Pentachlorophenol and By-products of Its Synthesis

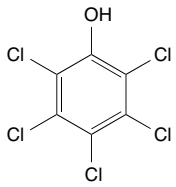
CAS No. 87-86-5 (Pentachlorophenol)

CAS No. 131-52-2 (Pentachlorophenol, sodium salt)

Reasonably anticipated to be a human carcinogen

First listed in the *Thirteenth Report on Carcinogens* (2014)

Also known as Dowicide EC-7 (a registered trademark of Dow Chemical Company)



Carcinogenicity

The complex mixture pentachlorophenol and by-products of its synthesis is *reasonably anticipated to be a human carcinogen* based on limited evidence of carcinogenicity from studies in humans and sufficient evidence of carcinogenicity from studies in experimental animals. This conclusion is supported by mechanistic studies whose findings are consistent with the biological plausibility of its carcinogenicity in humans.

Pentachlorophenol as it is used commercially is a mixture of pentachlorophenol and by-products formed or present during its production. Pentachlorophenol and by-products of its synthesis (hereinafter referred to collectively as "pentachlorophenol") includes higher-chlorinated dioxins and furans, polychlorinated phenols, hexachlorobenzene, and other by-products specified below, under Properties. People exposed to pentachlorophenol are also exposed to its by-products; therefore, the listing is for this complex mixture.

The epidemiological studies could not separate the effects of pentachlorophenol from any effects of its by-products. Dioxin (specifically 2,3,7,8-tetrachlorodibenzo-*p*-dioxin [2,3,7,8-TCDD]) (Cogliano *et al.* 2011) has been associated with non-Hodgkin lymphoma (NHL) in humans, and it is plausible that dioxin-like activity of the by-products may have contributed to the NHL observed in the epidemiological studies of workers exposed to pentachlorophenol. Also, the evidence from studies in experimental animals indicates that the observed carcinogenicity cannot be fully explained by either the presence of by-products alone or pentachlorophenol alone.

Cancer Studies in Humans

Evidence from epidemiological studies suggests that a causal relationship between exposure to pentachlorophenol and NHL in humans is credible. However, because the evidence is based on a small number of high-quality studies with relatively moderate risk estimates, alternative explanations cannot be adequately excluded, and a causal relationship has not been demonstrated. Therefore, the evidence of carcinogenicity from studies in humans is considered limited.

The body of literature with risk estimates specific for pentachlorophenol exposure consists of one cohort study of Canadian sawmill workers exposed to pentachlorophenol as a wood preservative (Demers *et al.* 2006); two partially overlapping cohort studies of U.S. pentachlorophenol-production workers (Collins *et al.* 2009b, Ruder and Yiin 2011); one nested case-control study of pentachlorophenol-production workers based on an IARC registry study of workers exposed to dioxins, phenoxy herbicides, and chlorophenols (Kogevinas *et al.* 1995); and two Swedish population-based case-control studies (Hardell *et al.* 1994, 1995, 2002). The largest and most informative study, the Canadian sawmill workers cohort study (Demers *et al.* 2006), included a detailed assessment of dermal exposure, reported on both mortality and incidence of cancer, and had an adequate number of cases (e.g., 92 cases of NHL) to evaluate exposure-response relationships for most cancer end points. One of the two cohort studies of U.S. pentachlorophenol-production workers, a Michigan cohort study (Ramlow *et al.* 1996, Collins *et al.* 2009a), also was considered to be informative because of its more detailed exposure assessments, although it had a much smaller sample size than the Canadian sawmill workers study. The other studies (Hardell *et al.* 1994, 1995, 2002, Kogevinas *et al.* 1995, Ruder and Yiin 2011) were considered to be less informative because of methodological or sample-size limitations, especially the Swedish population-based case-control studies (Hardell *et al.* 1994, 1995, 2002).

Overall, there is evidence of an association between NHL and exposure to pentachlorophenol based on consistent findings across studies in different occupational populations and in different geographical areas, and on evidence of an exposure-response relationship in the most informative studies. Increased risks of NHL were observed among workers exposed to pentachlorophenol in all of the studies; however, the strength of the evidence varied among the studies. The strongest evidence comes from the largest and most informative study, the cohort study of Canadian sawmill workers (Demers *et al.* 2006), which found statistically significant relationships between the duration of dermal exposure to pentachlorophenol and NHL mortality (P_{trend} = 0.06) and incidence (P_{trend} = 0.02 in lagged analyses that allowed for a 10-year latency period). The risk of NHL mortality was approximately twice as high among workers in the highest exposure categories than among workers in the lowest exposure category. This finding is supported by the observation of an increased risk of NHL among pentachlorophenol-production workers in the Michigan cohort (Collins et al. 2009a). In this study, the highest risks of NHL were observed among individuals with higher surrogates for pentachlorophenol exposure (e.g., measures of exposure to chlorinated dioxin by-products of pentachlorophenol synthesis). The evidence for an association between pentachlorophenol exposure and NHL in the other studies (Hardell *et al.* 1994, 2002, Kogevinas *et al.* 1995, Ruder and Yiin 2011) is considered to be more limited; nonetheless, these studies collectively provide some support for the associations found in the Canadian sawmill workers and Michigan pentachlorophenol-production workers studies.

Because the increased risks of NHL associated with pentachlorophenol were relatively moderate and the number of high-quality studies was limited, it is not possible to rule out the effects of chance, bias, or confounding across the entire body of studies. However, the effects of chance, bias, or confounding factors can be adequately ruled out in the Canadian sawmill workers study (Demers *et al.* 2006). The major occupational co-exposures in the cohort studies were to 2,4,5-trichlorophenol (and its by-product 2,3,7,8-TCDD) in the U.S. pentachlorophenol-production worker studies (Collins *et al.* 2009b, Ruder and Yiin 2011) and tetrachlorophenol in the Canadian sawmill workers study (Demers *et al.* 2006). Potential confounding by co-exposure to these chemicals can reasonably be ruled out, because there was little evidence that exposure to either of these chemicals was associated with increased risk of NHL among workers in these two studies (Demers *et al.* 2006, Friesen *et al.* 2007, Collins *et al.* 2009a,b). However, the U.S. pentachlorophenol-production workers potentially were co-exposed to other chemicals that are likely risk factors for NHL. Confounding was also a potential concern in the Swedish case-control studies (Hardell *et al.* 1994, 1995, 2002). Although few studies investigated lifestyle risk factors, such as smoking or al-

cohol use, these generally have not been associated with increased risk of NHL, and there is little reason to believe that they were associated with workers' exposure to pentachlorophenol or related to pentachlorophenol exposure levels. In addition, the use of internal analyses in the Canadian Sawmill workers study mitigates concern about uncontrolled confounding by these factors.

The evidence for an association between pentachlorophenol exposure and cancer at other tissue sites — specifically, multiple myeloma, soft-tissue sarcoma, or kidney cancer — was weaker. The Canadian sawmill workers cohort study (Demers *et al.* 2006) reported significant positive associations between pentachlorophenol exposure and both multiple myeloma and kidney cancer, but not soft-tissue sarcoma. In contrast, a pooled analysis of the Swedish population-based case-control studies found a significantly increased risk of soft-tissue sarcoma (Hardell *et al.* 1995). Statistical power to evaluate the risk of cancer at these tissue sites was limited in the other studies.

Cancer Studies in Experimental Animals

There is sufficient evidence for the carcinogenicity of pentachlorophenol from studies in experimental animals, based on increased incidences of malignant tumors or combined incidences of benign and malignant tumors in mice and rats at several different tissue sites. Several studies were conducted in mice and rats, using different routes of exposure (dietary and dermal), different purities of pentachlorophenol (with different levels of chemical by-products of synthesis), and different study designs (two-year carcinogenesis bioassays, studies in transgenic mice, and mechanistic studies). The National Toxicology Program (NTP) two-year dietary carcinogenicity studies in mice and rats (NTP 1989, 1999, Chhabra *et al.* 1999, McConnell *et al.* 1991) were the most informative and were of high quality (the chemicals were assessed for purity, the numbers of animals on study and the durations of observation periods were adequate, and comprehensive histopathologic evaluations of tissues were conducted).

In $B6C3F_1$ mice (NTP 1989, McConnell *et al.* 1991), increased incidences of tumors were observed in the liver, adrenal gland, and blood vessels following two-year dietary exposure to either Dowicide EC-7 (91% pure pentachlorophenol) or technical-grade pentachlorophenol (90.4% pure). Although the purities of Dowicide EC-7 and technical-grade pentachlorophenol were similar, their concentrations of individual by-products differed; in particular, technical-grade pentachlorophenol had over 60-fold greater dioxin-like activity than Dowicide EC-7.

The combined incidence of benign and malignant liver tumors (hepatocellular adenoma and carcinoma) was significantly increased in mice of both sexes following dietary exposure to Dowicide EC-7 and in males following exposure to technical-grade pentachlorophenol. In males exposed to either formulation, the separate incidence of malignant liver tumors also was significantly increased. Male mice exposed to technical-grade pentachlorophenol had a higher incidence of liver tumors than did males exposed to Dowicide EC-7 at the same concentration, suggesting that the dioxin-like by-products contributed to the carcinogenicity. The incidences of benign and malignant adrenal-gland tumors (pheochromocytoma) combined, benign adrenal-gland tumors, and preneoplastic adrenal-gland lesions (medullary hyperplasia) were significantly increased in mice of both sexes exposed to Dowicide EC-7. The incidences of benign adrenal-gland tumors and preneoplastic lesions were also significantly increased in male mice exposed to technical-grade pentachlorophenol. The incidence of malignant tumors of the blood vessels (hemangiosarcoma) of the spleen and/or liver was significantly increased in female mice exposed to technical-grade pentachlorophenol or Dowicide EC-7.

In male F344 rats (Chhabra *et al.* 1999, NTP 1999), increased incidences of tumors were observed in the tunica vaginalis of the testes and in the nose. In a stop-exposure study, the incidence of malignant mesothelioma of the tunica vaginalis was significantly increased after dietary exposure to 99% pure pentachlorophenol for one year, followed by one year of observation. Although the increased incidence of squamous-cell carcinoma of the nose was not statistically significant, this is a rare tumor, and its incidence exceeded the range for historical controls. However, no exposure-related effects were observed in male or female F344 rats following continuous dietary exposure to 99% pure pentachlorophenol for two years, which tends to decrease confidence in the findings of the stop-exposure study.

Other studies of dietary exposure to pentachlorophenol in mice and rats used different experimental designs than used in the NTP carcinogenesis studies and had some methodological and reporting limitations. These studies reported no malignancies (Innes *et al.* 1969, Schwetz *et al.* 1978, Boberg *et al.* 1983, Delclos *et al.* 1986, Mirvish *et al.* 1991, Spalding *et al.* 2000). In female transgenic mice with an oncogenic mutation, dermal exposure to 99% pure pentachlorophenol resulted in dose-related increases in the incidence and multiplicity of benign skin tumors (papilloma) (Spalding *et al.* 2000); however, the experimental model had limitations (Fuhrman et al. 2005).

Other Relevant Data

Studies in humans and experimental animals have shown that pentachlorophenol is efficiently absorbed following oral, inhalation, or dermal exposure. It is extensively bound to proteins in the blood and is mostly excreted in the urine either unchanged or as metabolites.

Metabolism and toxicokinetic studies of pentachlorophenol show considerable variation among species, which may account for the differences in the tissue sites at which cancer was reported in mice, rats, and humans. A primary metabolic pathway in rodents is oxidative and reductive dechlorination of pentachlorophenol leading to generation of potentially DNA-damaging metabolites (tetrachlorohydroquinones [TCHQ] and tetrachlorobenzoquinones [TCBQ]), followed by glucuronidation or sulfation. These metabolites and/or glucuronidated forms have been detected in the serum and urine of rodents. Limited information is available on metabolism of pentachlorophenol in humans. Primarily free and glucuronide-conjugated pentachlorophenol were detected in the urine of human volunteers following oral administration of pure pentachlorophenol (Braun *et al.* 1979, Uhl *et al.* 1986). The evidence for metabolism of pentachlorophenol to TCHQ in exposed humans (Ahlborg *et al.* 1974, Braun *et al.* 1979, Uhl *et al.* 1986) is conflicting, because of limitations in study design. However, there is evidence that metabolism to TCHQ can occur in human tissue. Human liver microsomes have been shown to metabolize pentachlorophenol to TCHQ (Juhl *et al.* 1985) and pentachlorophenol glucuronide (Lilienblum 1985). In addition, microsomal fractions and whole cells of yeast *(Saccharomyces cerevisiae)* expressing human cytochrome P450 3A4 (CYP3A4) metabolized pentachlorophenol to TCHQ (Mehmood *et al.* 1996).

Studies on Mechanisms of Carcinogenesis

Although the mechanisms by which pentachlorophenol causes cancer are not fully understood, the available evidence suggests biologically plausible mechanisms in both experimental animals and humans. Proposed mechanisms include metabolism to genotoxic and mutagenic metabolites resulting in DNA damage and chromosome breakage, immunosuppression, and inhibition of apoptosis. Although little is known about the pathogenesis of NHL in humans, proposed mechanisms include immunosuppression and DNA damage (strand breaks) (see NTP 2014).

Genotoxic effects of pentachlorophenol are most likely mediated by its metabolites, as pentachlorophenol was not mutagenic or genotoxic without metabolic activation in most of the standard *in vitro* assays. The pentachlorophenol metabolites TCHQ, which is mutagenic, and TCBQ, which causes DNA damage and DNA adduct formation, have been identified in the urine of rodents exposed to pentachlorophenol. These metabolites can generate DNA-damaging reactive oxygen species through reduction-oxidation cycling. Metabolism to DNA-damaging free radicals can occur at other sites in addition to the liver. A plausible mechanism for cancers of the white blood cells, such as NHL, lymphoma, and multiple myeloma, involves activation of pentachlorophenol by peroxidase or myeloperoxidase activity in lymphocytes and bone marrow. Peroxidases can metabolize pentachlorophenol to phenoxyl free radicals, preferentially forming O-bonded C8-deoxyguanosine (C8-dG) DNA adducts at these sites, resulting in DNA damage. Pentachlorophenol caused DNA adducts, mutations, DNA damage, and chromosomal aberrations *in vitro* under experimental conditions that included endogenous or exogenous mammalian metabolic activation. DNA adducts were found in primary cells in culture exposed to pentachlorophenol and in the livers of rats and mice exposed to pentachlorophenol. These results are supported by evidence of DNA strand breaks in human primary cells and cancer cell lines exposed to pentachlorophenol.

Dioxin-like by-products in some pentachlorophenol preparations are not directly genotoxic but have been shown to act as tumor promoters via activation of TCDD-responsive genes, some of which have a global effect on cell-cycle regulation, cell growth, apoptosis, immune surveillance, metabolism, and disruption of hormone and growth-factor signal transduction pathways. NHL is associated with immunosuppressive conditions (Filipovich *et al.* 1980, Hardell *et al.* 1998), and pentachlorophenol exposure has been associated with cellular and humoral immunodeficiencies in humans (Daniel *et al.* 2001). Some studies in rodents indicate that the dioxin-like by-products (particularly the hexa- and hepta-substituted congeners) in technical-grade pentachlorophenol formulations are primarily responsible for suppression of humoral immunity (Kerkvliet *et al.* 1985), and 2,3,7,8-TCDD itself has been associated with an increased risk of NHL in humans (IARC 2012).

Properties

Pentachlorophenol and By-products of Its Synthesis

The listing is defined as "pentachlorophenol and by-products of its synthesis" because people who are exposed to pentachlorophenol are also exposed to products formed during its synthesis, and many of the cancer studies in experimental animals also involved co-exposure to these by-products. During production of pentachlorophenol, the elevated temperatures and pressures used in the production processes result in the formation of several additional chlorinated molecules. The concentrations of these by-products can be altered somewhat by changes in the conditions of the manufacturing process, but all commercial forms of pentachlorophenol contain by-products of its synthesis in detectable amounts. Pentachlorophenol has been produced in the United States only by direct chlorination of phenol (Williams 1982, ATSDR 2001, Ruder and Yiin 2011). Another process, alkaline hydrolysis of hexachlorobenzene (HCB), might have been used in some instances in other countries (e.g., Europe or China) (Collins 2013, Dunn 2013).

Commonly found by-products of both synthesis processes are polychlorinated phenols (tetra- and tri-); HCB; hexa-, hepta-, and octachlorodibenzo-*p*-dioxins (HxCDD, HpCDD, and OCDD); and hexa-, hepta-, and octachlorodibenzofurans (Collins 2013, Dunn 2013). The alkaline hydrolysis of HCB to pentachlorophenol also results in formation of 2,3,7,8-TCDD; however, 2,3,7,8-TCDD has rarely been detected in commercial preparations of pentachlorophenol (IPCS 1987). Therefore, when 2,3,7,8-TCDD is present in a pentachlorophenol preparation, it is considered to be a contaminant rather than a by-product of synthesis.

Biomonitoring studies have provided evidence that people exposed to pentachlorophenol or pentachlorophenol-containing products are always exposed to a mixture of pentachlorophenol and by-products of its synthesis. The pentachlorophenol synthesis by-products most commonly found in serum samples from exposed individuals were the dioxin congeners 1,2,3,6,7,8-HxCDD, 1,2,3,4,6,7,8-HpCDD, and OCDD (Collins *et al.* 2006, McLean *et al.* 2009), which reflect the spectrum of by-products of synthesis found in pentachlorophenol. Levels of 2,3,7,8-TCDD in the same individuals differed little, if at all, from those observed in a non-exposed reference population (Collins *et al.* 2008). These specific by-products have been found consistently in serum samples from people exposed to pentachlorophenol in different geographical areas (e.g., the United States, New Zealand, and China), in different types of occupational settings (Päpke *et al.* 1992, Schecter *et al.* 1994, Smith and Lopipero 2001, Collins *et al.* 2006, 2007, 2008, McLean *et al.* 2009), and from the environment (Schecter *et al.* 1994, Dahlgren *et al.* 2007, Karouna-Renier *et al.* 2007). These same by-products have also been found in tissues and milk from cows and pigs exposed to pentachlorophenol-treated wood (Fries *et al.* 1999, 2002, Huwe *et al.* 2004).

Pentachlorophenol

Pentachlorophenol is a chlorinated aromatic compound. Pure pentachlorophenol exists as light tan to white, needle-like crystals at room temperature. It is relatively volatile and practically insoluble in water at the pH generated by its dissociation (pK_a = 4.7), but soluble in most organic solvents (IPCS 1987, NTP 1989). Salts of pentachlorophenol, such as sodium pentachlorophenate, are readily soluble in water. Technical-grade pentachlorophenol consists of brown flakes, and technical-grade sodium pentachlorophenate consists of cream-colored beads. Physical and chemical properties of pentachlorophenol are listed in the following table.

Property	Information
Molecular weight	266.3[a]
Density	1.978 g/cm^3 at 22°C[a]
Melting point	188°C[a]
Boiling point	310°C[a]
Log Kow	5.12[a]
Water solubility	14 mg/L at 25°C[b]
Vapor pressure	0.0003 mmHg at 25°C[a]
Vapor density relative to air	1.98[a]

Sources: [a]Akron 2013, [b]ChemIDplus 2013.

Use

Pentachlorophenol was first used in the United States in 1936 as a wood preservative to prevent fungal decay and insect damage. It also was used as a biocide and was found in ropes, paints, adhesives, leather, canvas, insulation, and brick walls. Since 1984, pentachlorophenol has been regulated in the United States as a restricted-use pesticide (restricted to certified applicators) for the treatment of utility poles, cross arms, wooden pilings (e.g., wharf pilings), fence posts, and lumber or timbers for construction. Utility poles and cross arms account for about 92% of all uses of pentachlorophenol-treated lumber (ATSDR 2001, EPA 2010). Because pentachlorophenol is registered for use as a heavy-duty wood preservative, its use on railroad crossties would be allowed; however, the Railway Tie Association (RTA 2012) reported that pentachlorophenol has not been used by

railroads in decades. Pentachlorophenol has also been used in the laboratory as a competitive inhibitor of sulfotransferase (Mulder and Scholtens 1977), but this use would involve very small quantities of the substance.

Production

Although pentachlorophenol is no longer produced in the United States, it is still considered to be a high-production-volume chemical, based on its importation into the United States in quantities of 1 million pounds or more per year. Pentachlorophenol was produced in the United States in the past; in 2012, it was reported to be manufactured by at least six companies worldwide, including at least one company in the United States (SRI 2012). No companies reported pentachlorophenol production activities in the United States in 2013, but one company in North America reported producing pentachlorophenol at a plant in Mexico and operating a formulation facility in the United States (Dunn 2013). Reported recent and historical volumes of U.S. production, imports, and exports of pentachlorophenol are listed in the following table.

Category	Year	Quantity (lb)
Production + imports[a]	2012	> 1 million to 10 million
U.S. imports:[b]		
recent	2013	14 million
historical	2007	0
U.S. exports:[b]		
recent	2013	88,000
historical	2007	697,000

Sources: [a]EPA 2014 (EPA Chemical Data Reporting Rule, formerly the Inventory Update Rule), [b]USITC 2014.

Exposure

A significant number of people living in the United States are or have been exposed to pentachlorophenol because of its widespread presence in the workplace and environment. Exposure has been documented by measurements of pentachlorophenol levels in blood and urine, which reflect current exposure (e.g., Dahlgren *et al.* 2007, CDC 2013), and levels in tissues such as liver, brain, kidneys, spleen, and body fat, which likely reflect long-term exposure (ATSDR 2001).

Occupational exposure to pentachlorophenol still occurs in the United States among workers who formulate pentachlorophenol for use, who treat lumber (such as fence posts or telephone poles), or who come in contact with treated lumber in their work activities. Exposure from treating lumber is primarily (~95%) through dermal contact (Fenske *et al.* 1987, Demers 2013). Wearing protective equipment (e.g., gloves and aprons) in areas where pentachlorophenol is sprayed or where basic joinery occurs (e.g., construction of roof trusses or pallets) can help mitigate these exposures (Jones *et al.* 1986). Inhalation exposure to pentachlorophenol can also occur in occupational settings where it is used; during pressure-treatment of wood, for example, inhalation exposure can occur when the door to the pressure chamber is opened.

In the past, the most important route of exposure for pentachlorophenol-production workers was inhalation. Pentachlorophenol was found in air samples taken at four U.S. manufacturing plants between 1971 and 1983 as part of the National Institute for Occupational Safety and Health Dioxin Registry. In addition, elevated levels of dioxin congeners (2 to 10 times the levels in unexposed workers), which are considered to be indicators of pentachlorophenol exposure, were found in the blood of former U.S. pentachlorophenol-production workers at least 20 years after their last exposure (Collins *et al.* 2007, 2008). Elimination half-lives of up to 10 years have been reported for dioxin by-products of pentachlorophenol synthesis (McLean *et al.* 2009, Collins 2013).

Although the use of pentachlorophenol has been restricted since 1984, there is evidence that people in the United States continue to be exposed to pentachlorophenol and by-products of its synthesis in the environment. This evidence includes (1) elevated levels of chlorinated dioxins in the blood of people living near wood-treatment facilities and in the soil at their homes (Dahlgren *et al.* 2007), (2) detection of pentachlorophenol in the urine of preschool children and in samples of indoor and outdoor air and dust from their homes and daycare centers (Wilson *et al.* 2003, 2007), and (3) detection of pentachlorophenol in the urine of U.S. residents in the National Health and Nutrition Examination Survey (NHANES). In the most recent NHANES that reported results for pentachlorophenol (2003 to 2004), the 95th-percentile urinary levels were 4.58 mg/L for men and 3.20 mg/L for women, and the levels were higher for children aged 6 to 11 (5.67 µg/L) than for adults aged 20 or older (3.4 µg/L) (CDC 2013). Another potential source of human exposure to pentachlorophenol is metabolic transformation of other chlorinated compounds within the body (IPCS 1987). Chlorinated compounds whose metabolism can give rise to pentachlorophenol include hexachlorobenzene, pentachlorobenzene, pentachloronitrobenzene, pentachlorocyclohexene, lindane, and other hexachlorocyclohexanes.

Although environmental and urinary pentachlorophenol levels in recent studies are consistent with continuing exposure of many individuals in the United States, the levels are generally lower than three or four decades ago (before the use of pentachlorophenol was restricted in the 1980s). Pentachlorophenol levels in the range of 10s to 100s of micrograms per liter in blood and generally around 10 mg/L in urine were reported for people living in the United States in studies published from the late 1960s through the 1980s (Zheng *et al.* 2011). Levels were also higher in the 1976 to 1980 NHANES II, which detected pentachlorophenol in the urine of 71.6% of the general population, at geometric mean concentrations of 6.7 ng/mL (mg/L) in males and 5.9 ng/mL in females (Kutz *et al.* 1992).

Exposure of the general population to pentachlorophenol was and is most likely to result from inhalation of air or from dietary or nondietary ingestion (e.g., in dust or soil). Dermal exposure also could occur. Exposure is primarily attributable to its release during production and, particularly, during processing and use in treating wood products. Pentachlorophenol can also be released into the environment from treated wood.

According to the EPA's Toxics Release Inventory, on- and off-site environmental releases of pentachlorophenol from about 30 facilities in 2011 totaled slightly over 96,000 lb (TRI 2013), of which 92.9% was released to landfills, 6.3% to off-site disposal, 0.5% to water, and 0.3% to air. Pentachlorophenol released to air can be transported over substantial distances (1,500 to 3,000 km [930 to 1,860 mi]), with a half-life in the environment of approximately 1.5 months (Borysiewicz 2008). Pentachlorophenol has been detected in air samples at concentrations ranging from less than 1 ng/m^3 in rural settings to about five orders of magnitude higher in industrial settings where pentachlorophenol is manufactured or used, in homes near sites where it is used (e.g., wood-treatment facilities), or in log homes treated with pentachlorophenol (IPCS 1987, Zheng *et al.* 2011). Several reports indicated that log homes were a source of high exposure to pentachlorophenol in the past, with the blood levels of some inhabitants exceeding 1,000 mg/L (MMWR 1980, Cline *et al.* 1989). Similar exposures were reported for workers in the log home museum at Fort Stanwix National Monument in Rome, NY; however, washing the surfaces of the logs with ethyl alcohol to remove crystals of pentachlorophenol greatly reduced workers' exposure (Lee and Lucas 1983).

Pentachlorophenol has been detected in drinking-water supplies (at < 1 to 50 µg/L), groundwater (at 0.6 to 19,000 µg/L), and surface water (from nondetectable to 10,500 µg/L); most measurements were made before the use of pentachlorophenol was restricted (IPCS 1987, ATSDR 2001, Zheng *et al.* 2011). Higher levels were reported for groundwater near industrial areas such as wood-preserving facilities (ATSDR 2001).

Contact of pentachlorophenol-treated wood products (e.g., utility poles) with soil provides another potential route of exposure, especially for small children (ATSDR 2001), who may eat soil or may put their hands or foreign objects in their mouths. Based on estimates of 120 to 200 million preservative-treated wood utility poles currently in service in the United States, 62% of the total treated with pentachlorophenol, and a 3% annual replacement rate, approximately 2.2 to 3.7 million pentachlorophenol-treated utility poles could be emplaced each year (EPA 2008, Bolin and Smith 2011). Nondietary ingestion of pentachlorophenol, such as that associated with dust, has been considered a minor contributor to exposure (Wilson *et al.* 2007, 2010), but it might be more important for small children.

Pentachlorophenol in food was found to be a major source of exposure (75% or more of total exposure) in some environmental-exposure models from the 1980s (e.g., Hattemer-Frey and Travis 1989). Its presence was reported in a wide variety of foods, such as meats, fish, dairy products, grains, and vegetables, in studies in Canada, the United Kingdom, and Germany during that period (Crosby *et al.* 1981, Jones 1981, IPCS 1987, Wild and Jones 1992). Low levels of pentachlorophenol continued to be found in food in the United States after restrictions were instituted (e.g., in 1991–93 and 2003) (FDA 2006).

Regulations

Consumer Product Safety Commission (CPSC)

Pentachlorophenol should not be used as a preservative for playground equipment wood.

Department of Transportation (DOT)

Pentachlorophenol is considered a hazardous material and a marine pollutant, and special requirements have been set for marking, labeling, and transporting this material, including transporting it in tank cars.

U.S. Environmental Protection Agency (EPA)

Clean Air Act

National Emission Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

Clean Water Act

Designated a hazardous substance.
Effluent Guidelines: Listed as a toxic pollutant.
Water Quality Criteria: Based on fish or shellfish and water consumption = 0.27 µg/L; based on fish or shellfish consumption only = 3.0 µg/L.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb.
Regional Screening Levels (formerly Preliminary Remediation Goals): Residential soil = 0.89 mg/kg; industrial soil = 2.7 mg/kg; residential air = 0.48 µg/m^3; industrial air = 2.4 µg/m^3; tap water = 0.035 µg/L; maximum contaminant level (MCL) = 1 µg/L.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Federal Insecticide, Fungicide, and Rodenticide Act

Pentachlorophenol is registered for use only as a heavy-duty wood preservative.

Resource Conservation and Recovery Act

Characteristic Hazardous Waste: Toxicity characteristic leaching procedure (TCLP) threshold = 100 mg/L.
Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of pentachlorophenol = D037, F021, F027, F028, F032, K001.
Listed as a hazardous constituent of waste.

Safe Drinking Water Act

Maximum contaminant level (MCL) = 1 µg/L.

U.S. Food and Drug Administration (FDA)

Maximum permissible level in bottled water = 0.001 mg/L.

Maximum level of pentachlorophenol in wood preservatives prepared from pentachlorophenol and its sodium salt used on wooden articles used in packaging, transporting, or holding raw agricultural products = 50 ppm in the treated wood (calculated as pentachlorophenol).
Pentachlorophenol may be used as a component of adhesives and coatings in packaging, transporting, or holding food provided that conditions prescribed in 21 CFR 175 are met.

Occupational Safety and Health Administration (OSHA)

This legally enforceable PEL was adopted from the 1968 ACGIH TLV-TWA shortly after OSHA was established. The PEL may not reflect the most recent scientific evidence and may not adequately protect worker health.
Permissible exposure limit (PEL) = 0.5 mg/m^3 [0.05 ppm].
Potential for dermal absorption.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.5 mg/m^3 [0.05 ppm].
Threshold limit value – short-term exposure limit (TLV-STEL) = 1 mg/m^3 [0.09 ppm].
Potential for dermal absorption.

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (REL) = 0.5 mg/m^3 [0.05 ppm].
Immediately dangerous to life and health (IDLH) limit = 2.5 mg/m^3 [0.23 ppm].
Potential for dermal absorption.

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