CHAPTER 3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

3.1 TOXICOKINETICS

- Pentachlorophenol is efficiently absorbed following inhalation, oral, and dermal exposure.
- Pentachlorophenol is distributed throughout the body, with the highest levels in the liver and kidneys. The binding of pentachlorophenol to plasma proteins plays a significant role in the distribution of pentachlorophenol.
- 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).
- The primary route of pentachlorophenol elimination in all species studied, including humans, is urine, with lesser amounts (around 10%) excreted in the feces. 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.

3.1.1 Absorption

The limited data available on the absorption of inhaled pentachlorophenol suggest that it is readily absorbed. In a study of two volunteers exposed to 0.230 or 0.432 ng/m^3 pentachlorophenol for 45 minutes, 88 and 76%, respectively, was absorbed, based on measurements of respiratory rates during exposure, total urinary pentachlorophenol recovered for up to 1 week postexposure, and tidal volume estimates (Casarett et al. 1969). In rats exposed to pentachlorophenol for 20 minutes, 70–75% of radioactivity was recovered in urine, plasma, liver, and lung by 24 hours postexposure (Hoben et al. 1976a).

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 µg/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.

Similar results were observed in studies of monkeys, rats, and mice. Following gavage administration of a single dose of pentachlorophenol, peak plasma levels were achieved 1.5–6 hours after administration (Braun and Sauerhoff 1976; Braun et al. 1979; Reigner et al. 1991, 1992b; Yuan et al. 1994), and the half-life of absorption ranged from 0.25 to 1.5 hours (Reigner et al. 1991; Yuan et al. 1994). Absorption efficiencies ranging from 86 to 100% were reported in rats administered pentachlorophenol via gavage (Reigner et al. 1991; Yuan et al. 1994). Yuan et al. (1994) estimated efficiencies of 100% at

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9.5 mg/kg/day and 86% at 38 mg/kg/day. In contrast, Pu et al. (2003) found slightly higher bioavailability in rats receiving a single 300 mg/kg dose (87.8%), as compared to a 100 mg/kg dose (75.0%). A somewhat lower absorption efficiency was observed in a dietary exposure study, absorption efficiencies of 52 and 30% were estimated in rats exposed to approximately 21 or 64 mg/kg/day pentachlorophenol, respectively, in the diet for 5 days (Yuan et al. 1994). A 1-week drinking water study in rats found that sodium pentachlorophenate (0.05 mg/kg/day) is almost completely absorbed (Meerman et al. 1983). The available data suggest that pentachlorophenol may interact with dietary constituents, which may decrease its absorption following dietary exposure.

Oral bioavailability of pentachlorophenol in several soil samples were 36–55% and 46–77% at 100 and 200 mg/kg doses, respectively (Pu et al. 2003). The relative bioavailability, as compared to pentachlorophenol in corn oil, were 48–62% at 100 mg/kg and 52–87% at 200 mg/kg. The study did not find any obvious correlations between bioavailability and soil properties.

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.

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 ($0.7 \ \mu g/cm^2$ in soil and $0.8 \ \mu g/cm^2$ in acetone of ^{14}C-pentachlorophenol applied for 24 hours to abdominal skin), 24.4% of the applied dose in soil and 29.2% of the applied dose in acetone were absorbed. In an *in vivo* swine model, $40 \ \mu g/cm^2$ [^{14}C-UL]-pentachlorophenol was applied occlusively or nonocclusively in a soil-based mixture to a clipped abdominal site of 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 co-dosed with occlusively applied [^{14}C-UL]-pentachlorophenol, total radiolabel absorption by 408 hours was 86.21%. If it is 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. In a second study using an *in vivo* swine model and a prolonged exposure period (264-408 hours) (Qiao and Riviere 2002), 50.15% of the pentachlorophenol was absorbed; pretreatment with benzo[a]pyrene (BaP) increased absorption to 56.77%. The investigators suggested that the increased absorption in pigs pre-exposed to BaP was due to BaP-induced cutaneous cytochrome P-450.

3.1.2 Distribution

There are limited data on the distribution of pentachlorophenol in humans. The distribution of background levels of pentachlorophenol was 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 μg/g), kidneys (0.043 μg/g), brain (0.047 μg/g), spleen (0.019 μg/g), and body fat (0.013 μg/g). The median pentachlorophenol levels in the urine and blood were 0.0044 and 0.033 μg/mL, respectively.

The distribution of pentachlorophenol following a 20-minute inhalation exposure was examined in rats exposed to an aerosol of pentachlorophenol for 1–5 days (Hoben et al. 1976a). Immediately after exposure, 1.8% of the dose was present in the lungs; 24 hours after exposure, approximately 0.7% of the dose was present in the lungs. Shortly after exposure, 35 and 25% of the dose was present in the plasma and liver, respectively; 24 hours post-exposure 8–10% was detected in these tissues. The investigators proposed that the similarity of the clearance rates in the plasma and liver suggests that there is no apparent storage or preferential binding at these sites. 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.

Nine days after oral administration of a single dose of 10 mg/kg [^{14}C]-pentachlorophenol in corn oil to rats, the highest levels of radioactivity were found in liver and kidneys (0.315 and 0.045% of the administered dose, respectively) and lower levels are found in the stomach, lungs, testes, ovaries, brain, heart, spleen, and adrenals (0.005% of dose) (Braun et al. 1977). Levels of radioactivity were uniformly higher in plasma and tissues of females as compared to males, although the distribution pattern was

qualitatively the same. In a study of two female monkeys orally administered 10 mg/kg [^{14}C]-penta-chlorophenol, the highest concentrations of radioactivity were found in the large intestine, small intestine, and liver (5.00, 2.60, and 1.41% of the administered dose) 15 days post-exposure (Braun and Sauerhoff 1976).

Studies in rats demonstrated that following oral repeated exposure, plasma pentachlorophenol concentrations are proportional to dose (NTP 1999; Yuan et al. 1994). In the NTP (1999) 2-year study, plasma pentachlorophenol concentrations were 24, 44, and 67 µg/mL in females and 17, 36, and 53 µg/mL in males at dietary concentrations of 200, 400, and 600 ppm, respectively. Similar to the findings of Braun et al. (1977), the plasma pentachlorophenol levels were higher in females than in males.

The distribution of radiolabelled pentachlorophenol was examined in female pigs following occlusive application of 40 µg/cm^2 [^{14}C-UL]-pentachlorophenol in a soil-based mixture (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. Similar results were found when the radiolabeled pentachlorophenol was administered in an ethanol vehicle (Qiao and Riviere 2002). After 264 hours, 22% was retained in local skin, fat, and muscle and 18% was found in inner organs of pigs; in the inner organs, the highest levels were found in the liver, ovaries, kidneys, lungs, gall bladder, uterus, and small intestine.

Distribution of radioactivity in mice following intraperitoneal and subcutaneous administration of single doses of [^{14}C]-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 [^{14}C]-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 [^{14}C]-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. 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) in 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).

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 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). An inhalation study found that the binding of pentachlorophenol to plasma proteins varies linearly with increasing dose (Hoben et al. 1976c). An *in vitro* study 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. Percent unbound pentachlorophenol was inversely correlated with serum protein concentrations (Reigner et al. 1993). These data suggest that the distribution of pentachlorophenol may be restricted due to extensive plasma protein binding.

A limited number of studies have evaluated maternal transfer of pentachlorophenol. A general population study of 15 women reported a correlation between maternal plasma pentachlorophenol levels and cord blood plasma levels (Guvenius et al. 2003). The median maternal plasma and cord blood plasma pentachlorophenol levels were 2,830 and 1,960 pg/g, respectively. Pentachlorophenol levels in breast milk were about 100 times lower; the median level was 20 pg/g. Other studies have also reported low levels of pentachlorophenol in breast milk (Gebefugi and Korte 1983; Veningerova et al. 1996). A study of participants in the Northern Norway Mother-Child Contaminant Cohort Study found a correlation between pentachlorophenol levels in infant meconium samples and second trimester maternal serum pentachlorophenol levels (Veyhe et al. 2013). Larsen et al. (1975) administered a single oral dose of 60 mg/kg pentachloro[U-^{14}C]phenol (99.54% radiochemical purity) to rats on GD 15. 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. By 32 hours after dosing, percentages of administered dose were 0.43% in serum, 0.08% in placentas, and 0.04% in fetuses. 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%).
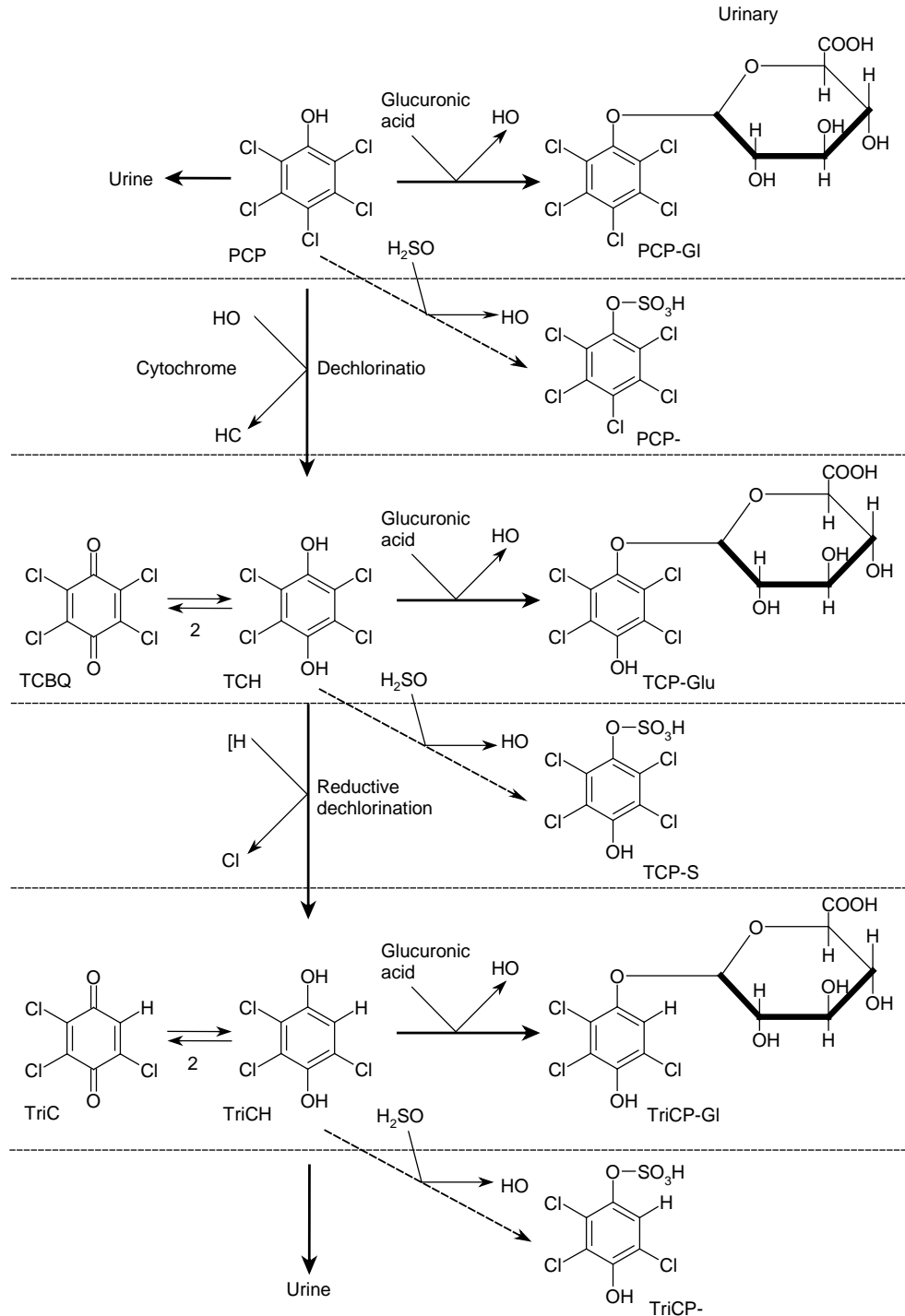
3.1.3 Metabolism

Available human and animal data indicate that metabolism of pentachlorophenol occurs in the liver, and the major pathways are conjugation to glucuronide and oxidative dechlorination to form TCHQ. A summary of possible metabolic pathways for pentachlorophenol is presented in Figure 3-1.

Studies in humans suggest that approximately 80–90% of an administered dose is excreted as unchanged pentachlorophenol or pentachlorophenol glucuronide conjugate in the urine (Reigner et al. 1992a; Uhl et al. 1986), with most excreted as the glucuronide conjugate. Another study reported that 78% of the administered dose was excreted as unchanged pentachlorophenol (Braun et al. 1979); however, the discrepancy may be due to the analytical method used to measure urinary levels, which resulted in hydrolysis of the pentachlorophenol glucuronide to form pentachlorophenol in the urine (Reigner et al. 1992a). A study of two workers exposed via inhalation reported the presence of TCHQ in the urine (Ahlborg et al. 1974); dechlorination is considered to be a minor route of metabolism.

In mice receiving a 20 mg/kg gavage dose, approximately 50% of the pentachlorophenol dose was excreted as glucurono- and sulfo-pentachlorophenol conjugates, 6–9% as unchanged pentachlorophenol, and the remainder as TCHQ or TCHQ conjugates (Reigner et al. 1992b). Studies in rats indicate that most of the administered dose was excreted as pentachlorophenol and TCHQ and their glucurono- and sulfo-conjugates (Ahlborg et al. 1974; Braun et al. 1977; Reigner et al. 1991; 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; Cl_4CAT; trichloro-1,4-benzenediol; tetrachloro1,4-benzenediol; tetrachlororesorcinol; trichlorohydroquinone; TCHQ; and traces of trichloro1,4-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 pentachloro-phenol 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. 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).

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Figure 3-1. Proposed Metabolic Scheme for Pentachlorophenol

PCP = pentachlorohenol; PCP-Glu = pentachlorophenol-β-glucuronide; PCP-S = pentachlorophenylsulfate;
TCHQ = tetrachloro-*p*-hydroquinone; TCP-Glu = tetrachlorophenol-β-glucuronide; TCP-S = tetrachlorophenylsulfate;
TCBQ = tetrachlorobenzoquinone; Tri CHQ = trichloro-*p*-hydroquinone; Tri CP-Glu = richlorophenyl-β-glucuronide;
Tri CP-S = trichlorophenylsulfate; Tri CQ = trichloro-*p*-quinone

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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 [^{14}C]-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. As noted previously, the lack of pentachlorophenol conjugates in urine may be due to hydrolysis of urinary pentachlorophenol glucuronide; thus, conclusions regarding the metabolism of pentachlorophenol cannot be drawn from this study.

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.

In vitro studies in both human and rat liver homogenates clearly demonstrate that pentachlorophenol is converted to TCHQ (Juhl et al. 1985). Pentachlorophenol was identified as an inducer of cytochrome P450 3A in cultured rat hepatocytes, quail hepatocytes, and human hepatoma (Hep G2) cells (Dubois et al. 1996). Mehmood et al. (1996) provided evidence that human cytochrome P450 3A may metabolize pentachlorophenol to TCHQ in phase I metabolism of pentachlorophenol. 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 and 4 years of age and then activity progressively declines, reaching adult levels at the conclusion of puberty (Leeder and Kearns 1997).

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. The relative concentration of pentachloro-phenol in microsomes was 6 times greater than in mitochondria in rats receiving a single gavage dose of pentachlorophenol (Arrhenius et al. 1977). Since maximum effects on inhibition of microsomal detoxification processes (requiring electron transport from flavin to cytochrome) occur at a pentachloro-phenol 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.

3.1.4 Excretion

Pentachlorophenol is primarily excreted in the urine, with smaller amounts excreted in the feces. Several studies have estimated elimination half-lives using only urinary excretion in workers exposed to airborne pentachlorophenol. The half-lives ranged from 10 to 19–20 days (Barbieri et al. 1995; Begley et al. 1977; Casarett et al. 1969; Pekari et al. 1991). In contrast, a single exposure study estimated a urinary half-life of 10 hours following a 45-minute exposure (Casarett et al. 1969). One study estimated an elimination rate constant using a one-compartment model of 0.044 ± 0.018/day (Pekari et al. 1991). 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. 1976a). The investigators noted that most of the pentachlorophenol was excreted unchanged.

Two studies have evaluated pentachlorophenol excretion in humans following oral administration of single low doses 0.016–0.31 mg/kg. 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. The authors concluded that slow elimination could be attributed to extensive plasma protein binding and tubular reabsorption. In contrast, Braun et al. (1979) found that the half-life of elimination of a 0.1 mg/kg dose 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 post-ingestion, 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.

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). Within 8–9 days of a single dose of 10 mg [^{14}C]-pentachlorophenol/kg to rats, 80% of the radioactivity was recovered in urine and 19% in feces (Braun et al. 1977); administration of 100 mg [^{14}C]-pentachlorophenol/kg resulted in 64% being detected in urine and 34% in feces. The investigators estimated elimination half-lives of 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. Consistent with these findings, Reigner et al. (1991) reported that 60% of the 2.5 mg/kg dose administered to rats was excreted in the urine within the first 72 hours and 8.9% was excreted in feces. In mice, a half-life of 5.8 hours was reported in animals receiving a single dose of 15 mg/kg pentachlorophenol (Reigner et al. 1992b); the urine was collected for 48 hours. The pentachlorophenol was primarily excreted as pentachlorophenol and TCHQ conjugates. Fecal excretion accounted for 6–9% of the dose, primarily as pentachlorophenol conjugates.

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 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, and total excretion (urinary plus fecal) increased from 38 to 59%. Seventy percent was excreted in bile during the control period, and 52% was excreted in bile after cholestyramine treatment (Rozman et al. 1982). The investigators suggested that the pentachlorophenol in bile binds to the cholestyramine resulting in a decrease in reabsorption and an increase in fecal secretion. They also suggested that the increase in fecal excretion, which exceeded the decrease in urinary excretion, may be indicative of cholestyramine treatment enhanced intestinal elimination.

No studies were located regarding excretion in humans after dermal exposure to pentachlorophenol. Two studies in pigs evaluated excretion following prolonged (264 or 408 hours) dermal exposure to 40 $\mu g/cm^2$ [^{14}C-UL]-pentachlorophenol in a soil mixture or an ethanol vehicle (Qiao et al. 1997; Qiao and Riviere 2002). After 264 hours, 3.31 and 5.60% of the absorbed pentachlorophenol in ethanol vehicle was excreted in the urine and feces, respectively (Qiao and Riviere 2002). In the soil mixture studies, 19 and 29% of the radiolabel was excreted in the urine and feces, respectively, after 408 hours under nonocclusive conditions and 21 and 20% under occlusive conditions (Qiao et al. 1997).

The clearance rate of pentachlorophenol from plasma was 0.026±0.003 L/hour/kg in rats receiving a single intravenous injection of 2.5 mg/kg pentachlorophenol (Reigner et al. 1991). 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). A second study estimated that the mean terminal elimination half-

life of pentachlorophenol was 5.6±0.37 hours in male rats and 9.5±4.2 hours in female rats receiving a single intravenous dose of 5 mg/kg pentachlorophenol (Yuan et al. 1994).

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

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 endpoints.

No PBPK modeling studies were identified for pentachlorophenol.

3.1.6 Animal-to-Human Extrapolations

Reigner et al. (1993) investigated the binding of radiolabeled pentachlorophenol to serum proteins *in vitro*, found that the percentages of unbound pentachlorophenol in serum were 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 4 times smaller than those obtained using body surface area.

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. 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. Children may be more or less susceptible than adults to health effects from exposure to hazardous substances and the relationship may change with developmental age.

This section also discusses unusually susceptible populations. A susceptible population may exhibit different or enhanced responses to certain chemicals than most persons exposed to the same level of these chemicals in the environment. Factors involved with increased susceptibility may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters can reduce detoxification or excretion or compromise organ function.

Populations at greater exposure risk to unusually high exposure levels to pentachlorophenol are discussed in Section 5.7, Populations with Potentially High Exposures.

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 years. 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. 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 are limited data on potential developmental effects in humans. One study did find an increase in congenital cataracts in children of male sawmill workers exposed to chlorophenate (Dimich-Ward et al. 1996). A number of oral exposure studies in laboratory animals have identified developmental toxicity as a sensitive endpoint. Observed developmental effects include fetal/neonatal mortality (Bernard and Hoberman 2001; Bernard et al. 2002; Exon and Koller 1982; Schwetz et al. 1974, 1978; Welsh et al. 1987), decreased growth (Beard et al. 1999a; Bernard and Hoberman 2001; Bernard et al. 2002; Courtney et al. 1976; Larsen et al. 1975; Schwetz et al. 1974; Welsh et al. 1987), malformation/variations (Schwetz et al. 1974; Welsh et al. 1987), and possibly functional deficits in rats.

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.

3.3   BIOMARKERS OF EXPOSURE AND EFFECT

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

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 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, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to pentachlorophenol are discussed in Section 3.3.1. The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of a generalizable sample of the U.S. population to environmental chemicals using biomonitoring (see http://www.cdc.gov/exposurereport/). If available, biomonitoring data for pentachlorophenol from this report are discussed in Section 5.6, General Population Exposure.

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 effect caused by pentachlorophenol are discussed in Section 3.3.2.

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 3.2, Children and Other Populations that are Unusually Susceptible.

3.3.1   Biomarkers of Exposure

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 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 1980a; Holler et al. 1989; NIOSH 1984; Pekari and Aitio 1982; Rick et al. 1982; Siqueira and Fernicola 1981), 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 1984) 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). Other potentially useful biomarkers include pentachlorophenol levels in hair (Hardy et al. 2021; Iglesias-Gonzalez et al. 2020) or meconium of neonates (Ostrea et al. 2002). 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/m^3 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 1989; 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).

3.3.2 Biomarkers of Effect

No specific biomarkers of effect were identified for pentachlorophenol.

3.4   INTERACTIONS WITH OTHER CHEMICALS

There is limited information on potential interactions between pentachlorophenol and other chemicals. No interactions between pentachlorophenol and the contaminants of technical-grade pentachlorophenol have been demonstrated in some tests of immunotoxicity (Kerkvliet et al. 1985a). The results of an *in vitro* study in HepG2 cells suggest that exposure to perfluorooctanoic acid (PFOA) or perfluorooctane

sulfonate (PFOS) could enhance the toxicity of pentachlorophenol by increasing cell permeability, which could result in increased intracellular pentachlorophenol levels (Shan et al. 2013).

Since pentachlorophenol is metabolized 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).

Various agents have been used in experimental animals to try to decrease the toxicity of pentachloro-phenol. Cholestyramine has been shown to enhance fecal elimination of chlordecone (Kepone) in rats and humans (Boylan et al. 1977). Ballhorn et al. (1981) and 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.