Annex E Information for Pentachlorophenol (PCP), its Salts and Esters

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(a) Sources

(i) Production data

Global production of pentachlorophenol (PCP) during the 1990s was 8,500-50,000 tons/year (UNECE, 2008 as reported in Hofercamp, 2010). Approximately 10% of technical or commercial grade PCP is comprised of impurities including several congeners of the chlorophenols, consisting primarily of the more highly chlorinated congeners of dibenzo-p-dioxins and dibenzofurans (Cooper and Jones, 2008).

(ii) Uses

Dow Chemical Company and Monsanto Chemical Company first introduced PCP as a wood preservative in 1936. Since then, PCP has been used as an herbicide, insecticide including control of termites, as an anti-microbial and disinfectant, in adhesives, paints, and in sealants, in the pulp and paper industry, and in leather tanning. In the U.S.A., the EPA cancelled all uses of PCP except for use as a wood preservative in 1988 (Fisher, 1991). From the 1930s, PCP and its sodium salt have been used extensively as an herbicide, algaecide, defoliant, wood preservative, antimicrobial, fungicide, and molluskicide. China restricted PCP to the use as a wood preservative in 1997, although re-emergence of schistosomiasis, caused an increase in the production and use of PCP in China for snail vector control and the production increased to 3,000 tons in 2000 (Zheng, 2011).

(iii) Releases

The production of PCP has been a major source of PCDD/Fs and the improper disposal of production by-products and wastes from PCP facilities has created major PCDD/F contaminated sites around the world (Li et al. 2012).

(b) Hazard assessment

In a study of the effects of PCP and other current-use pesticides on the development of *Paracentrotus lividus*, Buono et al. (2012) found that at low concentrations, PCP altered the deposition of the larval skeleton and at high concentrations modified the cytoskeleton assembly.

Adverse Human Health Outcomes Associated with PCP:

Exposure to PCP is associated with reproductive and developmental toxicities, immunodeficiency, and interference with thyroid hormone. Adverse endocrine effects are summarized in van den Berg (1990),McConnell et al. (1991), Tran et al. (1996), Danzo (1997), and Rawlings et al. (1998), and Kwiatkowski (2012), including: thyroid, anti-estrogen, anti-androgen, anti-progesterone, brain, development, reproduction, corticosterone, insulin,

metabolism. PCP affects multiple systems and hormones. In a review by Carrizo et al. (2008), the authors summarize adverse health effects associated with PCP exposure, including: increased lymphocyte responses in patients with high PCP levels in blood serum; adverse neurobehavioral effects including impairment of memory and learning ability; infertility in women; and alteration of thyroid metabolism. Daniel et al. (2001) found immunological abnormalities associated with plasma levels of PCP in individuals with long-term low-dose exposure, including significant associations with cellular and humoral immunodeficiencies. Gerhard et al. (1998) determined an association of higher PCP levels in women in Germany with abnormalities of their menstrual cycle and in an age-adjusted assessment, women had markedly higher levels of PCP if they had at least three miscarriages compared with women with two miscarriages. Duan (2008) found that bisphenol-A and PCP acted synergistically or antagonistically, depending on different endpoints (Li et al. 2010). With partial dechlorination of PCP, more toxic intermediate compounds are produced, such as 2,4,6-trichlorophenol. Toxic effects are "due to the uncoupling of oxidative phosphorylation in mitochondria and generation of reactive oxygen species."

PCP affects the vertebrate endocrine system which may adversely affect the immune system and disrupt sexual development, learning, and behavior. (Ma et al. 2011). In *in vitro* profiling of endocrine-disrupting effects in a set of recombined yeast cell strains, PCP showed agonistic and antagonistic effects at the estrogen receptor (ERα) and antagonistic effects at the progesterone receptor (Li et al. 2010). Ma et al. found that exposure of human adrenocortical carcinoma cell line (H295R cells) to PCP significantly reduced the production of testosterone and 17 β-estradiol. In H295R cells exposed to PCP, there was a dose-dependent reduction of cellular AMP (cAMP), indicating that PCP "may inhibit steroidogenesis by disrupting cAMP signaling." PCP exposure resulted in effects on serum levels of reproductive and metabolic hormones, including marked decreases in thyroxin levels, increases in serum levels of insulin, as well as increases in the severity of oviductal intraepithelial cysts in ewes (Rawlings et al. 1998).

Dallaire et al. (2009) found a significant adverse relationship between material PCP levels and umbilical cord serum T4 concentrations in Inuit mothers from Nunavik and their infants, consistent with the hypothesis that chlorinated phenolic compounds inhibit T4 binding to TTR in humans. Reduced transfer of maternal fT4 during brain maturation of the fetus can impair neurocognitive function in infants. In a study that correlated PCP levels in pregnant women in the Netherlands at 35 weeks (n=90) with sex hormone levels in their boy children at 3 months, Meijer et al. (2012) examined the endocrine-disrupting effects from prenatal exposures to PCP and other organohalogens in infant boys and found that PCP levels correlated positively with sex hormone binding globulin (SHBG) ($p=0.30$) and negatively with inhibin B (-0.43). This has implications for the functioning of the Sertoli cells and sexual maturation in these young boys. A study of women daycare workers exposed to PCP, lindane, and PCDFs from treated wood found a significantly reduced birth weight ($p=0.04$) and length ($p=0.02$) among their offspring. The detrimental effect could not be attributed to any substance, but to interactions of PCP, HCH, and PCDDs/PCDFs. (Karmaus and Wolf, 1995).

Ruder and Yiin (2011) found an excess of cancers among PCP production workers in the U.S. of *a priori* interest, including non-Hodgkin's lymphoma and leukemia, providing support for the carcinogenicity of PCP. In a review of the available epidemiological literature, researchers found a strong association between PCP exposure and hematopoietic cancer, not likely due to contamination with dioxins or other chlorophenols (Cooper and Jones, 2008). Demers et al. 2006 determined that dermal exposure to PCP among sawmill workers in British Columbia, Canada was associated with non-Hodgkin's lymphoma, multiple myeoma, and kidney cancer. Heacock et al. found an elevated risk of brain, ovarian, and eye cancer among girl children of British Columbia sawmill workers. Dimich-Ward et al. found an elevated risk of congenital anomalies of the eye (particularly congenital cataracts) and genital organs; as well as anencephaly or spina bifida among children born to fathers exposed to chlorophenate wood preservatives in the sawmill industry, including PCP. Wang et al. (2012) note that tetrachlorohydroquinone (TCHQ) is a major toxic metabolite of PCP and has "also been implicated in PCP genotoxicity." The authors conclude that TCHQ induces sequence-specific DNA mutations at high frequencies. PCP induced adverse changes in human lymphocyte morphology, severely increasing size and granularity of the cells and depleting intracellular ATP levels, with high loss of lymphocyte viability (Michalowicz, 2010). Lymphocytes that function as natural killer cells capable of killing tumor cells, viral-infected cells, and antibody-coated cells are significantly decreased by exposure to PCP, thus adversely affecting a critical immune defense and perhaps playing a role in the development of cancers associated with PCP exposures (Ndodu and Whalen, 2010).

Zheng et al. (2012) conducted a systematic review of PCP in the environment and humans and concluded: "The occurrence of PCP in the environment and humans positively correlated with the epidemic of schistosomiasis. Thyroid-disrupting effects and cancer risk caused by PCP and PCDD/Fs even at low environmental levels in China's schistosomiasis epidemic areas are of concern."

(c) Environmental fate

Pentachloroanisol (PCA) can be generated from PCP through methylation under aerobic conditions in the presence of certain bacteria and fungi. Additional studies confirm that certain bacteria and fungi enhance conversion of PCP to PCA (Walter et al. 2004; Okeke et al. 1997; Lamar et al. 1990a,b; Review in LRAT Dossier Addendum for PCP, 2010). Biological transformation of PCP has been demonstrated in aerobic and anaerobic environments, although under anaerobic conditions, methylation to PCA is a limited reaction (Murthy et al. 1979). The literature supports that PCP is readily transformed to PCA in the environment and several studies demonstrate that the % of PCP transformation to PCA is quite high—62% of PCP to PCA (Pfender et al. 2004); 75% of the volatile fraction in Walter et al. (2004); up to 82% in Badkoubi et al. (1996); c.a. 85% in Rigot and Matsumura (2002). Evidence supports that microbial metabolism in aerobic soils is a main source for transformation of PCP to PCA (LRAT Dossier Addendum for PCP, 2010).

Salminen et al. (1995) noted: "The use of this product [PCP] was banned in 1988, but the soils close to hundreds of sawmills are still highly contaminated. Chlorophenols decompose slowly in soil, especially at low temperatures. Researchers found that there was no significant decrease of PCP in soil around wood preserving sites up to five years after the last use of technical PCP, demonstrating persistence especially in cold northern environments where soil microflora are not able to degrade PCP completely (Kitunen et al. 1987). Even though chlorophenols were banned in the late 1980s, wood preservation sites remain heavily contaminated with PCP and its by-products PCDDs and PCDFs. (Kitunen et al. 1990 and Persson et al. 2003). PCP has been found in urban air in New Zealand, 7 years after it was banned. The New Zealand government concluded that the chlorophenols, especially PCP and tetraphenols, measured in air originate from the historic use of PCP as a timber preservative in New Zealand (Ministry for the Environment, New Zealand, 1998). Okeke (1997) concludes that PCP transformation by fungal metabolism is well-documented. Although no detectable levels of PCA were found after 10-week treatment in the sterilized soil culture, PCA was detected in the non-sterilized soil culture. The researchers also note: "PCA and other chloroanisoles are considered more hazardous in the environment than PCP, as such compounds have a higher lipophilicity and thus a greater tendency to bioaccumulate in animal tissues. However, chloranisoles may degrade *with prolonged treatment*, as observed with the sterile culture, in this study. Transformation of PCP to PCA is an important route of PCP depletion during the early stages of PCP biotransformation by *L. edodes*." Zheng et al. (2011a) report that high concentrations of PCP found in sediment relate to the reported long half-life of PCP in sediments (almost no degradation) (WHO, 1987). Zheng et al. also report the half-life of PCP in anaerobic water as 80-192 days.

Zaborina et al. (1997) identified additional PCP transformation products with POPs properties including tetra- and trichlorophenols, pentachlorobenzene, and chlorinated dioxins. Although PCP manufacturing results in the production of inevitable impurities including other chlorophenols, PCDDs, and PCDFs, experimental studies show that PCP can be converted to PCDD/F through exposure to available sunlight in the troposphere (Baker and Hites, 2000). Liu et al. (2002) also confirm formation of PCDDs through PCP photolysis. Chang et al. (2011) indicate the major sources of PCDD/F in contaminated soils could be attributed to the process of manufacturing PCP. Minomo et al. (2012) observed that PCP formulations are among the four major sources of dioxin in Japan. De la Torre et al. (2011), in a study of sewage sludge, found that the origin of PCDD/Fs should be related to "atmospheric deposition, faeces and presence of *PCDD/F precursors such as PCP* in the sludge." Li et al. (2012) measured levels of PCDD/Fs in air, soils, and sediments in the vicinity of an abandoned PCP factory and found that PCDD/Fs from the PCP manufacturing site have a "significant influence on the regional ambient air" and pose a long-term impact to the surrounding areas.

PCP bioaccumulates from ringed seal to polar bear trophic level for all tissues measured in the East Greenland marine mammals, however highest in the liver (n=20) at 36 ± SE (Letcher et al. 2009). PCP transformation from HCB in mammals is not conclusively demonstrated and likely a negligible pathway in humans (Figueras et al. 1997)(LRAT Addendum 2010).

(d) Monitoring data

PCP levels have been reported in polar bear, fish, and other Arctic biota. Hoekstra et al. (2003) determined that PCP was the most abundant halogenated phenolic compound found in the Arctic bowhead whale plasma. The researchers hypothesized that PCP in biota might result from biotransformation of HCB although they do not provide evidence for this hypothesis. Hoekstra et al. state: "The relatively high proportion of PCP in bowhead whale plasma may also be the direct result of the biotransformation of PCA, an abundant OC contaminant found in Arctic air." Time trend data are available for PCA in Arctic air. In the Canadian High Arctic, Hung et al. measured PCA concentrations ranging from 2.6-4.0 pg/$m^{3.}$ PCA was also found in snow crab muscle and liver at 0.66 ng/g lw and 0.45 ng/g lw, respectively. Levels of PCA were also found in king eider and thick-billed murre livers at concentrations of 0.36 and 0.22 ng/g lw respectively. Concentrations in Arctic marine mammals ranged from 0.08 ng/g lw in harp seal to 0.54 ng/g lw in narwhal muscle and 1.1 ng/g lw in beluga muscle. PCA in caribou muscle was found at 0.20 ng/g lw (Hofercamp 2010). Letcher et al. (2009) found levels of PCP in East Greenland ringed seal blubber at 1.0 ± 0.4 ng/g lw.

In a study of PCP concentrations of pine needles in Saskatchewan, Canada, researchers found levels of PCP in 100% of the samples ranging from 0.42-2.08 ng/g, indicating widespread distribution as an atmospheric pollutant (Thompson and Treble, 1995).

PCP in Human Biomonitoring Studies:

Due to its widespread use and disposal, PCP is detected in air, water, and soil throughout the world, as well as in the blood, urine, seminal fluid, breast milk and adipose tissue of humans (Zheng et al. 2011b).

Sandanger et al. (2004) found levels of PCP in blood plasma of the Indigenous Chukotka people of the Russian Arctic The median PCP level was measured at 642 pg g(-1) plasma. Sandau (2002) reported PCP as the dominant chlorinated phenolic compound in blood samples from Nunavik (Inuit people) and southern Quebec adults in Canada. The researchers noted that PCP may supercede HO-PCBs as the chlorinated compound of highest concern in humans. PCP was the dominant organochlorine compound, when compared with PCB and several other phenol compounds, found in the blood serum of pregnant and lactating women in Sweden, analyzed on a wet weight basis up to 3 ng/g serum in early pregnancy. The researchers found that the levels did not change significantly during pregnancy and observed a significant increase from late pregnancy to three weeks after delivery (Larsdotter et al. 2005). In a study of the levels of PCP and other compounds in maternal blood serum, cord blood, and breast milk of women in Sweden, Guvenius et al. (2003) results show that the fetus is likely to be continuously exposed to PCP during development, implicating a risk potential risk for developmental disturbances. PCP was the dominant phenolic compound in the maternal blood plasma, cord blood plasma, and breast milk samples of Swedish women with median levels of 2.83, 1.96, and 0.02 ng/g fresh weight, respectively (n=15), with PCP levels in maternal and cord blood plasma levels 30 and 36 times higher than the sum of OH-PCBs on average. The maternal blood samples had notably high levels. The researchers further conclude that the potential health impacts of halogenated phenolic compounds may have hitherto been underestimated compared with the

impact of neutral persistent chemicals. The U.S. Centers for Disease Control National Health and Nutrition Examination Survey (NHANES) III reported that the 95th percentile of PCP concentrations in urine was 1.0-2.0 µg/L in the 1999-2002 survey (Cooper and Jones, 2008). In a study of the levels of PCP in the urine of 197 children in Arkansas, researchers found detectable levels in 100% of the samples, with a median concentration of 14 ppb (Hill et al. 1989).

In the first population based study investigating plasma concentrations of pentachlorophenol, Rylander et al. (2012) found that PCP was one of the dominant organic contaminants within a representative population of women in Norway sampled in 2004. PCP and p,p'-DDE were the dominating compounds on a wet weight basis and present in considerably higher concentrations than PCBs and other chlorinated pesticides in 311 plasma samples of post-menopausal Norwegian women. "One of the main findings in the current study was that PCP was the second most dominating compound (711 ng/L w.w.) in this group of menopausal women from the general Norwegian population. The levels found were in the same range as samples from Canadian Inuit (801 ng/L, n=567). The authors note that; "High concentrations of PCP in human blood have been reported worldwide (Dirtu et al. 2010; Guvenius et al. 2003) also in Arctic populations (Sandanger et al. 2004) and there are indications that PCP may increase the risk of cancer (Cooper and Jones, 2008; Ruder and Yiin, 2011). Despite that, PCP has received little attention over the past years and to the best of our knowledge, this is the first population based study investigating plasma concentrations of PCP and its predictors." It is interesting to note these findings of PCP in Norwegian women in spite of the fact that PCP is not in use in Norway and that the government of Norway estimates that PCP emissions in Norway have been reduced by 99% in the period from 1995 – 2009.

Glynn et al. (2011) investigated pregnancy-related changes in serum concentrations of five PCB congeners, 3 hydroxylated PCB metabolites and PCP. They found no decline in PCP concentrations measured in the blood serum of women during pregnancy.

Dirtu et al. (2010) investigated the levels and profiles of PCBs and phenolic compounds in human blood serum and found that PCP accounted for up to 85% of the total quantified phenolics found in Belgian samples and 35% in Romanian samples. The researchers assert that to some extent, PCP may be formed through the metabolism of HCB, however, this does not explain the high levels of PCP found in the Belgian samples. The median concentration of the Belgian samples was 6,290 pg/g wet weight. In a study of human milk from 50 women in Bratislava, PCP was the dominant chlorophenol, with a median concentration of 2.21 µg/kg of whole milk (Veningerova et al. 1996). In a birth cohort from Slovakia, PCP was more abundant in infant cord blood than any PCB or OH-PCB congener measured with median concentrations in cord blood serum of $\sum_{17}$ PCBs, $\sum_{6}$ OH-PCBs, and PCP of 0.92, 0.33, and 0.69 ng/g wet weight, respectively (Park et al. 2008). In a study of the levels of PCP in blood serum of 4-year old children born between 1997 and 1999 in urban and rural communities of Spain, mean levels of PCP were found to be 6.4 ng/mL ± SD of 6.0 (with minimum of 1.5 ng/mL and maximum of 35 ng/mL in the urban population; n=66) and 0.61 ng/mL ± SD of 0.69 (with minimum ND, maximum 4.7 ng/mL in the rural population; n=131). In an exposure assessment of 257 children randomly selected from households and daycare centers in Ohio and North Carolina in the US,

PCP was found in nearly all of the urine samples at similar levels found nationally in children ages 6-11, with arithmetic mean levels of 0.605 ng/mL with SD of 0.629 in the 128 children from North Carolina and arithmetic mean levels of 1.27 ng/mL with SD of 2.20 in the 126 children from Ohio. Maximum levels in the children's urine samples were 3.45 ng/mL in North Carolina compared with a maximum level of 23.8 in Ohio. In the same study, PCP was found in more than 50% of the indoor air, outdoor air, and dust samples and children's exposures were predominantly through inhalation (Wilson et al. 2007). Bradman et al. 2003 detected PCP in amniotic fluid of women in California (USA), indicating direct exposure to the young fetus during critical development periods. Prenatal exposure to PCP correlates with worse coordination, less sensory integrity, worse attention, and worse visuomotor integration in children at school age. These researchers also found that PCP correlated with lower levels of thyroid hormone. Based on their results, the researchers concluded that "unrelenting efforts should be made to find safe alternatives for these compounds (Roze et al. 2009)."

(a) Exposure in local areas

(b) National and international risk evaluation

(c) Status of the chemical under international conventions

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