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.

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 [^{14}C]-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 [^{14}C]-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 [^{14}C]-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 [^{14}C]-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.

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/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). 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).

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

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.

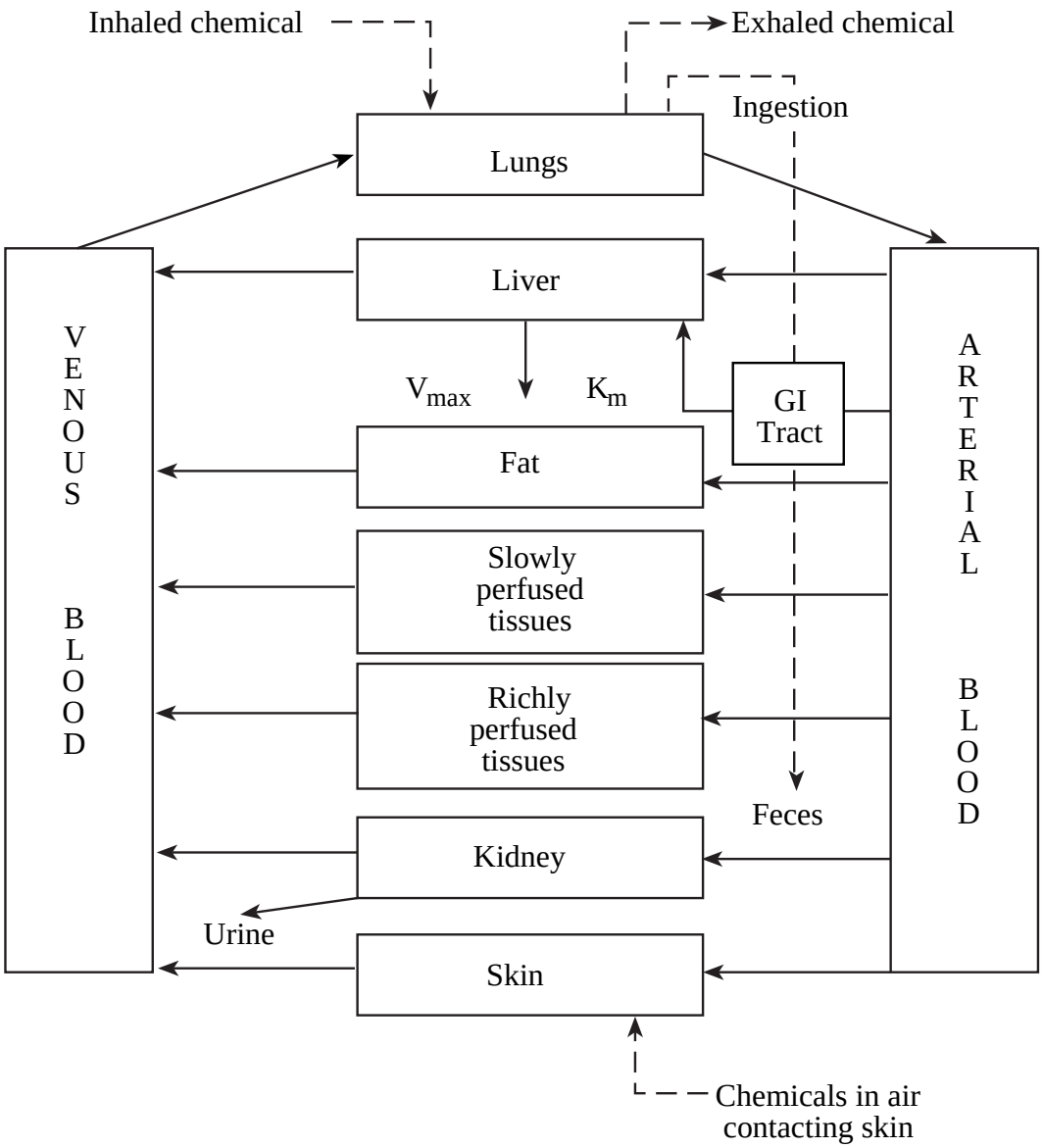
3.5 MECHANISMS OF ACTION

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).

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.

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.

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;

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 Cl_4CAT via microsomal cytochrome P 450 enzymes and that these quinols can be oxidized via semiquinone intermediates (tetrachloro-1,2-semiquinone [Cl_4-1,2-SQ] and tetrachloro-1,4-semiquinone [Cl_4-1,4-SQ]) into the corresponding quinones (tetrachloro-1,2-benzoquinone [Cl_4-1,2-BQ] and tetrachloro-1,4-benzo-quinone [Cl_4-1,4-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 Cl_4-1,4-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.

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 isoflavinoid 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).

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).

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

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 LD_{50} values provides evidence that infants may be more susceptible than children. Lower LD_{50} values were found in preweaning animals, as compared to juvenile rats (25–50 days); however, the LD_{50} value in adult rats was similar to the value for preweaning rats (St. Omer and Gadusek 1987).

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 chlorophenate (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 pentachloro-phenol (>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

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.

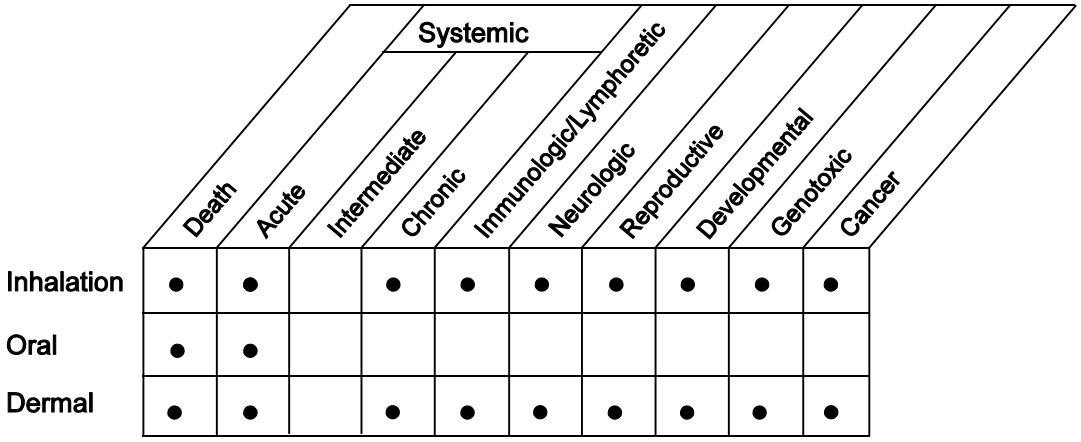
There are no pediatric-specific methods for reducing peak absorption or reducing body burden following exposure to pentachlorophenol.

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

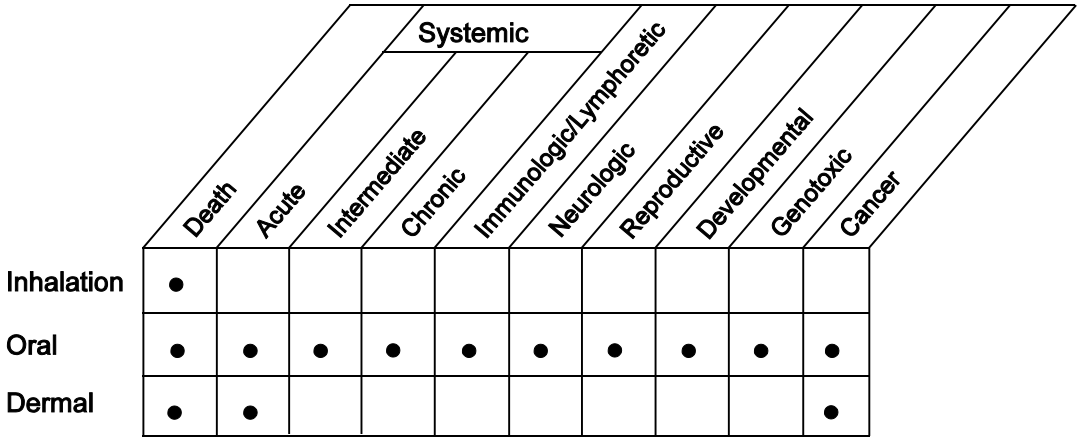
Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

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

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



Human



Animal

● Existing Studies

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

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

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 (McConnchie 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

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,

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

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

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

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

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,

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

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.

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.

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 catharisis) (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/

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-

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.