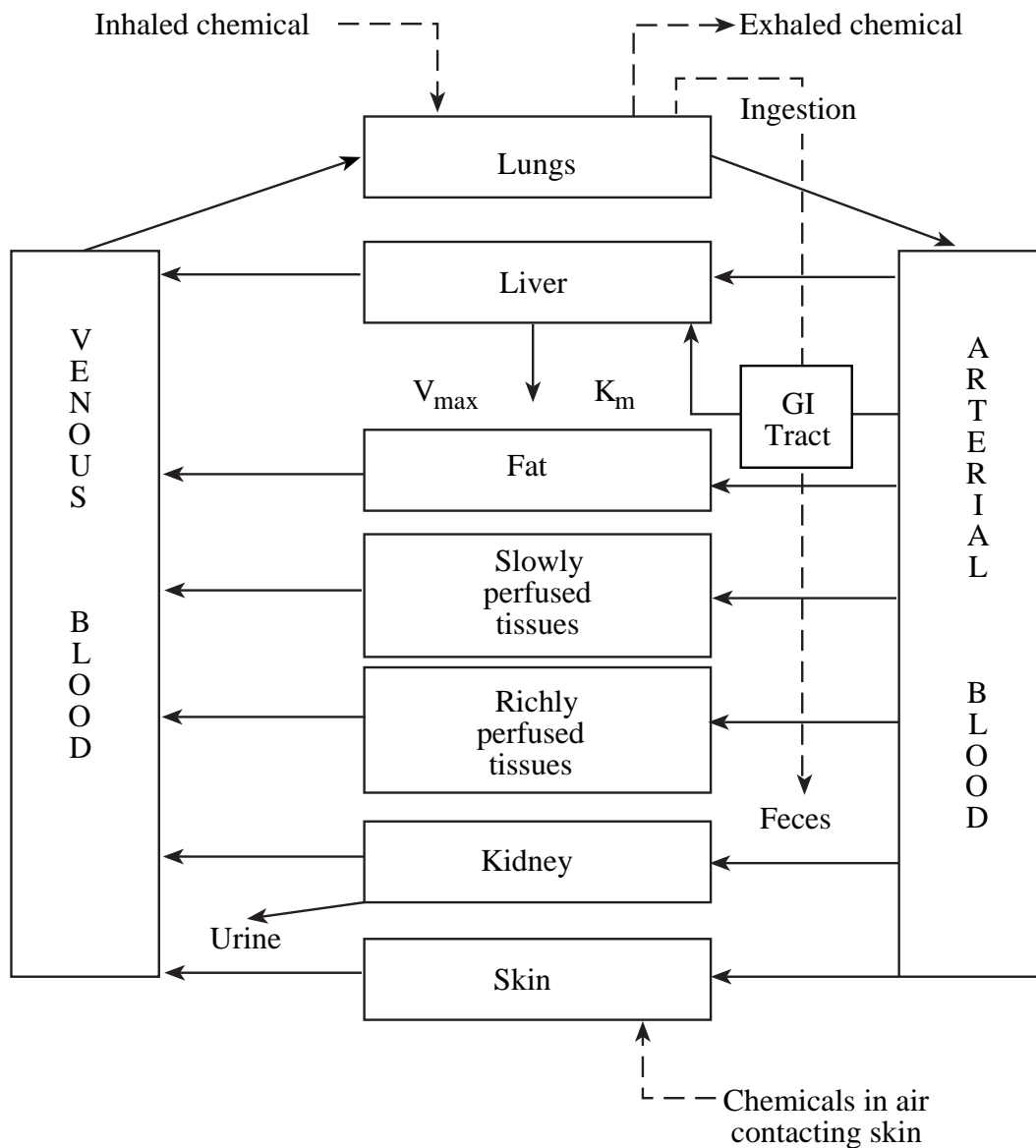
3.5.1 Pharmacokinetic Mechanisms

Pentachlorophenol is a nonpolar, lipophilic substance. While the exact mechanism of absorption is not known, it can be assumed that because of its lipophilicity it can easily cross cell membranes and be absorbed in lungs, gastrointestinal tract, and skin. Toxicokinetic studies in animals and humans demonstrate this to be the case (see Section 3.4.1).

Binding of pentachlorophenol to plasma proteins plays a role in the distribution of pentachlorophenol. It has been demonstrated, using an *in vitro* diafiltration technique (Braun et al. 1977), that 95% of the pentachlorophenol in plasma is protein bound. Extensive plasma protein binding of pentachlorophenol may account for the low degree of metabolism seen with this compound (most pentachlorophenol is excreted unchanged) because protein-bound material is not readily distributed to tissues where it can be metabolized. van Raaij et al. (1994) demonstrated a dose- and time-dependent uptake of pentachlorophenol into the cerebrospinal fluid of rats following single intraperitoneal injections. Since similar doses of pentachlorophenol also significantly decreased the uptake of radiolabeled T4 into cerebrospinal fluid, the study authors suggested that pentachlorophenol may interact with the T4 binding site of transthyretin and compete with T4 for uptake into cerebrospinal fluid (van Raaij et al. 1994). This is a plausible explanation since the affinity of pentachlorophenol for the T4 binding site on transthyretin is 2.5-fold greater than that of T4 itself (den Besten et al. 1991).

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Figure 3-3. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1994

Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

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3.5.2 Mechanisms of Toxicity

It is widely believed that pentachlorophenol exerts its toxic effects, at least in part, by uncoupling mitochondrial oxidative phosphorylation, thereby causing accelerated aerobic metabolism and increased heat production. Pentachlorophenol has been found to bind to purified rat liver mitochondrial protein. This may induce conformational changes in enzymes involved in oxidative phosphorylation (Weinbach and Garbus 1965). The pattern of pentachlorophenol-induced toxicity often seen in humans and animals supports this proposed mechanism of action. A young worker who died following 3 weeks of exposure to pentachlorophenol dust in a chemical plant was found to have cerebral edema and fatty degeneration of liver and lungs at necropsy (Gray et al. 1985). The study authors concluded that these clinical findings are consistent with a hypermetabolic state resulting from a derangement of aerobic metabolism and characterized by hyperthermia, which can lead to tachycardia, tachypnea, hyperemia, diaphoresis, and metabolic acidosis. This is usually followed by death and rapid, profound rigor mortis. Toxicity resulting from uncoupling of oxidative phosphorylation was generally seen prior to death in animals acutely exposed to pentachlorophenol. These included accelerated respiration, hyperemia, cardiac and muscular collapse, asphyxial convulsions, death, and rapid rigor mortis (St. Omer and Gadusek 1987). The ultrastructural changes observed in mitochondria from liver cells of rats treated with technical-grade pentachlorophenol for 15 days are consistent with uncoupling of oxidative phosphorylation (Fleischer et al. 1980).

The cell membrane is apparently a possible site of action for pentachlorophenol. Lipid bilayers of purified and total cell membranes have been reported to destabilize following sublethal pentachlorophenol treatment (Duxbury and Thompson 1987). This was evidenced by a 50% decrease in bulk lipid fluidity attributable to disruption of the bilayer by pentachlorophenol. These authors also found that pentachlorophenol partitions into the hydrophobic interior of the bilayer. Other membrane changes observed by these investigators included a decrease in phospholipid phosphate levels that they believe was a result of a selective chemical effect on phospholipase C. However, the authors concluded that this was only a sublethal effect since the cells remained viable.

In another investigation of the physicochemical basis of pentachlorophenol membrane effects, membrane toxicity was associated with the pentachlorophenol-induced change in hydrogen ion permeability of the membrane lipid matrix (Smejtek 1987). The onset of toxic effects was correlated with the loss of membrane electrical resistance and a measurable amount of pentachlorophenol binding to the membrane.

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Studies described above indicate that pentachlorophenol can disrupt membrane structure and function. These effects could conceivably occur throughout the body and could therefore explain the wide range of toxic effects associated with pentachlorophenol, including the uncoupling of oxidative phosphorylation.

Oral and intraperitoneal administration of pentachlorophenol to animals causes adverse effects on thyroid homeostasis (e.g., decreased serum thyroxine) and on the thyroid gland (Beard and Rawlings 1998; Beard et al. 1999b; Jekat et al. 1994; van Raaij et al. 1991a). These effects may occur during gestation, pregnancy, and lactation (Beard and Rawlings 1998; Beard et al. 1999b). Further *in vitro* studies by van Raaij et al. (1991b) revealed that the likely mechanism of action for this anti-thyroid effect of pentachlorophenol was competition for serum protein thyroxine binding sites. van Raaij et al. (1994) subsequently demonstrated a dose- and time-dependent uptake of pentachlorophenol into the cerebrospinal fluid of rats following single intraperitoneal injections. Since similar doses of pentachlorophenol also significantly decreased the uptake of radiolabeled T4 into cerebrospinal fluid, the study authors suggested that pentachlorophenol may interact with the T4 binding site of transthyretin and compete with T4 for uptake into cerebrospinal fluid (van Raaij et al. 1994). This is a plausible explanation since the affinity of pentachlorophenol for the T4 binding site on transthyretin is 2.5-fold greater than that of T4 itself (den Besten et al. 1991).

Such effects on thyroid parameters, combined with the activity of pentachlorophenol as a potent inhibitor of oxidative phosphorylation (Weinbach 1954), may be expected to have general adverse effects on basal metabolic rate and many critical processes including development, reproduction, nervous system function, and the specific functioning of endocrine and other organs.

In addition, the effects of pentachlorophenol on thyroid homeostasis and the availability of T4 to the central nervous system may have adverse effects on development of the nervous system. Deficiencies in thyroxine during prenatal and postnatal life can cause decrements in intellectual function in children (Bargagna et al. 1997; Birrell et al. 1983; Kooistra et al. 1994), and hypothyroidism in animals leads to disorders in structural and functional development of the brain (Gould et al. 1990; Neveu and Arenas 1996; Stein et al. 1991; Vega-Nunez et al. 1995). However, testing has not been performed on animals exposed to pentachlorophenol, either prenatally or postnatally, to examine the potential for the anti-thyroid effects of pentachlorophenol to produce adverse effects on neurobehavior.

Recent studies in rats and mice involved the characterization of chlorinated protein adducts arising from pentachlorophenol metabolism following oral administration of pentachlorophenol (Lin et al. 1997;

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Waidyanatha et al. 1994, 1996). Results from these studies and previously summarized studies suggest that the metabolism of pentachlorophenol can proceed through the quinols TCHQ and Cl₄CAT via microsomal cytochrome P 450 enzymes and that these quinols can be oxidized via semiquinone intermediates (tetrachloro-1,2-semiquinone [Cl₄-1,2-SQ] and tetrachloro-1,4-semiquinone [Cl₄-1,4-SQ]) into the corresponding quinones (tetrachloro-1,2-benzoquinone [Cl₄-1,2-BQ] and tetrachloro-1,4-benzoquinone [Cl₄-1,4-BQ]). Both the quinones and semiquinones are electrophilic and can bind to cellular macromolecules (Lin et al. 1997). The redox cycling associated with oxidation of TCHQ and reduction of Cl₄-1,4-BQ generates oxygen radicals that caused an increase in 8-hydroxy-2-deoxyguanosine levels in liver DNA in mice that had been fed pentachlorophenol (Sai-Kato et al. 1995; Umemura et al. 1996) or TCHQ (Dahlhaus et al. 1994) in the diet for up to 4 weeks. It is possible that the formation of such adducts is involved in the induction of hepatic neoplasms in mice (NTP 1989). Lin et al. (1997) measured levels of chlorinated protein adducts arising from pentachlorophenol metabolism in the livers of mice and rats administered pentachlorophenol in the diet for up to 4 weeks. After aggregation of the estimated contributions of all quinone species derived from pentachlorophenol metabolism, mice had a four-fold greater dose to liver nuclei than rats, whereas rats had a three-fold greater dose to liver cytosol than mice. The increased nuclear dose to mouse liver compared to that of the rat suggests that the mouse is at greater risk to hepatic DNA damage from pentachlorophenol-derived quinones. Using a model to predict quinone and semiquinone production, Lin et al. (1999) estimated that at low doses of pentachlorophenol, the production of semiquinone adducts was proportionally greater in rats than mice; in mice, direct oxidation to quinones and the production of quinone adducts is favored in mice exposed to low doses of pentachlorophenol. These data suggest that both the types and amounts of adducts differ in rats and mice, which may account for the occurrence of liver tumors in mice but not in rats in bioassays conducted by NTP (1989, 1999).

In an epidemiologic study of male factory workers who brushed pentachlorophenol onto wood strips, sometimes without gloves, serum biliary acid concentrations were elevated in the high-exposure group, but not the low-exposure group, compared with controls (Colosio et al. 1993b). This effect may have been caused in part by the impurities in the pentachlorophenol. The presence of elevated concentrations of bile acids in serum is a sensitive indicator of liver dysfunction (Franco et al. 1986). Since bile acids are essential for lipid transport, are the major products of cholesterol metabolism, and regulate the transcription of genes that control cholesterol homeostasis (Makishima et al. 1999; Parks et al. 1999), the elevation of serum bile acids by exposure to high levels of pentachlorophenol may have some effect on biochemical pathways involved in cholesterol metabolism and homeostasis.

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3.5.3 Animal-to-Human Extrapolations

Reigner et al. (1993) investigated the binding of radiolabeled pentachlorophenol to serum proteins *in vitro*, found that the percentage of unbound pentachlorophenol in serum was 1.37 in mice, 0.85 in rats, 0.67 in monkeys, 0.53 in humans, and 0.43 in cows and found that these percentages correlated inversely with the total protein levels in the same serum samples. These investigators, assuming that pentachlorophenol itself is responsible for carcinogenicity in mice, developed a new method for interspecies extrapolation in which the interspecies differences in clearance and serum protein binding of pentachlorophenol were taken into account in interspecies scaling. Several pharmacokinetic parameters, including volume of distribution, unbound volume of distribution, clearance, unbound clearance, and unbound clearance time maximum life potential, were scaled to body weight. The method produced estimates of equivalent human doses of pentachlorophenol (derived from experimental doses in mice that caused increased tumor incidences in the NTP [1989] 2-year bioassay) that are up to four times smaller than those obtained using body surface area.

3.6 ENDOCRINE DISRUPTION

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones, or otherwise interfere with the normal function of the endocrine system. Chemicals with this type of activity are most commonly referred to as endocrine disruptors. Some scientists believe that chemicals with the ability to disrupt the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. Others believe that endocrine disrupting chemicals do not pose a significant health risk, particularly in light of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavonoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These compounds are derived from plants and are similar in structure and action as endogenous estrogen. While there is some controversy over the public health significance of endocrine disrupting chemicals, it is agreed that the potential exists for these compounds to affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis, reproduction, development, and/or behavior (EPA 1997). As a result, endocrine disruptors may play a role in the disruption of sexual function, immune suppression, and neurobehavioral function. Endocrine disruption is also thought to be involved in the induction of breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

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Several studies have documented effects of pentachlorophenol on thyroid homeostasis (Beard and Rawlings 1998, 1999; Beard et al. 1999a, 1999b; Jekat et al. 1994; van Raaij et al. 1991a). These effects include decreased serum thyroxine concentration (Beard and Rawlings 1998, 1999; Beard et al. 1999a, 1999b; Jekat et al. 1994; van Raaij et al. 1991a), decreased thyroxine and triiodothyronine response to thyroid stimulating hormone (Beard and Rawling 1999), and decreased uptake of thyroxine into cerebrospinal fluid (van Raaij et al. 1994); these effects may be linked with a demonstrated competition of pentachlorophenol with the thyroxine binding site on transthyretin, a major thyroxine transport protein (den Besten et al. 1991).

Developmental toxicity studies provide some limited evidence that pentachlorophenol has the ability to disrupt endocrine function. A marked increase in the sex ratio (most female fetuses did not survive) was observed in the offspring of rats administered pure or technical-grade pentachlorophenol on gestational days 6–15 (Schwetz et al. 1974). However, the finding was not confirmed in other developmental toxicity studies (Argus 1993b/Bernard et al. 2001b, Argus 1997/Bernard et al. 2001c). In a multigeneration study in rats, significant increases in the average day of vaginal patency and preputial separation were observed in the F1 offspring exposed to an unspecified purity pentachlorophenol (Argus 1997/Bernard et al. 2001c).

In an *in vitro* test system, pure pentachlorophenol inhibited the activity of the human progesterone receptor. Tran et al. (1996) transformed a yeast strain with an expression plasmid for the human progesterone (hPR) receptor and a reporter containing two progesterone response elements. In the resulting yeast strain, hPR-PRE, beta-galactosidase activity was measured as an indicator of stimulation of the hPR signaling pathway. When the signaling pathway was stimulated by progesterone, 1 μM pentachlorophenol (99% pure) significantly inhibited hPR activity. Competitive binding studies indicated that pentachlorophenol effectively competed with a radiolabeled synthetic progestin for binding to hPR. Investigation of the interaction of pentachlorophenol with the progesterone-signaling pathway in animals might be another avenue for future research.

In rainbow trout hepatocytes, pentachlorophenol inhibited the induction of the estrogen receptor by estradiol and inhibited the induction of vitellogenin messenger RNA by estradiol (Flouriot et al. 1995). In short-term, whole-embryo assays using *Xenopus laevis*, pentachlorophenol significantly decreased the rates of tail resorption in metamorphs studied from day 50 (stage 60) to day 64 (stage 66) of development (Fort and Stover 1997).

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3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation.

Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6 Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient

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tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility while others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

There have been several reports of children accidentally exposed to pentachlorophenol; the children were predominantly exposed via dermal contact and, to a lesser extent, by the inhalation route. The observed health effects include symptoms of hyperthermia (high fever, profuse sweating, increased respiratory rate, labored breathing, tachycardia, hepatomegaly, and irritability) due to the uncoupling of oxidative phosphorylation and death in newborn infants following dermal contact with diapers and bedding washed in an antimildew agent containing pentachlorophenol (Robson et al. 1969; Smith et al. 1996) and in a child exposed to bath water contaminated with pentachlorophenol (Chapman and Robson 1965). The Chapman and Robson (1965) report provides suggestive evidence that young children may be more susceptible to the toxicity of pentachlorophenol than adults. All members of the child's family bathed in the contaminated bath water over a 13-day period; however, the only symptoms reported in the other family members were nasal stuffiness and swollen, painful eyes. A study by McConnachie and Zahalsky (1991) also reported health effects in children. Alterations in immunological parameters were observed in individuals living in log homes treated with a wood preservative containing pentachlorophenol. Fifteen of the 38 subjects were children aged 8–18. This study cannot be used to assess whether children would be more susceptible to the toxicity of pentachlorophenol because no comparisons across age groups were made. In addition to these health effects, hematological disorders (Cheng et al. 1993; Hryhorczuk et al. 1998; Klemmer et al. 1980; Roberts et al. 1981, 1990; Rugman and Cosstick 1991) and liver (Armstrong et al. 1969; Bergner et al. 1965; Colosio et al. 1993b; Gordon 1956; Robson et al. 1969; Smith et al. 1996) effects have been observed in adults exposed to pentachlorophenol, and these are likely targets in children. An animal study that compared LD₅₀ values provides evidence that infants may be more susceptible than children. Lower LD₅₀ values were found in preweaning animals, as compared to juvenile rats (25–50 days); however, the LD₅₀ value in adult rats was similar to the value for preweaning rats (St. Omer and Gadusek 1987).

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There is some limited evidence that the developmental process in humans is altered by paternal exposure to pentachlorophenol. An increased risk of congenital eye cataracts was observed in the children of men presumably exposed to CDD-contaminated chlorophenolate (Dimich-Ward et al. 1996); however, as discussed in Section 3.2.1.5, deficiencies in the study design limits interpretation of these results. Studies of potential developmental effects of pentachlorophenol in animals indicate that the developing organism is a sensitive target of toxicity. Fetal/neonatal mortality (Argus 1993b/Bernard et al. 2001b, Argus 1997/Bernard et al. 2001c; Schwetz et al. 1974; Welsh et al. 1987), malformations/anomalies (Argus 1993b/Bernard et al. 2001b; Schwetz et al. 1974), decreased growth (Argus 1993b/Bernard et al. 2001b; Beard et al. 1999b; Courtney et al. 1976; Larsen et al. 1975; Schwetz et al. 1974; Welsh et al. 1987), and possibly impaired development of the reproductive system (Argus 1997/Bernard et al. 2001c) have been observed in rats and sheep following gestational exposure. In most of these studies, the developmental effects occurred at maternally toxic doses; however, decreases in fetal body weight gain have been observed at doses that were not associated with maternal toxicity (Argus 1997/Bernard et al. 2001c; Welsh et al. 1987). A number of studies in rats (Jekat et al. 1994) and sheep (Beard and Rawlings 1998; Beard et al. 1999a, 1999b) have demonstrated that exposure to pentachlorophenol can result in decreased serum thyroxine and triiodothyronine levels. Deficiencies in thyroxine during prenatal and postnatal life can cause decrements in intellectual function in children (Bargagna et al. 1997; Birrell et al. 1983; Kooistra et al. 1994). It is not known if this will also occur following exposure to pentachlorophenol, and neuro-behavioral testing has not been performed on animals exposed to pentachlorophenol either prenatally or postnatally. Such testing might be an avenue for future research.

There is no information regarding pharmacokinetics of pentachlorophenol in children or regarding nutritional factors that may influence absorption of pentachlorophenol. There are no PBPK models for pentachlorophenol. Mehmood et al. (1996) has provided evidence that human cytochrome P450 3A4 may metabolize pentachlorophenol to TCHQ in phase I metabolism of pentachlorophenol; however, the purity of the pentachlorophenol used in this study was not indicated. In humans, this enzyme has low activity in the first month of life, with approach toward adult levels by 6–12 months of postnatal age; adult activity may be exceeded between 1–4 years of age and then activity progressively declines, reaching adult levels at the conclusion of puberty (Leeder and Kearns 1997). By Western immunoblotting using monoclonal antibodies to identify the different P 450 isozymes, pure pentachlorophenol (>99%) was identified as an inducer of cytochrome P450 3A7 in studies in cultured rat hepatocytes, quail hepatocytes, and human hepatoma (Hep G2) cells (Dubois et al. 1996). In humans, functional activity of cytochrome P450 3A7 in the fetus is approximately 30–75% of adult levels (Leeder and Kearns 1997). UDP-glucuronosyl transferase and sulfotransferases are involved in phase II

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metabolism of pentachlorophenol. Both of these enzymes are thought to be developmentally regulated (Leeder and Kearns 1997). Although the ontogeny of UDP-glucuronosyl transferase is isoform-specific, the adult level of activity seems to be achieved in humans by 6–18 months of age (Leeder and Kearns 1997). Ontogeny for the sulfotransferases seems to be more rapid than that for UDP-glucuronosyl transferase, and the activity for some isoforms of sulfotransferase may exceed adult levels during infancy and early childhood (Leeder and Kearns 1997). Larsen et al. (1975) provided evidence that pentachlorophenol (0.05–0.08% of an oral dose administered on day 15 of gestation) may cross the placenta; the chemical nature of the radioactive material present in the fetuses was not investigated.

Low levels of pentachlorophenol were found in human breast milk of women living in Germany or Slovakia (Gebefugi and Korte 1983; Veningerova et al. 1996). It is likely that pentachlorophenol will also be present in the breast milk of women living in the United States, particularly since pentachlorophenol has been detected in more than half of the urine samples of adults living in the United States (Hill et al. 1995). However, it is not known if the pentachlorophenol present in the breast milk or urine samples resulted from exposure to pentachlorophenol or to other industrial chemicals that are metabolized to pentachlorophenol.

There is no reason to suspect the mechanism of action of pentachlorophenol is different in children. There are no specific biomarkers of exposure or effect for pentachlorophenol that have been validated in children or adults exposed as children. No studies were located regarding interactions of pentachlorophenol with other chemicals in children.

There are no pediatric-specific methods for reducing peak absorption or reducing body burden following exposure to pentachlorophenol.

3.8 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).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. 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

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molecule(s) or cell(s) 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(s), 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 substance (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 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 pentachlorophenol are discussed in Section 3.8.1.

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 cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by pentachlorophenol are discussed in Section 3.8.2.

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 substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10. "Populations That Are Unusually Susceptible".

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Pentachlorophenol

Since pentachlorophenol is excreted in the urine largely unchanged (Ahlborg et al. 1974; Braun et al. 1979; Larsen et al. 1972; Reigner et al. 1991) and since it can be easily detected and quantified in the urine at concentrations as low as <1 ppb (Chou and Bailey 1986; Drummond et al. 1982; Edgerton et al. 1979; EPA 1980b; Holler et al. 1989; NIOSH 1984b; Pekari and Aitio 1982; Rick et al. 1982; Siqueina and Fernicola 1981), pentachlorophenol in the urine is a useful biomarker of exposure. In addition,

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pentachlorophenol can be easily detected and quantified in blood serum at concentrations as low as <1 ppb (Bevenue et al. 1968; EPA 1980b; Needham et al. 1981; NIOSH 1984b) and adipose tissue (Kuehl and Dougherty 1980; Needham et al. 1981; Ohe 1979; Shafik 1973). It has been demonstrated that pentachlorophenol is present in human adipose tissue as an ester of palmitic acid (Ansari et al. 1985). The detection limit for pentachlorophenol in adipose tissue is approximately 5 ppb (Kuehl and Dougherty 1980; Ohe 1979; Shafik 1973). However, measuring pentachlorophenol in body fluids and tissues is not a specific biomarker for pentachlorophenol exposure because other compounds to which exposure may occur (e.g., hexachlorobenzene and lindane) may be metabolized to pentachlorophenol in the body. In addition, the available data do not permit the establishment of a quantitative relationship between levels of pentachlorophenol in the environment and levels in human fluids or tissues. However, it has been reported that repeated workday exposure to pentachlorophenol at a concentration of 0.5 mg/m³ has resulted in a maximum steady state level of pentachlorophenol in plasma of about 0.5 mg/L (Wood et al. 1983). Based on samples taken prior to 1989, background levels of up to 0.1 ppm pentachlorophenol could be found in blood and urine of members of the general population who had no recognized exposure to pentachlorophenol (Cranmer and Freal 1970; EPA 1989b; Hill et al. 1989; Kutz et al. 1978).

TCHQ, a major urinary metabolite of pentachlorophenol, has potential use as an indicator of exposure to pentachlorophenol. It has been demonstrated that pentachlorophenol is converted to TCHQ by human microsomal enzymes (Juhl et al. 1985). In human and animal studies, TCHQ has been identified as the major urinary metabolite of pentachlorophenol (Ahlborg et al. 1974; Braun et al. 1977; Reigner et al. 1991; Renner 1989). However, the presence of TCHQ in the urine is not specific to pentachlorophenol and would also be present following exposure to chemicals that are metabolized to pentachlorophenol.

The presence of elevated levels of 8-hydroxydeoxyguanosine in the liver may serve as a nonspecific marker of oxidative DNA damage by pentachlorophenol. Administration of pentachlorophenol (98.6% pure) to mice in the diet for up to 4 weeks produced oxidative damage to hepatic nuclear DNA as evidenced by an increase in the amount of 8-hydroxydeoxyguanosine in DNA (Sai Kato et al. 1995; Umemura et al. 1996). A single oral dose of pentachlorophenol (98.6% pure) produced an increase in the amount of 8-hydroxydeoxyguanosine in liver DNA but not in kidney or spleen DNA (Sai-Kato et al. 1995).

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3.8.2 Biomarkers Used to Characterize Effects Caused by Pentachlorophenol

Two of the major target organs for both humans and animals exposed to pentachlorophenol are liver and kidney. Clinical manifestations of hepatic and renal toxicity include elevated serum ALT and AST levels for toxicity to the liver (Armstrong et al. 1969; Bergner et al. 1965; Gordon 1956; Gray et al. 1985; Klemmer 1972; Robson et al. 1969) and increased enzyme levels, increased blood urea nitrogen, and loss of proximal tubular alkaline phosphatase activity for toxicity to the kidney (Greichus et al. 1979; Kimbrough and Linder 1978; Nishimura et al. 1980). Indices of changes in hepatic oxidative phosphorylation may also be useful as biomarkers for pentachlorophenol-induced liver changes (Ellinger et al. 1991). These effects are not specific for exposure to pentachlorophenol and have been associated with exposure to other compounds such as some chlorinated hydrocarbons. Therefore, the major use of these biomarkers is restricted to comparisons between work groups exposed to the chemical in the workplace and control subjects. Other data indicate that contaminants in the commercial grade product may play an important role in these observed hepatotoxic effects.

Human case reports of pentachlorophenol exposure suggest that the central nervous system appears to be a target of pentachlorophenol exposure (Chapman and Robson 1965; Gray et al. 1985; Haley 1977; Robson et al. 1969). As discussed in Section 3.2.2.4, the neurologic syndrome observed following exposure to pentachlorophenol is possibly the direct result of hyperthermia generated by uncoupling of mitochondrial oxidative phosphorylation rather than a direct effect on the nervous system. The neurological syndrome observed following exposure to pentachlorophenol can be manifested by lethargy, tachypnea, tachycardia, intermittent delirium, convulsions, cerebral edema, focal swelling of the myelin sheath, and respiratory distress (Chapman and Robson 1965; Gray et al. 1985). However, these symptoms are not specific for pentachlorophenol exposure.

In general, there is no simple relationship between nonfatal health effects and levels of pentachlorophenol detected in serum and urine. Serum levels of pentachlorophenol ranging from 23 to 162 mg/L (ppm) have been reported in cases of fatal overexposure to pentachlorophenol. Serum levels of pentachlorophenol below 1.3 mg/L have not been associated with any adverse health effects (Cline et al. 1989; Klemmer et al. 1980).

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3.9 INTERACTIONS WITH OTHER CHEMICALS

No studies were located regarding the direct toxic interactions of pentachlorophenol with other chemicals in humans, including children, or animals. No interactions between pentachlorophenol contaminants and the pure pentachlorophenol component of technical-grade pentachlorophenol have been demonstrated in some tests of immunotoxicity (Kerkvliet et al. 1985a).

Pentachlorophenol may alter the toxicities of other compounds through its inductive action on microsomal metabolic enzymes (Vizethum and Goerz 1979). While this inductive effect has not specifically been demonstrated to alter the toxicity of other compounds, these types of alterations in enzyme activity may influence metabolism and toxicity of many compounds. Pentachlorophenol inhibits cytosolic sulfotransferases (Mulder and Scholtens 1977). Compounds such as n-hydroxy-2-acetylaminofluorene, which are activated by the formation of a sulfate ester, are considerably less toxic in animals pretreated with pentachlorophenol (Meerman et al. 1980). Pentachlorophenol, an inhibitor of arylsulfotransferase, significantly decreased 2-acetylaminofluorene-induced DNA damage in rat hepatocytes *in vitro*. *In vivo*, pentachlorophenol alone induced a significant increase in unscheduled liver DNA synthesis, but also caused a significant decrease in 2-acetylaminofluorene-induced unscheduled liver DNA synthesis (Monteith 1992).

Male rats were given pentachlorophenol (91.6%) daily by gavage at a dose of 20 mg/kg. At 1, 2, 4, and 5 weeks, the animals were given a single gavage dose of 2,6-dinitrotoluene, and urine was collected for 24 hours and tested for mutagenicity in *Salmonella typhimurium* strain TA98. A statistically-significant increase in revertants at week 5 in pentachlorophenol-treated animals, compared with controls that did not receive pentachlorophenol, suggested that pentachlorophenol caused an increase in the excretion of mutagenic metabolites of 2,6-dinitrotoluene. A slight, but statistically-significant, decrease in nitroreductase activity in the small intestine was also reported in the pentachlorophenol-treated rats compared with controls (Chadwick et al. 1993).

Since pentachlorophenol is metabolized to a small extent by hepatic microsomal enzymes, chemicals that alter the activity of these enzymes can modify metabolism, and subsequently, the toxicity of pentachlorophenol (see discussion above). For example, phenobarbital, a microsomal enzyme inducer, increases biotransformation of pentachlorophenol to TCHQ thereby reducing the level of pentachlorophenol in the body (Ahlborg et al. 1978).

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A great deal of pentachlorophenol is bound to plasma proteins (Braun et al. 1977). Other agents that also have a high affinity for protein bonds (e.g., anticoagulants such as warfarin) could compete with and displace pentachlorophenol from proteins. This action could then result in a higher level of free-circulating pentachlorophenol that can be metabolized, or excreted, and/or induce toxic effects. However, this hypothesis has not been experimentally confirmed.

Various agents have been used in experimental animals to try to decrease the toxicity of pentachlorophenol. Cholestyramine is known to bind phenols (Reiman and Walton 1970) and to enhance fecal elimination of chlordecone (Kepone) in rats and humans (Boylan et al. 1977). Rozman et al. (1982) found that cholestyramine enhances excretion of pentachlorophenol in Rhesus monkeys and recommends that its use be considered in cases of human pentachlorophenol overexposure.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to pentachlorophenol than will most persons exposed to the same level of pentachlorophenol in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of pentachlorophenol, or compromised function of organs affected by pentachlorophenol. Populations who are at greater risk due to their unusually high exposure to pentachlorophenol are discussed in Section 6.7, Populations With Potentially High Exposures.

Groups possibly at greater-than-average risk of suffering from the toxic effects of pentachlorophenol include persons laboring in hot environments, persons with an inability or decreased ability to disperse body heat, geriatric and pediatric subpopulations, pregnant women, and those that are malnourished or consume an unbalanced diet. People with impaired liver and kidney function are likely to be susceptible to the toxic effects of any chemical/product that is metabolized and/or excreted by these organs, and therefore, may be unusually susceptible to the toxic effects of pentachlorophenol.

Persons laboring in hot environments are unusually susceptible to the acute toxic effects of pentachlorophenol. One of the principal effects of pentachlorophenol is hyperthermia induced by the uncoupling of oxidative phosphorylation. The manifestations of overexposure to pentachlorophenol, particularly in persons laboring in a hot environment, are usually those associated with hyperthermia: flushing, intense thirst, sweating, weakness and, occasionally, muscle spasms. Persons working in hot environments are

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unable to disperse excess body heat, resulting in potentially life-threatening hyperthermia. For example, occupational deaths reported by Bergner et al. (1965), Gray et al. (1985), and Menon (1958) were all due to hyperthermia, and the symptoms of hyperthermia described above were exhibited by affected workers prior to death.

There is some evidence that young children are more susceptible than older children or adults to the toxic effects of pentachlorophenol often associated with the uncoupling of oxidative phosphorylation. In a study by Chapman and Robson (1965), signs of hyperthermia (resulting from the uncoupling of oxidative phosphorylation) were observed in a 3-year old child exposed to pentachlorophenol in contaminated bath water. However, no signs of hyperthermia were observed in older children or adults in the family. Prewaning and adult rats have been reported to have lower oral LD₅₀s for technical-grade pentachlorophenol than juvenile rats (25–50 days old) (St. Omer and Gadusek 1987); similar differences in sensitivity are possible in humans.

Age-related differences in the frequency or severity of toxic effects from pentachlorophenol exposure may arise from developmental regulation of cytochrome P-450s, which are involved in phase I metabolism of pentachlorophenol, and sulfotransferases and UDP-glucuronosyl transferase, which are involved in phase II metabolism of pentachlorophenol (see Section 3.7).

Oral and intraperitoneal administration of pentachlorophenol to animals causes adverse effects on thyroid homeostasis (e.g., decreased serum thyroxine) and on the thyroid gland, and such effects may occur during gestation, pregnancy, and lactation. Pentachlorophenol also significantly decreased the uptake of radiolabeled thyroid hormone into cerebrospinal fluid (see Section 3.7). These effects of pentachlorophenol on the thyroid gland, thyroid homeostasis, and the availability of thyroid hormone to the central nervous system may have adverse effects on development of the nervous system. Deficiencies in thyroxine during prenatal and postnatal life can cause decrements in intellectual function in children (Bargagna et al. 1997; Birrell et al. 1983; Kooistra et al. 1994), and hypothyroidism in animals leads to disorders in structural and functional development of the brain (Gould et al. 1990; Neveu and Arenas 1996; Stein et al. 1991; Vega-Nunez et al. 1995).

Individuals with liver or kidney disease may be unusually susceptible to the toxic effects of pentachlorophenol. In certain fatal human cases, the victim was found to have renal insufficiency (Hayes 1982). Experiments have shown that rabbits made nephrotic experimentally were much more susceptible to the toxic effects of pentachlorophenol than were normal rabbits (Hayes 1982). Individuals exposed to other

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chemicals that bind to plasma proteins (e.g., anticoagulants such as warfarin) may be at greater risk of suffering from pentachlorophenol-induced toxicity as well.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to pentachlorophenol. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to pentachlorophenol. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to pentachlorophenol:

Ballhorn L, Rozman T, Rozman K, et al. 1981. Cholestyramine enhances fecal elimination of pentachlorophenol in Rhesus monkeys. *Chemosphere* 10:877-888.

EPA. 1989b. Recognition and management of pesticide poisonings. 4th ed. Washington, DC: U.S. Environmental Protection Agency. EPA-540/9-88-001.

Goodman AG, Rall TW, Nies AS, et al. 1990. Goodman & Gilman's the pharmacological basis of therapeutics. 8th ed. New York, NY: Pergamon Press, 1635.

Rozman T, Ballhorn L, Rozman K, et al. 1982. Effect of cholestyramine on the disposition of pentachlorophenol in Rhesus monkeys. *J Toxicol Environ Health* 10:277-283.

3.11.1 Reducing Peak Absorption Following Exposure

Means of limiting absorption of phenols include washing exposed skin and eyes and removing contaminated clothing in the case of dermal exposure, and inducing emesis, performing gastric lavage, and administering activated charcoal and a cathartic in the case of oral exposure (EPA 1989b). Emesis is induced only if the patient is fully alert and the pentachlorophenol has not been ingested in a solvent so that there is no chance that the stomach contents may be aspirated. If the patient is unconscious or vomiting cannot be induced, intubation, aspiration, and lavage of the stomach are suggested (EPA 1989b).

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3.11.2 Reducing Body Burden

Various agents have been used in experimental animals to try to decrease the toxicity of pentachlorophenol by reducing body burden. Cholestyramine is known to bind phenols (Reiman and Walton 1970) and to enhance fecal elimination of chlordecone (Kepone) in rats and humans (Boylan et al. 1977). In studies performed on Rhesus monkeys, oral administration of cholestyramine enhanced fecal excretion of pentachlorophenol by interrupting enterohepatic circulation of pentachlorophenol and/or its metabolites (Ballhorn et al. 1981; Rozman et al. 1982). Thus cholestyramine administration may be an effective means of reducing the body burden of pentachlorophenol in humans (Goodman et al. 1990); it should be noted that testing would be required to determine whether or not cholestyramine treatment would be effective for humans. Hemodialysis and forced diuresis may not be effective means of reducing body burden of phenolic substances, and hemoperfusion has not been sufficiently tested as a means of accelerating elimination of phenols (EPA 1989b).

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

The naturally occurring antioxidants ellagic acid, epigallocatechin gallate, and vitamin C provided partial protection from pentachlorophenol-induced oxidative damage to liver DNA during daily oral administration of pentachlorophenol at 60 mg/kg/day for 5 days to male B6C3F₁ mice (Sai-Kato et al. 1995). Since these antioxidants are protective of animals, they may reduce toxic effects in humans.

3.12 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 the 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 pentachlorophenol.

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 the uncertainties of human health assessment. This definition should not be interpreted to mean

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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.

3.12.1 Existing Information on Health Effects of Pentachlorophenol

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to pentachlorophenol are summarized in Figure 3-4. The purpose of this figure is to illustrate the existing information concerning the health effects of pentachlorophenol. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure 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.

Much of the literature reviewed concerning the health effects of pentachlorophenol in humans described case reports of individuals exposed occupationally, in log homes treated with pentachlorophenol as a preservative, or in the home following misuse of pentachlorophenol-containing solutions. The predominant route of exposure in such cases is often dermal, but the possibility of some degree of inhalation exposure cannot be ruled out. Therefore, Figure 3-4 reflects that information exists for both inhalation and dermal routes of exposure. However, all of these reports are limited because of the possibility of concurrent exposure to other potentially toxic substances, present as either contaminants in technical-grade pentachlorophenol (i.e., chlorinated dibenzo-*p*-dioxins and dibenzofurans), as other components in pentachlorophenol-containing mixtures (i.e., pesticides and herbicides), or simply other compounds also in the environment. Additionally, duration and level of exposure to pentachlorophenol generally cannot be quantified from information presented in these anecdotal reports.

The database for health effects of pentachlorophenol following ingestion in experimental animals is substantial. However, as can be seen in Figure 3-4, very little information is available on the effects of inhalation and dermal exposure to pentachlorophenol in animals. Furthermore, the health effects associated with acute and intermediate exposure durations are more fully characterized than those associated with chronic exposure. Genotoxicity data on pentachlorophenol are available from both *in vitro* and *in vivo* studies. Finally, when evaluating much of the data on health effects of pentachlorophenol, the toxicity of its impurities (which may themselves present a hazard at disposal sites) must be

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Figure 3-4. Existing Information on Health Effects of Pentachlorophenol

	Systemic									
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation	•	•		•	•	•	•	•	•	•
Oral	•	•								
Dermal	•	•		•	•	•	•	•	•	•

Human

	Systemic									
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation	•									
Oral	•	•	•	•	•	•	•	•	•	•
Dermal	•	•								•

Animal

- Existing Studies

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taken into account. However, it is now clear that pure pentachlorophenol is toxic to several organs and systems in rats and mice and is oncogenic in mice.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. Information on the acute toxicity of pentachlorophenol in humans comes from a number of case reports involving home use of pentachlorophenol-containing products, such as wood preservatives or herbicides in the garden (Gordon 1956; Hassan et al. 1985) and from a series of reports of newborn infants exposed to pentachlorophenol from diapers and linens treated with an antimildew agent (Armstrong et al. 1969; Robson et al. 1969; Smith et al. 1996). In many of the cases, it is likely that the individuals were primarily exposed to technical-grade pentachlorophenol via dermal contact, although there may have also been some inhalation exposure. There are also cases of individuals ingesting pentachlorophenol (Cretney 1976; Dreisbach 1980; Haley 1977). In general, no information on exposure concentration, duration of exposure, exposure to other chemicals, or the impurities present in the technical-grade pentachlorophenol is available. A number of health effects were consistently observed in these individuals, including death, symptoms of hyperthermia generated by uncoupling of oxidative phosphorylation (e.g., tachycardia, increased respiratory rate, labored breathing, profuse sweating, fever, metabolic acidosis), hemolytic anemia, hepatic enlargement, and dermal toxicity (irritation and chloracne).

The only available inhalation study in animals (Hoben et al. 1979b) reported death, but did not examine other end points. The lack of exposure information in the human studies and the inadequate animal study precluded deriving an acute-duration inhalation MRL. Additional inhalation studies are needed to characterize target organs and establish exposure-response relationships.

Most of the available information on the acute toxicity of pentachlorophenol in animals comes from oral exposure studies. A number of adverse effects were observed in oral exposure studies including death (Borzelleca et al. 1985; Deichmann et al. 1942; Renner et al. 1986; St. Omer and Gadusek 1987), cardiovascular effects (extensive vascular damage and heart failure) (Deichmann et al. 1942), hepatotoxicity (increased relative liver weight) (Nishimura et al. 1982), impaired immune function (Holsapple et al. 1987; Kerkvliet et al. 1985a; White and Anderson 1985), reproductive toxicity (Schwetz et al. 1974), and developmental toxicity (Schwetz et al. 1974). The developing fetus was identified as the most sensitive target in rats following acute gavage exposure to pure pentachlorophenol (Schwetz et al. 1974). The observed effects included delayed ossification at the lowest dose tested (5 mg/kg/day

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administered on gestational days 6–15) and skeletal anomalies, decreased fetal body weights, increased male:female sex ratio, and increased resorptions at higher doses. The Schwetz et al. (1974) study is the basis for an acute-duration oral MRL of 0.005 mg/kg/day.

Pentachlorophenol is well absorbed through the skin, and is expected to produce effects in the same tissues affected by exposure via other routes. Human reports describe numerous systemic effects in individuals predominantly exposed through dermal contact. Skin irritation was reported in a dermal study in rabbits (Deichmann et al. 1942). Additional studies via dermal exposure would be useful in determining target organs and dose-response relationships following acute-duration exposures.

Intermediate-Duration Exposure. There is limited information on the toxicity of pentachlorophenol in humans following intermediate-duration exposure. Case reports of individuals exposed either occupationally or in the home during misuse of pentachlorophenol-containing solutions as a result of failure to adhere to appropriate precautionary measures provide some information on the toxicity of pentachlorophenol in humans. The observed effects include hematological alterations (aplastic anemia), hyperthermia (due to uncoupling of oxidative phosphorylation), hepatic enlargement, and impaired immune function (Daniel et al. 1995; Gray et al. 1985; Roberts 1963, 1981, 1990; Rugman and Cosstick 1990). Dermal contact is probably the primary exposure route in these cases, although the possibility of inhalation exposure cannot be ruled out. The interpretation of the reports is limited by the small number of subjects and the lack of information on exposure concentration, route, and duration, concomitant exposure to other chemicals, and description of impurities present in the commercial- or technical-grade pentachlorophenol. No studies were located that examined the toxicity of pentachlorophenol in humans following intermediate-duration oral exposure.

No inhalation studies in animals were located. An intermediate-duration inhalation MRL was not derived due to the lack of human and/or animal data. A 90-day inhalation study is necessary to identify sensitive end points and dose-response relationships.

Information on the toxicity of pentachlorophenol in animals following intermediate-duration exposure primarily comes from oral exposure studies. The results of these studies suggest that the reproductive system is the most sensitive target of toxicity following intermediate-duration exposure. An increase in the severity of cystic uterine glands and decreases in the proportion of female mink accepting a second mating and the number of mink that whelped have been observed in a single-generation mink study (Beard et al. 1997). Other sensitive end points include the liver (increased liver weight, centrilobular

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hepatocyte hypertrophy and vacuolation, hepatocellular degeneration, and periportal fibrosis) (Blakley et al. 1998; Greichus et al. 1979; Johnson et al. 1973; Kerkvliet et al. 1982; Kimbrough and Linder 1978; Knudsen et al. 1974; Nishimura et al. 1980; Umemura et al. 1996), endocrine system (decreased thyroxine levels, increased thyroid gland follicle size) (Beard et al. 1999; Rawlings et al. 1998), immune system (Blakley et al. 1998; Kerkvliet et al. 1982, 1985a, 1985b; NTP 1989), and the developing fetus (decreased litter size, decreased fetal body weights, embryo lethality) (Argus 1997/Bernard et al. 2001c; Beard et al. 1999; Welsh et al. 1987). The studies in sheep suggest that the thyroid system is a sensitive target of pentachlorophenol toxicity. Additional studies are needed in conventional laboratory species to confirm the sensitivity of this organ and to evaluate the relevance of the effect to human health; other endocrine tissues should also be examined for potential effects. The LOAEL identified for reproductive effects in mink was used to derive an intermediate-duration oral MRL. Additional studies are needed to better define dose-response relationships and to identify no adverse effect levels.

Information on the dermal toxicity of pentachlorophenol in animals is limited to a study that reported death and dermal irritation in rabbits following application of pentachlorophenol in fuel oil; the vehicle may have contributed to the observed effects (Deichmann et al. 1942). Studies examining systemic end points following dermal exposure would be useful to establish thresholds.

Chronic-Duration Exposure and Cancer. Occupational exposure studies and reports of families living in log homes that were treated with pentachlorophenol provide information on the chronic toxicity of pentachlorophenol in humans. The reported effects include inflammation of the upper respiratory tract and bronchitis (Baader and Bauer 1951; Klemmer et al. 1980), reduced glomerular filtration rate and tubular function (Begley et al. 1977), hepatic effects (increased levels of biliary acid concentrations, urinary porphyrin, and serum alanine and aspartate transaminases) (Cheng et al. 1993; Colosio et al. 1993a; Hryhorczuk et al. 1998; Klemmer 1972), and impaired immune function (McConnachie and Zahalsky 1991). It is likely that the individuals were exposed via inhalation and dermal contact. In general, the epidemiology studies involved exposure to technical-grade or undefined purity pentachlorophenol; therefore, other chemicals may have contributed to these effects. Little information on exposure concentrations is available. No chronic oral human studies were located.

Chronic-duration animals studies are only available for the oral route. Liver effects (hepatocyte cystic degeneration, hepatodiaphragmatic nodules) (Chhabra et al. 1999; NTP 1999; Schwetz et al. 1978) and effects on the thyroid (decreased serum thyroxine and decreased relative thyroid weight) (Beard and Rawlings 1998, 1999; Beard et al. 1999a) were reported in these studies. A chronic-duration oral MRL of

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0.001 mg/kg/day was calculated based on a LOAEL of 1 mg/kg/day for significantly decreased serum thyroxine concentrations in males of the first generation and males and females of the second generation, and decreased relative thyroid weight in females of the second generation when mink were administered pentachlorophenol of unspecified purity continuously in the diet in a multigeneration reproduction study (Beard and Rawlings 1998). A chronic-duration inhalation MRL was not developed because concentrations that cause toxic effects in humans were not quantified and no animal studies were identified. Chronic inhalation studies are necessary for establishing exposure-response relationships and identifying sensitive targets of toxicity. No dermal animal studies were identified; chronic dermal exposure studies would be useful for identifying sensitive targets of the toxicity and establishing exposure-response relationships.

Epidemiology studies have not provided a firm association between pentachlorophenol exposure and an increased risk of cancer. Several occupational studies reported no association between inhalation of pentachlorophenol in any form and cancer in humans (Gilbert et al. 1990; Jappinen et al. 1989; Johnson et al. 1990; Robinson et al. 1985). However, each of the individual studies had a low power to detect elevated risk estimates. In contrast, other occupational studies reported an association between pentachlorophenol exposure and soft tissue sarcoma (Eriksson et al. 1990; Hardell et al. 1995; Hoppin et al. 1998; Lampi et al. 1992) or non-Hodgkin's lymphoma (Hardell et al. 1994; Hertzman et al. 1997; Lampi et al. 1992). Many of these studies also reported significant associations between increased cancer risk and exposure to other chemicals (e.g., other chlorophenols, phenoxyacetic acids, cutting oil components). Additional follow-up of pentachlorophenol-exposed cohorts using epidemiological methods and study designs of sufficient power and discrimination to distinguish effects of pentachlorophenol from effects attributable to other possible causes would be useful for assessing the carcinogenic potential of pentachlorophenol in humans. Sufficient information exists from animal studies to support the conclusion that pentachlorophenol may cause cancer in humans. Significant increases in the incidence of hemangiosarcomas, liver adenomas and carcinomas, and adrenal gland pheochromocytomas were observed in mice (NTP 1989), and mesotheliomas and nasal squamous cell carcinomas were observed in rats orally exposed to pure pentachlorophenol (Chhabra et al. 1999; NTP 1999). No information is available on the carcinogenic potential following inhalation or dermal exposure; chronic bioassays by these routes would be useful in determining whether pentachlorophenol induces cancer of the respiratory tract and skin, respectively.

The suggestive human data and the positive carcinogenicity results from animal bioassays (Chhabra et al. 1999; NTP 1989, 1999), along with genotoxicity data suggesting that pentachlorophenol is clastogenic,

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provide sufficient evidence to suggest that pentachlorophenol may be a human carcinogen. The International Agency for Research on Cancer (IARC 1999) has placed pentachlorophenol in group 2B (possibly carcinogenic to humans). EPA classified pentachlorophenol as a group B2 carcinogen (probable human carcinogen) (IRIS 2001).

Genotoxicity. The available genotoxicity data indicate that pentachlorophenol may have genotoxic potential. Two studies investigated the genotoxicity of pentachlorophenol in humans; both of these are inadequate because of the small number of subjects studied (Bauchinger et al. 1982; Wyllie et al. 1975). The observed effects included a small increase in the frequency of dicentrics and acentrics, but no increases in sister chromatid exchange, and an increase in chromosome aberrations. In general, *in vitro* and *in vivo* studies have not reported evidence of genotoxicity. Pentachlorophenol did not induce gene mutations in *Salmonella typhimurium* (Donnelly et al. 1998; Markiewicz et al. 1996; NTP 1999; Simmon et al. 1977; Waters et al. 1982) or *Escherichia coli* (Anderson et al. 1972; Lemma and Ames 1975; Moriya et al. 1983; Simmon et al. 1977; Waters et al. 1982); or DNA damage in *E. coli* (Fahrig 1974), *Bacillus subtilis* (Waters et al. 1982), Chinese hamster ovary cells (Ehrlich 1990), Chinese hamster V79 cells (Dahlhaus et al. 1996), or mouse embryonic fibroblast cells (Wang and Lin 1995). Several *in vitro* studies suggest that pentachlorophenol has clastogenic activity (Fahrig 1974; NTP 1999). Increases in the occurrence of chromosomal aberrations in human lymphocytes and Chinese hamster ovary cells and sister chromatid exchange in Chinese hamster ovary cells have occurred (NTP 1999). In *Saccharomyces cerevisiae* assays for recombination, positive and negative results have been found (Fahrig 1974; Fahrig et al. 1978; Waters et al. 1982), and positive results were found for induction of gene mutations (Fahrig et al. 1978). In *in vivo* studies, negative results have been found for gene mutations in a mouse spot test assay (Fahrig and Steinkamp-Zucht 1996), sex-linked recessive lethal mutations in *Drosophila melanogaster* (Sai-Kato et al. 1995; Umemura et al. 1996), and micronuclei occurrence in mouse and rat bone marrow (NTP 1999). Given the availability of a number of genetic toxicology studies, there is no apparent need for additional genotoxicity testing at this time.

Reproductive Toxicity. The possible association between pentachlorophenol exposure and reproductive effects in women has been investigated by Gerhard et al. (1991). Elevated blood levels of pentachlorophenol were found in women with histories of reproductive effects (e.g., habitual abortions, unexplained infertility, menstrual disorders). However, a causal relationship cannot be established due to limitations such as the lack of information on the exposure route and exposure to other chemicals (e.g., increased levels of PCBs were detected in the blood). In addition, matched controls were not used and

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other confounding factors were not controlled. No other human studies examined reproductive end points.

Adverse reproductive effects were observed in animals following oral exposure to technical-grade and pure pentachlorophenol. In a two-generation reproductive toxicity study in rats, decreased fertility was observed the first generation exposed to 60 mg/kg/day pentachlorophenol (purity not reported) (Argus 1997/Bernard et al. 2001c). Decreased frequency of second mating, decreased birth rate for the second mating, and increased severity of cystic uterine gland were observed in mink exposed to 1 mg/kg/day (Beard et al. 1997). In contrast, no reproductive effects were observed in a multigeneration study in mink using the same dietary concentration (Beard and Rawlings 1998). No effect on fertility was observed in sheep exposed to 1 mg/kg/day prior to mating and throughout gestation and lactation (Beard et al. 1999b). No animal studies examined the reproductive toxicity of pentachlorophenol following inhalation or dermal exposure; studies by the inhalation and dermal routes would be valuable in establishing an exposure-response relationship for these exposure routes. The intermediate-duration oral MRL is based on a LOAEL for reproductive effects observed in the single-generation mink study (Beard et al. 1997).

Developmental Toxicity. An increased risk of congenital eye cataracts was observed in the children of male sawmill workers presumably exposed to CDD-contaminated mixtures of the sodium salts of pentachlorophenol and tetrachlorophenol (chlorophenate) (Dimich-Ward et al. 1996). Interpretation of the study results is limited because exposure levels were not measured and a surrogate for chlorophenate exposure was used. No other human developmental toxicity studies were located.

A number of animal studies reported developmental effects following oral exposure to pure or technical-grade pentachlorophenol. The observed effects included fetal/neonatal mortality (Argus 1993b/Bernard et al. 2001b, Argus 1997/Bernard et al. 2001c; Schwetz et al. 1974; Welsh et al. 1987), malformations/anomalies (Argus 1993b/Bernard et al. 2001b; Schwetz et al. 1974), and decreased growth (Argus 1993b/Bernard et al. 2001b; Beard et al. 1993b; Courtney et al. 1976; Larsen et al. 1975; Schwetz et al. 1974; Welsh et al. 1987). A threshold for developmental toxicity has not been identified. A comparison between the adverse effects levels for developmental effects with those for systemic, immune, and reproductive effects, suggests that the fetus/neonate is a sensitive target for pentachlorophenol. Note that the acute duration oral MRL is based on a LOAEL for developmental effects (Schwetz et al. 1974). A common limitation of these developmental toxicity studies is that only one dose level was tested in most of these studies. Additional studies using a range of doses would be useful for establishing the threshold for developmental toxicity. Additionally, several oral studies provide evidence that the thyroid

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gland is sensitive to the toxicity of pentachlorophenol (Beard and Rawlings 1998; Beard et al. 1999; Jekat et al. 1994; Rawlings et al. 1998). It is not known whether this would also be a sensitive target in the developing organism. Developmental studies that assessed thyroid function and tested for potential neurobehavioral and neuropathological effects would be useful since deficiencies in thyroxine during prenatal and postnatal periods can cause decrements in intellectual function in children (Bargagna et al. 1997; Birrell et al. 1983; Kooistra et al. 1994). The available developmental toxicity studies involve maternal exposure; no studies have examined the potential developmental effect of paternal exposure. No animal inhalation or dermal developmental toxicity studies are available for pentachlorophenol. Studies by these exposure routes would be useful for establishing dose-response relationships.

Immunotoxicity. Several human studies provide suggestive evidence that pentachlorophenol is an immunotoxicant. Impaired mitogen-induced lymphocyte stimulation was observed in individuals exposed to pentachlorophenol-containing pesticides (Daniel et al. 1995); T-cell activation, autoimmunity, immunosuppression, and B-cell dysregulation were observed in family members living in pentachlorophenol-treated log homes (McConnachie and Zahalsky 1991); and decreased proliferative response to a mitogen was observed in factory workers exposed to high levels of pentachlorophenol (Colosio et al. 1993b). Oral studies in animals provide strong evidence that technical-grade pentachlorophenol is an immunotoxicant, although none of the identified studies performed a complete immunotoxicity battery. Humoral and cellular immunity (Holsapple et al. 1987; Kerkvliet et al. 1985a; NTP 1989), susceptibility to tumor induction (Kerkvliet et al. 1982), and complement activity (White and Anderson 1985) have been adversely affected following oral exposure. Studies that tested both technical-grade and pure pentachlorophenol provide strong evidence that the immune effects are related to the level of impurities in the technical-grade product (e.g., CDDs, CDFs). Support for the immunotoxicity of pure pentachlorophenol is less conclusive, with some rat and mouse studies reporting altered immune function (Blakley et al. 1998; Kerkvliet et al. 1982) and other studies reporting no effects (Kerkvliet et al. 1985a; NTP 1989). No studies that tested the immunotoxicity of pentachlorophenol following inhalation or dermal exposure were located. The available data suggest that the immune system may be a sensitive target of toxicity following oral exposure to technical-grade pentachlorophenol and possibly pure pentachlorophenol.

Neurotoxicity. In a number of case reports, neurological effects have been described in individuals likely exposed via inhalation and dermal contact. The symptoms of central nervous system neurotoxicity include intermittent delirium, fever, convulsions, profuse sweating, and increased respiratory rate and labored breathing (Chapman and Robson 1965; Robson et al. 1969; Smith et al. 1996). Similar neurological symptoms were reported in an individual intentionally ingesting a weed killer containing

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12% pentachlorophenol (Haley 1977). These effects are probably due to hyperthermia resulting from uncoupling of oxidative phosphorylation, rather than to a direct effect on the central nervous system. Neurological effects have also been observed in animals ingesting pentachlorophenol. Although a study examining a complete neurotoxicology battery of tests has not been identified, the available oral exposure data provide evidence that pentachlorophenol is a neurotoxicant at high doses. Oral exposure to relatively high doses of technical-grade or pure pentachlorophenol resulted in impaired motor activity and startle response in mice exposed to pentachlorophenol for 26 weeks, but not after 5 weeks (NTP 1989). Degenerative changes in the sciatic nerve myelin sheath were observed in rats administered pentachlorophenol of unspecified purity (Villena et al. 1992). No neurological studies involving inhalation or dermal exposure to pentachlorophenol were identified.

Epidemiological 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 comes from case reports involving home use of pentachlorophenol-containing products such as wood preservative or herbicides in the garden (Gordon 1956; Hassan et al. 1985) or a series of reports of newborn infants exposed to pentachlorophenol from diapers and linens treated with an antimildew agent (Robson et al. 1969; Smith et al. 1996). Long-term toxicity information comes from families living in log homes that were treated with pentachlorophenol (McConnachi and Zahalsky 1991) and occupational exposure in agricultural and wood-treatment industries (Baader and Bauer 1951; Cheng et al. 1993; Colosio et al. 1993b; Hryhorczuk et al. 1998; Klemmer et al. 1980). As discussed previously, these studies are limited by incomplete exposure characterization. In general, information on exposure concentrations, exposure route, duration of exposure, possible concomitant exposure to other chemicals, and impurities present in technical-grade pentachlorophenol are not available. In most cases, exposure was by the inhalation and dermal routes. The consistently observed effects include death (Cretny 1976; Dreisbach 1980; Gordon 1956; Roberts 1981, 1990; Rugman and Cosstick 1990), inflammation of the upper respiratory tract and bronchitis (following inhalation exposure) (ACGIH 1991; Baader and Bauer 1951; Klemmer et al. 1980), symptoms of hyperthermia generated by uncoupling of oxidative phosphorylation (e.g., tachycardia, increased respiratory rate, labored breathing, profuse sweating, fever, metabolic acidosis) (Bergner et al. 1965; Gordon 1956; Gray et al. 1985; Haley 1977; Hassan et al. 1985; Menon 1958; Robson et al. 1969; Smith et al. 1996), hemolytic anemia (Hassan et al. 1985; Roberts 1981, 1990; Rugman and Cosstick 1990), hepatic enlargement (Bergner et al. 1965; Cheng et al. 1993; Colosio et al. 1993b; Gordon 1956; Hassan et al. 1985; Hryhorczuk et al. 1998; Smith et al. 1996), impaired immune function (Colosio et al. 1993b; Daniel et al. 1995; McConnachi and Zahalsky 1991), and dermal

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toxicity (irritation and chloracne) (Baader and Bauer 1951; Hosenfeld et al. 1986; Klemmer et al. 1980; Lambert et al. 1986; O'Malley et al. 1990).

Additionally, several epidemiology studies have examined the carcinogenic potential of pentachlorophenol. These data are inconclusive with some studies reporting no association between cancer risk and exposure to pentachlorophenol (Gilbert et al. 1990; Jappinen et al. 1989; Johnson et al. 1990; Robinson et al. 1985) and other studies indicating a significant risk of soft tissue sarcoma (Eriksson et al. 1990; Hardell et al. 1995; Hoppin et al. 1998; Lampi et al. 1992) or non-Hodgkin's lymphoma (Hardell et al. 1994; Hertzman et al. 1997; Lampi et al. 1992). Hepatotoxicity (Blakley et al. 1998; Chhabra et al. 1999; Greichus et al. 1979; Johnson et al. 1973; Kerkvliet et al. 1982; Kimbrough and Linder 1978; Knudsen et al. 1974; Nishimura et al. 1982; NTP 1999; Schwetz et al. 1978; Umemura et al. 1996), impaired immune function (Blakley et al. 1998; Holsapple et al. 1987; Kerkvliet et al. 1982, 1985a, 1985b; NTP 1989; White and Anderson 1985), and increased incidence of malignant tumors (Chhabra et al. 1999; NTP 1989, 1999) have also been reported in animal studies involving oral exposure. A number of other sensitive end points for animals, including thyroid toxicity, reproductive toxicity, and developmental toxicity, have not been fully investigated in humans. Additional epidemiological studies that provide sufficient information for exposure characterization and examine a number of systemic end points would be useful for establishing sensitive targets of toxicity in humans and dose-response relationship data.

Biomarkers of Exposure and Effect.

Exposure. Pentachlorophenol is excreted in the urine largely unchanged (Ahlborg et al. 1974; Braun et al. 1979; Larsen et al. 1972) and can easily be detected and quantified in the urine at concentrations as low as <1 ppb (Chou and Bailey 1986; Drummond et al. 1982; Edgerton et al. 1979; EPA 1980a; Holler et al. 1989; NIOSH 1984b; Pekari and Aitio 1982; Rick et al. 1982; Siqueina and Fernicola 1981). Thus, measurement of pentachlorophenol in the urine is a useful biomarker of exposure. In addition, pentachlorophenol can be easily detected and quantified in blood serum at concentrations as low as <1 ppb (Bevenue et al. 1968; EPA 1980a; Needham et al. 1981; NIOSH 1984b) and adipose tissue (Kuehl and Dougherty 1980; Needham et al. 1981; Ohe 1979; Shafik 1973). However, measuring pentachlorophenol in body fluids and tissues is not a specific biomarker for pentachlorophenol exposure because other compounds to which exposure may occur (e.g., hexachlorobenzene and lindane) may be metabolized to pentachlorophenol in the body. In addition, the available data do not permit the establishment of a quantitative relationship between levels of pentachlorophenol in the environment and levels in human fluids or tissues. Additionally, a major pentachlorophenol urinary metabolite, TCHQ,

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has potential use as an indicator of exposure to pentachlorophenol (Ahlborg et al. 1974; Braun et al. 1977; Juhl et al. 1985; Reigner et al. 1991; Renner 1989), although this biomarker is not specific for pentachlorophenol. Additional studies are needed to establish a relationship between exposure level and urinary concentration of TCHQ.

Effect. The liver is a target organ for both humans and animals exposed to pentachlorophenol. Clinical manifestations of hepatic and renal toxicity include elevated serum ALT and AST levels for toxicity to the liver (Armstrong et al. 1969; Bergner et al. 1965; Gordon 1956; Gray et al. 1985; Klemmer 1972; Robson et al. 1969). Indices of changes in hepatic oxidative phosphorylation may also be useful as biomarkers for pentachlorophenol-induced liver changes (Ellinger et al. 1991). These effects are not specific for exposure to pentachlorophenol and have been associated with exposure to other compounds, such as some chlorinated hydrocarbons. Therefore, the major use of these biomarkers is restricted to comparisons in which pentachlorophenol-exposed and control groups can be identified (e.g., between workers exposed to chemical in the workplace and control subjects). Oral exposure of animals to pentachlorophenol induces a decrease of thyroxine levels in serum (Beard et al. 1999b; Jekat et al. 1994; Rawlings 1998). Comparison of the levels of thyroxine in control and pentachlorophenol-exposed populations could also serve as a nonspecific biomarker of pentachlorophenol effect. In general, there is no simple relationship between nonfatal health effects and levels of pentachlorophenol detected in serum and urine. Development of additional, more 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. Evidence for absorption of pentachlorophenol by humans after exposure by the inhalation and dermal routes is provided by the observation of elevated urine and plasma levels in workers (Casarett et al. 1969; Jones et al. 1986; Pekari et al. 1991) and residents of log homes treated with pentachlorophenol (Cline et al. 1989; Hosenfeld et al. 1986). A study of two humans exposed to pentachlorophenol vapors for 45 minutes provides evidence that it is well absorbed (Casarett et al. 1969). Similarly, human studies also indicate that pentachlorophenol is readily absorbed following oral exposure (Braun et al. 1979; Uhl et al. 1986). The results of inhalation (Hoben et al. 1976c) and oral (Ahlborg et al. 1974; Braun and Sauehoff 1976; Braun et al. 1977; Meerman et al. 1983; Reigner et al. 1991) exposure studies in animals confirm the results of the human studies that pentachlorophenol is well absorbed following inhalation or oral exposure. *In vivo* animal studies (Qiao et al. 1997; Wester et al. 1993) are sufficient to characterize the extent of absorption of pentachlorophenol in soil. However, additional animal studies would be useful for

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determining the absorption efficiency of an aqueous solution of pentachlorophenol and neat pentachlorophenol.

No human studies examined the distribution of pentachlorophenol following inhalation, oral, or dermal exposure. The distribution of pentachlorophenol following inhalation (Hoben et al. 1976c), oral (Braun et al. 1977; Gómez-Catalán et al. 1991; Larsen et al. 1975), or dermal (Qiao et al. 1997) 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. Pentachlorophenol has been found in human breast milk from German and Slovakian women (Gebefugi and Korte 1983; Veningerova et al. 1996).

Results from human and animal studies indicate that pentachlorophenol is not extensively metabolized, as evidenced by a large portion of the administered dose being excreted in urine unchanged in humans exposed by the inhalation (Ahlborg et al. 1974) and oral (Braun et al. 1979; Uhl et al. 1986) routes and in animals exposed to pentachlorophenol by the inhalation (Hoben et al. 1976a) and oral (Ahlborg et al. 1974; Braun et al. 1977; Renner 1989; Renner and Hopfer 1990) routes. The major metabolite is tetrachloro-*p*-hydroquinone (TCHQ) in humans exposed to pentachlorophenol by the inhalation route (Ahlborg et al. 1974) and in animals exposed to pentachlorophenol by the oral route (Ahlborg et al. 1974; Braun et al. 1977; Reigner et al. 1991; Renner and Hopfer 1990). Additional studies of metabolites formed in humans after exposure to pentachlorophenol by the dermal and oral routes and in animals after exposure to pentachlorophenol by the inhalation and dermal routes would be useful. The available human and animal data indicate that metabolism of pentachlorophenol occurs in the liver, and the major pathways are glucuronide conjugation and oxidative dechlorination to form TCHQ. However, recent studies in rats and mice following oral administration of pentachlorophenol (Lin et al. 1997; Waidyanatha et al. 1994, 1996) suggest that the metabolism of pentachlorophenol can also proceed through the quinols, TCHQ, and tetrachlorocatechol, via microsomal cytochrome P 450 enzymes, and that these quinols can be oxidized via semiquinone intermediates. Both the quinones and semiquinones are electrophilic and can bind to cellular macromolecules (Lin et al. 1997). Additional studies in animals to determine if chlorinated quinones and semiquinones are produced following inhalation and dermal exposures to pentachlorophenol would be useful. Studies in animals by the inhalation, oral, or dermal routes to examine the potential role of peroxidases in pentachlorophenol metabolism would also be useful. Additional studies examining the metabolism of pentachlorophenol following inhalation and dermal exposure would be useful for determining if there are route-specific differences in metabolism.

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No information was found on the relative amounts of excreted pentachlorophenol and its metabolites in urine and feces after humans or animals were exposed to pentachlorophenol by inhalation.

Approximately 74 and 12% (total of 86%) of pentachlorophenol ingested by humans was eliminated in the urine as pentachlorophenol and its glucuronide conjugate, respectively (Braun et al. 1979). In rodents, from 60–83% of the administered oral dose is eliminated in the urine (Ahlborg et al. 1974; Braun et al. 1977; Larsen et al. 1972; Reigner et al. 1991); in monkeys, 45–75% of the administered oral dose is eliminated in the urine (Braun and Sauerhoff 1976). Fecal elimination of pentachlorophenol and its metabolites accounted for 4% of the administered oral dose in humans (Braun et al. 1979), 8–34% of the administered oral dose in rodents (Braun et al. 1977; Larsen et al. 1972; Reigner et al. 1991, 1992), and 3–20% in monkeys (Ballhorn et al. 1981; Braun and Sauerhoff 1976; Rozman et al. 1982). Only trace amounts were eliminated in expired air. Excretion data in animals indicate that the kinetics of pentachlorophenol elimination in humans following oral exposure is similar to that seen in monkeys in that they are first order (Braun and Sauerhoff 1976; Braun et al. 1979); additional studies examining potential species differences would be useful. No studies were located regarding excretion in humans after dermal exposure to pentachlorophenol. After application of radioactively-labeled pentachlorophenol in a soil-based mixture to the skin of swine, one-third to one-half of the absorbed dose was almost equally excreted through urinary and fecal routes (Qiao et al. 1997). Additional studies on routes of elimination of pentachlorophenol following exposures of animals by the dermal and inhalation routes would be useful. Two animal studies (Braun and Sauerhoff 1978; Braun et al. 1974) 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 toxicokinetics of pentachlorophenol and to identify the most appropriate model for humans.

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Methods for Reducing Toxic Effects. Pentachlorophenol can be absorbed through inhalation, oral, or dermal routes. Methods are available for reducing absorption following oral and dermal exposure to pentachlorophenol; however, since gastrointestinal absorption of pentachlorophenol in humans is rapid (Braun et al. 1979), these methods (washing skin and eyes, emesis, lavage, activated charcoal, and catharsis) (EPA 1989, 1989b) are useful only immediately following exposure to the chemical. Based on animal studies, cholestyramine administration is recommended in cases of human pentachlorophenol overexposure to enhance elimination of pentachlorophenol (Goodman et al. 1990); however, its use in humans has not been sufficiently tested. Data on cholestyramine administration, hemoperfusion, and administration of sedatives and antipyretics as treatment methods would be useful.

The mechanism of toxicity of pentachlorophenol is not clear. Although pentachlorophenol has been shown to uncouple oxidative phosphorylation, affect thyroid homeostasis, and produce oxidative damage to DNA, the extent to which these effects contribute to toxicity in the various organs and systems affected by pentachlorophenol is not clear. It is possible that these effects contribute to the toxicity spectrum seen in some organs, but are secondary unrelated to toxic effects seen in other organs. Therefore, additional studies on the relative contributions of these effects (uncoupling of oxidative phosphorylation, disturbances in thyroid homeostasis, and oxidative damage to DNA) to pentachlorophenol toxicity and examination of other potential mechanisms of toxicity (e.g., interactions with specific cell or tissue receptors) would be useful steps toward identifying methods that may reduce the toxic effects of pentachlorophenol.

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 (Smith et al. 1996), and suppression of the immune system was seen in older children exposed to pentachlorophenol (McConnachie and Zahalsky 1991). Additional studies to confirm and expand these findings would be useful. In animals, pentachlorophenol also causes a decrease in serum thyroxine levels, adverse effects on thyroid homeostasis, and inhibition of the uptake of thyroid hormone into the central nervous system. Long-term epidemiological studies of possible health effects in large cohorts of individuals who were exposed to pentachlorophenol as children would be useful, particularly with regard to reproductive function, the immune system, neurobehavioral testing, and cancer.

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 (Schwetz et al. 1978), decreased fetal and neonatal body weight (Argus 1993b/Bernard et al. 2001b, Argus 1997/

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Bernard et al. 2001c; Beard et al. 1999b; Courtney et al. 1976; Larsen et al. 1975; Schwetz et al. 1978; Welsh et al. 1987), increased male:female sex ratio (Schwetz et al. 1974), delayed ossification (Schwetz et al. 1974), and skeletal anomalies (Schwetz et al. 1974, 1978). There is some suggestive evidence that effects on the thyroid can lead to neurological deficiencies in the offspring; a neurodevelopmental toxicity study is needed to assess this potentially sensitive end point.

There are no studies to indicate whether the pharmacokinetics and metabolism of pentachlorophenol in children are different from those in adults, and there are no PBPK models for pentachlorophenol. However, given the large number of potential reactive metabolites that can be formed from pentachlorophenol and the different levels of active metabolites among rodent species (Lin et al. 1997), well-conducted studies on potential pharmacokinetic and metabolic differences between children and adults would be useful. A rationale for such studies is that UDP-glucuronosyl transferase and sulfotransferases, which are involved in phase II metabolism of pentachlorophenol, and two of the cytochrome P-450s, which are involved in the phase I metabolism of pentachlorophenol, are all thought to be developmentally regulated (Leeder and Kearns 1997). The need for a PBPK model for pentachlorophenol is not apparent at this time. There are some data to show that radiolabeled pentachlorophenol may cross the placenta of animals and enter the developing fetus (Larsen et al. 1975), and can be present in human breast milk (Gebefugi and Korte 1983; Veningerova et al. 1996). However, studies to confirm that pentachlorophenol crosses the placenta into developing fetuses and to characterize levels of pentachlorophenol in human breast milk in the United States would be useful. There are no studies to evaluate whether the mechanism of action of pentachlorophenol is different in children, but there is no apparent reason to suspect that it would be different. However, studies to determine whether children have a different susceptibility to health effects from pentachlorophenol than adults would be useful, starting with studies that compare immature animals to adult animals.

Child health data needs relating to exposure are discussed in 6.8.1 Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

Information on the ongoing studies cited in this section was obtained from FEDRIP (2001).

Dr. I. Hertz-Picciotto at the University of North Carolina is assessing the feasibility of self-administered devices for collection of breath, urine, tap water, and indoor air monitoring samples in studies of penta-

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chlorophenol; generating data on background variability of body burdens and protein adducts from exposures to pentachlorophenol; and determining factors that influence such variability, including point sources of contamination and workplace, in addition to background factors such as sociodemographic, geographic, lifestyle, and home characteristics.

Dr. S. M. Rappaport of the University of North Carolina at Chapel Hill is investigating the development and application of biomarkers of exposure to pentachlorophenol, including the levels of the parent compound in blood, exhaled air, and urine, and the levels of adducts with hemoglobin and serum albumin.