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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Pentachlorophenol (PCP) Epidemiogic Studies Related to Carcinogenicity

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The following review is provided in response to the request to review 30 studies considered by the Pesticides Directorate of Agriculture Canada.

Earlier EPA Reviews on the Carcinogenicity of PCP

Three reviews conducted by EPA were located as follows:

1. Office of Solid Waste and Remedial Response (1984) Health Effects Assessment for Pentachlorophenol. EPA/540/1-86/043. National Technical Information Service PB86-134541, Springfield, VA.

   No human data on the carcinogencity of PCP were located in the available literature. Dioxin contamination was not discussed.

2. Environmental Criteria and Assessment Office (1986) Health and Environmental Effects Profile for Pentachlorophenol. Draft document, not formally released.

This review mentions dioxin contamination but does not cite any human studies.

3. Environmental Criteria and Assessment Office (1987) Drinking Water Criteria Document for Pentachlorophenol. Final document, not yet released to public.

   This review cited only one human study of PCP, which was judged inconclusive because of serious limitations. The contamination of PCP with dioxins was noted. No attempt was made to quantify human carcinogenic potential because the available human and animal data were judged inadequate.

Canadian Review of Carcinogenicity of PCP

The Pesticides Directorate of Agriculture Canada considered 30 different epidemiologic studies related to exposure to PCP. Most of these studies related to exposure to phenoxy herbicides, chlorophenols in general and/or dioxin. Only two of these studies related specifically to exposure to PCP itself or PCP in mixtures. In the first (a letter to Lancet, Bishop and Jones 1981) two cases of non-Hodgkin's lymphoma (NHL) were reported among 158 workers at a plant manufacturing PCP and its sodium salt. The expected number of such cases was calculated to be 0.3. In the second (a case control study in New Zealand), 23 cases involved in fencing work and exposed to creosote, arsenic, and sodium pentachlorophenate exhibited a significantly elevated odds ratio of 2.0 (90 percent confidence interval 1.3 to 3.0) for NHL. However, sawmill workers (in the same study) also exposed to sodium pentachlorophenate and PCP did not exhibit excess risk for NHL.

Nine studies mentioned exposure to chlorophenols in general. Of the nine, three did not find significant increases in cancer (liver, nasal and respiratory) in exposed workers (Hardell et al. 1984, Kauppinen 1986, Olsen 1984). Of the other six studies, three examined soft-tissue sarcomas (STS), one examined NHL, one examined both STS and NHL, and one examined nasal cancers. For the three positive studies involving STS, significant odds ratios ranged from 2.7 for highly exposed lumber graders in the United States, 3.3 for workers exposed to chlorophenols in Sweden, and up to 6.6 in a second Swedish case-control study with the same type of workers. (Woods et al. 1987, Eriksson et al. 1981, and Hardell and Sandstrom 1979). A fourth study (Smith et al. 1984) did not find a significant risk among workers in New Zealand exposed to chlorophenols. Contradictory results were found in the two studies of NHL. The Swedish study (Hardell et al. 1981) found an odds ratio of 8.4 (95 percent confidence interval 4.2-16.9) based on 25 cases judged to have high levels of chlorophenol exposure. However,

the Washington State study (Woods et al. 1987) found no increased risk either for chlorophenol exposure (odds ratio 1.0, 95 percent confidence interval 0.8-1.2) or for high levels of chlorophenol exposure (odds ratio 0.9, 95 percent confidence interval 0.9-1.4). Woods et al. suggested that differences in intensity of exposure, levels of contaminants, or inherited susceptibility might account for the different findings. The one remaining study of nasal cancer found an odds ratio of 6.7 (95 percent confidence interval 2.8-16.2) based on 11 cases with high grade chlorophenol exposure. Six of the 11 cases were exposed from sawmill work and five were exposed from painting.

Eight of the studies specifically listed exposure to trichlorophenol. Two studies (Cook et al. 1980, Cook 1981) reported two cases of soft tissue sarcoma at a Dow chemical plant. Another study at a 2,4,5-T plant with potential exposure found no excess of cancer. A fourth study at a West Virginia TCP plant followed up on an accident that occurred 29 years earlier. No excess cancer was found but there was one case of STS (Zack and Suskind 1980). In a letter to the editor of Lancet, Honchar and Halperin (1981) combined these four studies and showed that three cases of STS had been observed in 105 deaths where only 0.07 STS deaths would have been expected. A followup letter identified a fourth case with potential exposure to TCP (Moses and Selikoff 1981). A study in New Zealand (Smith et al. 1984) identified six cases of STS potentially exposed to TCP, which yielded a significant odds ratio of 7.2. However, detailed work histories on the six cases found that only two had potential exposure to TCP and a third case was uncertain. The eighth study in Germany found seven cancers where only 4.1 were expected. However, all of the excess was found to be due to stomach cancer and there were no cases of STS.

The remaining studies, not considered above, are principally concerned with phenoxy acid herbicide exposure and not PCP. While some of these studies had positive results for STS and NHL (Lynge 1985, Olsson and Brandt 1981), others showed no association between these diseases and phenoxy herbicide exposure (Riihimaki et al. 1982, Wilklund and Holm 1986). Other studies looked at occupations to determine which ones had higher rates of cancer in the lymphopoietic system, but did not identify specific chemical exposures (Milham 1982, Petersen and Milham 1974, Milham 1983, Morton and Marjanovic 1984).

International Reviews of PCP

In 1982, the International Agency for Research on Cancer classified the evidence for carcinogenicity in humans for PCP as inadequate. They noted that in none of the studies examined "could exposure to pentachlorophenol be distinguished from

exposure to dioxins." A more recent review by the World Health Organization (WHO) (Environmental Health Criteria 71, 1987) concluded as follows:

> Epidemiological investigations and animal studies, conducted to date, are insufficient for an evaluation of the carcinogenicity of technical PCP.

In reference to the studies described above, the WHO report stated:

> Several epidemiological studies from Sweden and the USA have indicated that occupational exposure to mixtures of chlorophenols is associated with increased incidences of soft tissue sarcomas, nasal and nasopharyngeal cancers, and lymphomas. In contrast, surveys from Finland and New Zealand have not detected such relationships. The major deficiency in all of these studies appears to be a lack of specific exposure data.
>
> There are no conclusive reports of increased incidences of cancers in workers exposed specifically to PCP; however, there have not been any carefully conducted studies of a suitably exposed occupational group large enough to provide the necessary statistically power to identify an increase in cancer mortality. Furthermore, there are few occupational groups that have been exposed to a single chemical, such as PCP. Finally, the various levels of microcontaminants in different formulations make inferences to PCP in general difficult.

The section from the WHO report on PCP which reviews epidemiology studies related to carcinogenicity is attached. In my opinion, this attachment provides an excellent summary of the evidence and supports the conclusion that epidemiologic evidence is currently inadequate to support a conclusion of carcinogenicity for PCP.

The recent 1986 report by the International Agency for Research on Cancer found that there was limited evidence for carcinogenicity due to occupational exposure to chlorophenols but did not evaluate PCP or dioxins individually (see attached).

Conclusion

Conflicting evidence from studies and inadequate measures of specific exposure make it difficult to reach a conclusion on PCP. As the IARC reviews indicate, there does appear to be limited evidence that exposure to PCP, TCP, dioxins, and phenoxy herbicides either in combination with each other or with other chemicals or risks does contribute to excess human cancer. However, there is inadequate evidence to say that PCP by itself contributes to excess risk of human cancer.

Attachment

See pages 162-165

9. EFFECTS ON MAN

There are no studies or case reports of the effects of pure or purified PCP on human beings. Human exposure is nearly always to technical grades of PCP or Na-PCP in a variety of formulations. Reference to "PCP" in this section is to the technical grade.

9.1 Acute Toxicity - Poisoning Incidents

In man, the minimum lethal oral dose (LD_{LO}) of PCP has been estimated to be 29 mg/kg body weight (Ahlborg & Thunberg, 1980). Kozak et al. (1979) report that this value depends on the ambient temperature at the time of exposure, and the general health and renal competence of the individual. PCP is approximately 5 times more toxic than phenol (estimated oral LD_{LO} is 140 mg/kg body weight). The proportional lethality of these 2 chemicals (LD_{LO} phenol:LD_{LO} pentachlorophenol) in man is almost identical to the proportional lethality of the LD_{50} values for these substances in rats.

Numerous accidental or suicidal poisonings with commercial chlorinated phenols have been reported (Nomura, 1954; Menon, 1958; Blair, 1961; Bergner et al., 1965; Mason et al., 1965; Armstrong et al., 1969; Robson et al., 1969; Watanabe & Watanabe, 1970; Haley, 1977; Stevens & Richardson, 1979; Gjovik et al., 1981; Wood et al., 1983), and nearly 60% of these acute exposures have resulted in death. These cases together with the results of animal studies provide a relatively clear picture of the signs and symptoms of acute exposure to technical pentachlorophenol in man.

In contrast to the lower chlorinated phenols, PCP does not cause convulsions. Ataxia, mental and physical fatigue, headaches, dizziness, disorientation, anorexia, nausea, vomiting, dyspnoea, hyperpyrexia, tachycardia, and a rise in metabolic rate are common signs and symptoms of PCP poisoning. Most prominent are extreme weakness, elevated body temperature, and profuse sweating. Death is due to cardiac arrest and poison victims usually show a marked rigor mortis (Truhaut et al., 1952a,b; Nomura, 1954; Mason et al., 1965; Robson et al., 1969; Watanabe & Watanabe, 1970).

The gross pathology and histological lesions associated with acute exposures to PCP are generally consistent between laboratory animals and man. Oral exposures result in gastric and intestinal inflammation; however, the severity can depend on the carrier solvent and the presence of other chemicals (Menon, 1958; Stevens & Richardson, 1979). Pulmonary oedema and congestion have been reported after inhalation exposure, and occasionally oral exposure, if aspiration of ingested PCP has occurred. Splenomegaly, cardiomegaly, renal congestion, hepatomegaly, and hepatic congestion are also frequently observed at autopsy. Histologically, fatty degeneration, and necrosis in the centrilobular region of the liver have been reported, together with degenerative lesions in renal tubules (Gordon, 1956; Menon, 1958; Blair, 1961; Bergner et al., 1965; Mason et al., 1965; Robson et al., 1969).

It is generally agreed that the signs and symptoms of acute toxicity observed in animals and human beings exposed to chlorophenols result from the effects of the chlorophenol molecule itself rather than the microcontaminants, with hyperthermia, profuse sweating, and the rapid onset of morbidity and early death associated with acute chlorophenol exposures. These signs are not observed in animals exposed only to PCDD and PCDF; death is delayed by up to 3 weeks in acute exposure studies with these microcontaminants.

9.2 Effects of Short- and Long-Term Exposures

Most data on the effects of non-acute exposures to chlorophenols in man come from occupational studies. The clinical outcome of repeated exposure to PCP has been reviewed by Fielder et al. (1982), Williams (1982), and Exon (1984). The high rate of employee turnover and variation in the level and duration of exposure make it difficult to distinguish between subacute, short- and long-term exposures. For this reason, the following studies concerning occupational PCP toxicity in man are not separated on the basis of duration of exposure. Interpretation of these studies is frequently confounded by factors such as age, alcohol consumption, tobacco smoking, and other aspects of life style.

9.2.1 Occupational exposure

Clinical studies have identified a number of toxic effects of short-term PCP exposure in man, some of which are also characteristic of acute intoxication (section 9.1). Symptoms include irritation of the skin, mucous membranes, and respiratory tract, signs of chloracne, neurasthesia, depression, headaches, porphyria cutanea tarda, and liver and kidney functional changes (Fielder et al., 1982). These effects are discussed in greater detail in the following sections. Among workers employed in pressure-treating wood with PCP, insomnia and vertigo have also been reported (Arsenault, 1976).

9.2.1.1 Skin and mucous membranes

Workers exposed to airborne concentrations of 1 mg PCP/m^3 or more have reported painful nasal irritation

(Deichmann & Keplinger, 1981). Variations in the effect level are associated with the historical exposure of the individual to inhaled PCP. Workers accustomed to exposure may have a higher threshold for irritating effects and may tolerate up to 2.4 mg PCP/m^3 air.

As in the case of experimental animals (section 8), persons exposed to large amounts of technical PCP develop chloracne. Fielder et al. (1982) summarized published cases of chloracne in workers at PCP-manufacturing sites in Czechoslovakia, the Federal Republic of Germany, the United Kingdom, and the USSR. Kozak et al. (1979) reported other cases in Japan and the USA. The use of Na-PCP and Na-tetrachlorophenol has also resulted in chloracne in woodworkers (Behrbohm, 1959). Baxter (1984) reported chloracne and minor disturbances of the lipid metabolism among 40 workers from a PCP-manufacturing plant over a 3-year study period. However, the author concluded that the abnormalities observed were due to the PCDD contaminants and could not be attributed to the PCP preparation.

A survey of sawmill workers in British Columbia, Canada, carried out using self-administered questionnaires, indicated that dermatological and respiratory symptoms were significantly higher in a PCP/T_4CP exposed group than in the control group (Sterling et al., 1982). However, no reliable estimates of exposure were provided.

A more detailed study carried out in the same geographical area made use of personal monitors carried by individual workers to determine exposure levels of PCP and T_4CP (Embree et al., 1984). Blood and urine samples were collected and analysed, and health and employment histories were recorded by a trained interviewer. The workers were divided into 3 groups: a high exposure group handling wet-treated lumber; a medium exposure group with no manual contact with treated lumber; and a control group with no exposure to PCP, T_4CP, or related chemicals. Exposure concentrations for PCP are shown in Table 20. The authors reported a correlation between exposure levels and serum- and urine-chlorophenol concentrations. However, they were unable to substantiate the findings of Sterling et al. (1982) of increased incidences of respiratory and dermatological health problems in workers exposed to PCP/T_4CP.

A study on 113 employees at a wood-treatment facility found that workers were in good health overall, but with a greater than expected prevalence of skin pustular eruptions (Flickinger & Lawrence, 1982). Airborne exposures were less than 0.03 mg/m^3.

Klemmer et al. (1980) reported the results of a 7-year study on 400 Hawaiians, many of whom had long-term, high-level exposure to PCP. Concentrations of PCP in blood-serum far

exceeded the 1.05 mg/litre reported in Arsenault's (1976) study; workers treating wood in open-vats had a mean level of 3.78 mg PCP/litre, pressure-tank workers 1.72 mg/litre, and farmers and controls 0.25 and 0.32, mg/litre, repectively. After considering data on 189 individuals of the total of 400, Klemmer et al. (1980) concluded ... "despite high chronic exposures to PCP, individuals in the wood treatment group of workers had not undergone any serious health effects from this exposure. The only evidence of tangible health effects, part of which could have been caused by exposures to chemicals other than PCP, were the low-grade infections or inflammations of the skin and subcutaneous tissue, of the protective membrane of the eye, and of the mucous membrane of the upper respiratory tract. No specific long-term effects could be elicited in the exposed group".

9.2.1.2 Liver and kidney

Indications of significant liver damage have not been found. Elevations in circulating levels of some hepatic enzymes have been reported; however, they are usually transitory and do not suggest severe functional impairment (Kozak et al., 1979; Fielder et al., 1982). These findings are consistent with those reported in studies on rats with short-term exposure to technical PCP (section 8.2).

Kidney functional changes resulting in reductions in creatinine clearance and resorption of phosphorus have been reported by Begley et al. (1977). The spontaneous normalization in kidney function during a 3-week non-exposure period indicated that this effect on kidney is largely reversible.

Jirasek et al. (1974) reported the clinical signs exhibited by workers who suffered intoxication during the manufacture of Na-2,4,5-T_3CP and Na-PCP. These workers displayed abnormal porphyrin metabolism (increased uroporphyrin and delta-aminolevulinic acid in urine, UV fluorescence of liver), and indications of hepatotoxicity (liver enlargement, mild steatosis or fibrosis of liver tissue, elevated levels/activities of bilirubin, serum-glutamic-oxaloacetic transaminase and serum-glutamic-pyruvic transaminase).

Mild dysfunction of the liver has been reported among Soviet workers engaged in the production of Na-PCP (Vinogradova et al., 1973) including, for example, a reduced ability to synthesize protein.

Zober et al. (1981) reported a study on a small group of woodworkers involved in the application of PCP. The average concentration of PCP in the air at the time of the study was 2.4 µg/m^3, the average exposure period for the cohort was 3 years and the average levels in urine and serum were 46 µg PCP/g creatinine and 1 µg/ml, respectively. Elevations in

serum-aminotransferases and α-glutamyl transpeptidase were observed; however, confounding factors of sample size and alcohol consumption prevented the formation of any conclusions concerning the effects of PCP on liver function.

As part of a similar study (Embree et al., 1984) (section 9.2.1.1), Enarson et al. (1986) found that serum levels of creatinine, bilirubin, glutamic oxaloacetic transaminase, and alkaline phosphatase in sawmill workers exposed to a mixture of Na-PCP and Na-tetrachloropenate did not differ from those measured in the controls.

9.2.1.3 Blood and the haematopoietic system

Aplastic anaemia has been associated with PCP use (Roberts, 1981); however, sample sizes were small and exposures were not quantified. Incidental references to haematological changes in isolated workers in a German chemical plant manufacturing PCP and HCB were made by Baader & Bauer (1951). Effects on the haematopoetic systems of animals have been reported in studies with PCDD contaminated PCP (Johnson et al., 1973; Knudsen et al., 1974; McConnell et al., 1980) and 2,3,7,8-T_4CDD (Allen & van Miller, 1978). Wood (1980) examined the relationship between anaemias (with no established cause) in 128 Canadian woodworkers and exposure to PCP. No significant differences between the haematology values of exposed and unexposed workers were found. Wood (1980) concluded that PCP exposure did not appear to have any significant effects on the prevalence of anaemias in these woodworkers.

In a companion report to that of Embree et al. (1984) (section 9.2.1.1), Enarson et al. (1986) found few exposure effects in sawmill workers exposed to Na-PCP and Na-tetrachlorophenate. Most blood variables monitored were within normal ranges and did not differ between exposed and unexposed workers. A significant decrease in haematocrit and an increase in haematuria were reported in workers handling treated lumber, but not in workers exposed solely through inhalation.

Urinary-PCP values (2.2 mg/litre) reported by Shirakawa et al. (1959) in primarily female workers at several rubber manufacturing factories indicated that these workers were exposed to high levels of Na-PCP (presumably technical grade). Increased blood sugar levels, decreased blood pressure, and dermatoses were reported, but no worker was reported to have missed work through the effects of PCP exposure.

9.2.1.4 Nervous system

Investigation of clinical reports of neuropathy did not indicate any overt significant signs of peripheral neuropathy in a recent study on PCP workers (Triebig et al., 1981). Sensory nerve conduction velocity was significantly reduced in exposed workers, but was not correlated with urinary levels of PCP.

Skin, blood, and neurological disorders have been reported among workers at a Na-PCP manufacturing factory in the USSR (Vinogradova et al., 1973). The workers were exposed to air levels of PCP and Na-PCP ranging between 0.03 and 1 mg/m^3. Readings for 21% of the air samples ranged from 0.21 to 1 mg/m^3, exceeding the maximum permissible concentration in the USSR of 0.1 mg/m^3. Washings taken from clothing and exposed skin yielded PCP and Na-PCP values of 21 - 212 mg/dm^2 and 7.6 - 75 mg/dm^2, respectively. However, concentrations of hexachlorobenzene were also 2 - 3 times higher than the maximum permissible concentration (0.9 mg/m^3) set in the USSR and may have had an influence on the disorders reported.

9.2.1.5 Immunological system

McGovern (1982) suggested that man may suffer an immunotoxic response to phenolic compounds, including chlorinated phenolic compounds. Marked T-cell suppression has been observed in several patients exposed to phenols. Zober et al. (1981) reported that some woodworkers exposed to PCP displayed increased concentrations of immunoglobulins, though this increase was not correlated with exposure. Ning (1984) reported that workers exposed to PCP showed significant decreases in IgG and IgA immunoglobulins. The results of animal studies, while indicating that PCP is not strongly immunotoxic, confirm that PCP exposure can lead to immunological changes (section 8.7).

9.2.1.6 Reproduction

There are few published data on the effects on male or female reproductive capacity of short- or long-term exposure to chlorophenols. Schrag & Dixon (1985) classified PCP as "agents with inconclusive effects" on male reproduction. Corddry (1981) investigated pregnancy outcomes in women married to sawmill workers in Canada. Analysis of data from 43 women, with a total of 100 pregnancies, did not reveal any significant differences in the pregnancy outcomes of women living with "exposed" compared with "unexposed" men. There was a slight trend towards more adverse pregnancy outcomes in

the exposed group, but this trend disappeared when the alcohol consumption was considered as a confounding factor. Male fertility was not studied.

9.2.1.7 Cytogenetic effects

There is no evidence to indicate that PCP or other chlorophenols exert cytogenetic effects on human cells. A study of circulating lymphocytes in a small group of workers in Idaho, USA, indicated that individuals exposed to PCP had a slightly higher rate of chromosome breakage than controls, but the increase was not statistically significant (Wyllie et al., 1975). Bauchinger et al. (1982) reported that lymphocytes from 22 workers in a PCP-manufacturing factory had a significantly elevated number of chromosomal aberrations (dicentrics and acentrics). These data are not adequate for assessing the cytogenetic effects of PCP in man.

9.2.1.8 Carcinogenicity

Only 2 reports associating exposure to PCP specifically with human cancer are available. Greene et al. (1978) suggested that there was an association between exposure to wood treatment chemicals (PCP) and the incidence of Hodgkin's disease, on the basis of a family case history (2 of 4 siblings contracting the disease were occupationally exposed to PCP) and a relative risk (RR) of 4.2 (from death certificates, in the USA) for persons employed in carpentry and lumbering. Bishop & Jones (1981) reported 2 cases of non-Hodgkin's lymphoma in PCP workers in the United Kingdom; both cases were associated with chloracne. These data are not adequate for the identification of a positive and statistically sound correlation between lymphomas and PCP.

However, there is some epidemiological evidence that exposure of workers to mixtures of chlorophenols, but not specifically PCP, increases their risk of developing soft-tissue sarcomas and lymphomas. Considerable debate has ensued since the initial report of chlorophenol-related cancer by Hardell (1977) and the subsequent reports of Hardell and his co-workers in Sweden. Case control studies of soft-tissue sarcoma patients in Sweden indicated a relative risk (RR) of 6.6 for those "exposed" to chlorophenols compared to those who did not appear to have been exposed (Hardell & Sandström, 1979). Individuals exposed to 2,4,5-T had an RR of 5.8. A follow-up study in another area of Sweden involving 330 subjects tended to confirm the overall risk of soft-tissue sarcomas in individuals exposed to phenoxyacetic acids and chlorophenols (Erickson et al., 1981). The authors reported RR values of 6.8 for all phenoxyacetic acid exposures and 3.3

for chlorophenol exposures. Exposures to phenoxyacetic acids, assumed by the authors to be free of PCDD and PCDF impurities resulted in an RR of 4.2. Hence, Erickson et al. (1981) concluded that impurities in these chlorinated phenols and phenoxyacids were probably not the sole cause of the elevated cancer rates reported, though they might have played a role in this apparent carcinogenicity.

The validity of the assumption that 2,4-D is free of PCDD and PCDF "impurities" is questionable inasmuch as 2,4-D has been found to be contaminated, in one case, with H_6CDD (IARC, 1977) and, in another, with T_4CDF (Norström et al., 1979). However, it is reasonable to assume that the contamination of the phenoxy-acid herbicides 2,4-D, MCPA, necoprop, and dichlorprop with PCDDs and PCDFs is very low.

Hardell et al. (1981) have also applied their case-referent technique to malignant lymphoma patients (both Hodgkin's disease and non-Hodgkin's lymphomas) in Sweden. They reported RR values in individuals exposed to phenoxy acids, chlorophenols, and other organic solvents to be 4.8, 4.3, and 2.4, respectively. The RR value for high-level exposure to chlorophenols was as high as 8.4. A possible explanation for the lymphomas may rest with the immunological effects (in animals) of the PCDD contaminant, 2,3,7,8-T_4CDD. Some immunosuppressive chemicals have been shown to cause an increase in histiocytic lymphomas in man (Hardell, 1979).

In response to criticisms that recall bias was a significant factor in his studies, Hardell (1981a) applied his case-control method to study colon cancer, a disease that correlates positively with asbestos exposure, but not with chlorophenol exposure. His findings indicated that recall and observer bias were negligible in his earlier studies, since colon cancers correlated significantly only with asbestos exposure, and not with phenoxy acids or chlorophenols exposure. Hardell et al. (1982) also used their technique to demonstrate an increased risk of nasal/nasopharyngeal cancer (RR = 7) among workers exposed to chlorophenols.

Others have not found associations between cancer and human exposure to chlorophenols. In contrast to Hardell et al. (1982), Tola et al. (1980) did not find any relationship between nasal cancer and chlorophenol exposure in Finnish workers. A case-control study in New Zealand (Smith et al., 1984) did not reveal a higher incidence of soft-tissue sarcoma in workers exposed to chlorophenols. Gilbert et al. (1983) conducted a cohort study in Hawaii with workers employed in the wood-treatment industry, in which chromated copper-arsenate, tributyl tin oxide, and PCP were used. They did not find any adverse health effects, but urinary-PCP levels were higher in the exposed group.

In a recent Swedish study on the risks of soft-tissue sarcoma, a cohort of 354 620 men employed in agriculture or forestry was compared to a reference cohort of 1 725 845 men employed in other industries during the period 1961-79 (Wiklund & Holm, 1986). A relative risk of 0.9 (95% confidence interval 0.8 - 1) was found. When the cohort was divided into 6 subgroups, based on assumed exposure to phenoxy acid herbicides, no significant differences in relative risks were found. Despite the increased use of phenoxy acid herbicides in Sweden between 1947 and 1970, no time-related increase in the relative risk of soft-tissue sarcomas was found. The authors concluded that their study did not confirm the results of Hardell (1981b). However, they pointed out that only a small percentage of their total cohort of agricultural and forestry workers in Sweden were possibly exposed to phenoxy acid herbicides (15%) and chlorophenols (2%). Hence, a relative risk of 1.5 observed for sarcomas in these groups, as defined in their study, would be equivalent to an actual 6-fold risk from exposure to these compounds. Thus, it is unlikely that their study would have detected a true increased risk from such exposures, if the risk were less than 6-fold.

Pearce et al. (1986) studied 82 cases of non-Hodgkin's lymphoma in New Zealand with 168 cancer controls and 228 general population controls. They obtained statistically significant odds ratios (OR) of 2.7 and 2, respectively, for workers in the pelt department of meat works with potential exposure to 2,4,6-trichlorophenol and for workers who carried out fencing with potential exposure to both 2,4,6-trichlorophenol and pentachlorophenol. Further examination of the data revealed that: 2 of the 4 lymphoma cases who worked in the pelt department were possibly not exposed to TCP; that a significant proportion of the fencing workers also worked in the meat works; and that no significant risk was found for exposure to chlorophenols as a group. Pearce et al. (1986) concluded that the excess risk observed in these 2 groups of workers might not be due to chlorophenol exposure. In a second study, Pearce et al. (in press) added other lymphoma cases to their previous study sample and found similar relationships. They concluded that, though an association with chlorophenol exposure was unlikely, it could not be ruled out. They proposed that alternative hypotheses, such as exposure to oncogenic zoonotic viruses should be considered to explain their findings.

While there is some evidence that chlorophenols, and in particular trichlorophenols, are associated with elevations in the rates of certain cancers in exposed individuals, there is no clear-cut dose-effect relationship. "Exposure" has been loosely defined in most studies and no quantitative assessments have been published. In addition, it has been suggested that, since other environmental chemicals such as hexachlorobenzene, pentachlorobenzene, and pentachloronitrobenzene, are metabolized to PCP in animals and man, there is no necessary relationship between PCP concentrations in body fluids and exposure to PCP (Renner & Mücke, 1986). Other factors that could have a bearing on the conflicting reports of chlorophenol exposure and cancer incidence include differences in study methods and the diagnosis of soft-tissue sarcoma cases, and inadequacies in death-certificate data. The results of epidemiological studies, currently underway in several countries, could confirm or refute the association between chlorophenol exposure and human cancer (Fingerhut et al., 1984).

9.2.1.9 Other systems

It is not unusual to find few or no signs of toxicity in workers with long-term exposure to low levels of PCP or Na-PCP. Arsenault (1976) reported a prospective clinical evaluation of 21 PCP workers involved in the pressure-treatment of wood, who had been exposed for an average of 9 years and had elevated blood-serum levels of PCP (on average, 1.05 mg/litre, versus 0.1 mg/litre in controls). The only significant clinical findings in the pressure-treatment workers were vertigo and insomnia. Arsenault (1976) also provides information obtained from the health records of 1330 workers in a large wood-processing company. From 1961 to 1971, only 26 cases of health problems related to PCP use and exposure were identified; however, it is probable that this is an underestimate because of under-reporting.

Similarly, in a cohort study comparing 88 wood-treatment workers with 61 controls (Gilbert et al., 1983), no significant effects of exposure (by history or physical examination) to wood preservatives, including PCP, were reported on: skin or mucous membranes of the eyes or upper respiratory tract; mental status; cardiovascular, gastrointestinal, genitourinary, or neuromuscular systems; or reproduction. In the accompanying historical perspective study, calculations of age-specific deaths rates from all causes for 125 workers, over 21 years, showed that observed rates were similar to, or lower than, those expected.

9.2.2 General population exposure

References to non-occupational exposure to chlorophenols, for example from wood in homes, confirm that pulmonary, and, to a lesser extent, dermal exposure to PCP can produce symptoms of poisoning similar to those documented in occupational settings. These studies (section 5.2) may be of

significance in as much as they identify new sources of exposure; however, they add little to the toxicology data base for PCP. Concentrations of PCP in the indoor air of homes and in the urine and serum of their residents are elevated relative to those in the general population (Table 21). The limited effects of this exposure are considered briefly here.

In cases where individuals display symptoms of PCP intoxication, usually as a result of the application of PCP in the interior of houses, typical acute symptoms are observed, but other parameters (haematological, biochemical) may be normal. Sangster et al. (1982) outlined case histories of 3 families in PCP-treated houses who reported experiencing one or more of the following signs or symptoms: generalized itching or burning dermatosis, nausea, vomiting, decreased appetite, headache, dizziness, and fatigue. Haematological, urinary, and biochemical parameters were unaffected by exposure. Similarly, a young girl poisoned by bathwater stored in a PCP-contaminated tank displayed fever, intermittent delirium, rigors, acidosis, and elevated urine levels of ketones and amino acids, but her respiratory rate and other clinical symptoms were normal (Chapman & Robson, 1965). However, longer-term exposure may have more profound effects. Brandt et al. (1977) reported that exposure to PCP for several years in the air of a treated wooden house resulted in liver damage and elevated activities of several liver enzymes in a German woman (Ahlborg & Thunberg, 1980).

A Sacramento woman lost weight, and complained of weakness and tightness in the chest after the interior of her house was treated with PCP (Anon, 1970).

Krause & Englert (1980) examined several medical and laboratory parameters in 250 persons with elevated PCP exposure (section 5.3). No clear relationship could be found between elevated concentrations of PCP in the urine and biochemical parameters related to the liver, kidney, and blood. However, significantly more complaints of headache, fatigue, tonsillitis, hair loss, and bronchitis were reported in persons with PCP exposure. Because the signs and symptoms usually reported in connection with indoor PCP exposure are relatively non-specific, thye cannot be definitively ascribed to PCP. However, the observation that many symptoms disappeared when exposure was reduced (by improving ventilation, sealing wood surfaces, or leaving the premises) is indicative that PCP or the substances included in the formulated product might well be the causative agents. The persistence of some biochemical and dermatological signs, similar to those reported in the work-place, is a further indication that PCP may induce subacute effects in these exposed persons.

In general, however, no adverse effects can be ascribed to the low ambient concentrations of PCP resulting from the diffuse sources to which most people are exposed.

10. EVALUATION OF HUMAN HEALTH RISKS AND EFFECTS ON THE ENVIRONMENT

10.1 Evaluation of Human Health Risks

In this subsection, PCP and Na-PCP are referred to as PCP.

10.1.1 Occupational exposure

10.1.1.1 Exposure levels and routes

Occupational exposure to technical PCP mainly occurs through inhalation and dermal contact. Virtually all workers exposed to airborne concentrations take up PCP through the lungs and skin. In addition, workers handling treated lumber or maintaining PCP-contaminated equipment would be exposed dermally to PCP in solution, and may take up from one-half (based on urinary-PCP concentrations) to two-thirds (using serum levels) of their total PCP burden through the skin.

The actual concentrations to which workers have been exposed are seldom measured but, where they have been monitored, they are predictably high. Airborne levels at PCP-production and wood-preservation facilities have ranged from several $\mu g/m^3$ to more than 500 $\mu g/m^3$ in some work areas. The outer layer of treated wood can contain up to several hundred mg/kg, though levels are usually less than 100 mg/kg.

These exposures result in concentrations of PCP in the serum and urine that are 1 - 2 orders of magnitude higher than those in the general population without known exposure. Mean/median urinary-PCP concentrations of approximately 1 mg/litre are typical for workers in contact with PCP, compared with urinary concentrations of approximately 0.01 mg/litre for the general population (section 5.4).

Automated processes and the use of closed systems have greatly reduced worker exposure in large-scale manufacturing and modern wood-treatment factories and sawmills. Other improvements in industrial hygiene can significantly reduce exposure, as measured by lower urinary-PCP concentrations.

10.1.1.2 Toxic effects

Past use of PCP has affected workers producing or using this chemical. Chloracne, skin irritation and rashes, respiratory disorders, neurological changes, headaches, nausea, weakness, irritability, and drowsiness have been documented in exposed workers. Work-place exposures are to technical PCP, which usually contains mg/kg quantities of

microcontaminants, particularly H_6CDD. Subacute effects such as chloracne and potential subchronic and chronic effects such as hepatotoxicity, fetotoxicity, and immunotoxicity (as reported in animal studies) are probably mainly caused by microcontaminants. However, the PCP molecule itself appears to play a role in the pathology of the last 3 effects and is likely to be wholly responsible for the reports of skin and mucous membrane irritation, hyperpyrexia and, in severe cases, coma and death. The toxicity of pure or purified PCP has not been evaluated for human beings, because human exposure has usually been to technical PCP.

Investigations of biochemical changes in woodworkers with long-term exposure to PCP have failed to detect consistently significant effects on major organs, nerves, blood, reproduction, or the immune system. However, the statistical power of these studies has been limited as a result of the small sample sizes used. Overall, the body of research suggests that long-term exposure to levels of PCP encountered in the work-place is likely to cause borderline effects on some organ systems and biochemical processes.

Some epidemiological studies from Sweden and the USA have revealed an association between exposure to mixtures of chlorophenols, especially 2,4,5-T_3CP, and the incidences of soft-tissue sarcomas, lymphomas, and nasal and nasopharyngeal cancers. Other studies have failed to detect such a relationship. None of these studies has managed to address the effects of exposure to PCP itself.

Animal studies designed to assess the carcinogenicity of PCP and reported to date have been negative. Carcinogenicity bioassays with one other chlorophenol (2,4,6-T_3CP) and a mixture of two H_6CDD congeners found in PCP have been positive. Hence, the carcinogenic effects of long-term exposure of animals to technical PCP are not clear.

10.1.1.3 Risk evaluation

It is clear that the levels of PCP found in work-places have adversely affected some aspects of the health of exposed workers. Potentially the most deleterious effect of technical PCP is on the fetus, and pregnant women should avoid exposure, whenever possible. There is limited evidence that PCP may cause hepatotoxicity, neurological disorders, and effects on the immune system. No convincing data for or against a carcinogenic link exists.

The National Academy of Sciences (1977) calculated an acceptable daily intake (ADI) for PCP of 3 µg/kg body weight per day. This ADI is based on data from a feeding study on rats and a 1000-fold safety factor. The results of long-term

studies indicate that the no-observed-adverse-effect level for rats is below 3 mg/kg body weight per day (section 8.2). A recent human study has shown that the steady-state body burden is 10 - 20 times higher than the value extrapolated from rat pharmacokinetic data, suggesting that caution should be applied when extrapolating directly from the rat model to man. Furthermore, the US ADI was not based on an inhalation study, and does not account for the possibly greater toxicity of PCP via inhalation, as indicated by animal studies (sections 8.1 and 8.3). Hence, the safety factor of 1000 used to derive this ADI value is by no means too conservative. The intake for a 60-kg adult exposed to concentrations of PCP at the ADI level would be 180 µg/person per day.

A rough estimate of occupational exposure alone can be calculated, assuming a moderate breathing rate of 1.8 m^3/h for a 60-kg worker, 100% uptake of all inhaled PCP (which takes some account of the often significant dermal uptake), and an 8-h working shift per day, 5 days per week. Hence, an exposure to 500 µg PCP/m^3 per shift (section 5.2) would result in an average daily PCP intake of approximately 5000 µg/person per day, averaged over the entire week. Under these circumstances, the ADI level proposed by the National Academy of Sciences is significantly exceeded, even when consideration is given to the effects of intermittant exposures during the working week and the high health status assumed for workers.

There is a clear need for a reduction in occupational exposure to PCP. Emphasis must be placed on reducing airborne concentrations at production and wood-treatment facilities, as well as dermal contact with solutions containing PCP. In addition, reductions in the concentrations of microcontaminants in technical PCP, particularly PCDDs and PCDFs, would reduce the potential for expression of several effects and would better protect the health of workers in these industries.

10.1.2 Non-occupational exposure

10.1.2.1 Exposure levels and routes

Domestic use of products containing technical PCP, especially the indoor application of wood preservatives and paints based on PCP, has led to elevated concentrations of PCP in indoor air. Indoor exposures have been well documented in houses constructed with PCP-treated wood, or in which interior wood panels or boards have been treated with PCP. PCP concentrations in indoor air can be expected to reach 30 µg/m^3 during the first month after treatment. Considerably higher levels, up to 160 µg/m^3, have been reported in houses with concomitant poor indoor ventilation. Even higher concentra-

tions can be encountered immediately after do-it-yourself applications of PCP-containing wood preservatives.

In the long term, values of between 1 and 10 µg/m³ are typical, though higher levels, up to 25 µg/m³, have been found in rooms treated one to several years earlier. Indoor air concentrations are influenced by a variety of factors, e.g., intensity of treatment, solvents and additives involved, species of wood treated, environmental conditions, and time elapsed since treatment.

In many cases, levels of PCP in the serum and urine of people exposed in the home overlap those for occupationally exposed persons; but, on average, urine-PCP levels are approximately 0.04 mg/litre for non-occupationally exposed persons.

In the long term, exposure to PCP in treated buildings continuously decreases, because of the high volatility of PCP. Because of their lower vapour pressure, the volatilization of PCDDs and PCDFs from the wood surface is much slower than that of PCP. Hence, these microcontaminants are emitted at a low rate, but over a longer period of time. Long-term exposure to these lipophilic contaminants is likely to lead to accumulation of PCDDs and PCDFs in fatty body tissues.

As a result of regulations restricting the use of PCP, and also changing use patterns, indoor exposure to PCP is probably declining in most developed countries.

10.1.2.2 Risk evaluation

Assuming a daily respiratory volume of 20 m³/adult and 100% uptake of all inhaled PCP (a worst case that takes some account of dermal uptake), the exposure of persons living in PCP-treated buildings, shortly after treatment, or, in some cases, after a long period of time, could be expected to range between 600 and 3200 µg/person per day. Long-term exposure to concentrations of 1 - 25 µg PCP/m³ could result in a daily PCP intake of 20 500 µg/person per day. The median value of 5 µg/m³ reported from a survey of 104 homes (section 5.3) corresponds to a daily PCP uptake of 100 µg/person per day. Other potential sources of exposure to PCP including food, drinking-water, and consumer products contribute further to PCP uptake (section 10.1.3.1).

The indoor air data suggest that, at least during the first weeks following indoor treatment, and occasionally for quite prolonged periods of time, the ADI level of 180 µg/person per day is significantly exceeded. Under these circumstances, there is a potential health risk. This conclusion is supported, in part, by reports of signs and symptoms similar to those in persons occupationally exposed to PCP (dermatosis, nausea, headache, dizziness, fatigue). These signs and symptoms are most likely associated with the effects

of the PCP molecule and, in some cases, the solvents associated with the wood treatment chemicals used. The long-term significance of exposure to low levels of PCDDs and PCDFs and their accumulation in human tissues is not entirely clear; however, at least 2 isomeric groups of the PCDDs family are carcinogenic for animals. Animal data indicate that low concentrations of PCP in biological tissues or body fluids do not signify an absence of biologically active PCDDs and PCDFs.

It is worth noting that exposure in the home is frequently for longer periods of time than exposures in the work-place and can affect subpopulations potentially at greater risk than workers, for example, children, the elderly, pregnant women, or those with an existing adverse health condition.

10.1.3 General population exposure

10.1.3.1 Exposure levels and routes

Exposure of the general population to low levels of PCP is common. PCP has been found in air, food, water, and other consumer products. Biotransformation of some chlorinated hydrocarbons (e.g., lindane, hexachlorobenzene) to PCP also contribute to the human body burden.

The ambient air in urban areas typically contains several ng/m³, while concentrations in less developed areas are roughly an order of magnitude lower (section 5.1.1).

Drinking-water concentrations of PCP rarely exceed several µg/litre, even in highly industrialized regions, and most are less than 1 µg/litre (section 5.1.5).

Fruits, vegetables, and other produce usually contain much less than 10 µg/kg, but may on occasion exceed this level. Most meats contain similar concentrations of PCP (< 10 µg/kg) but, a few samples, particularly liver, can contain over 100 µg/kg. Fish skeletal muscle typically contains PCP levels of 4 µg/kg or less. Overall estimates of PCP intake from all foods, based on total diet samples in the USA and the Federal Republic of Germany, are remarkably similar, i.e., up to 6 µg/person per day (section 5.1.5).

PCP is also present in a wide variety of consumer products, including veterinary supplies, disinfectants, photographic solutions, fabrics, home-care products, and pharmaceutical products. No calculated estimates of the contribution made by consumer products to overall exposure to PCP are available.

10.1.3.2 Risk evaluation

On the basis of the PCP levels in the various compartments, the overall exposure of an average person without known

specific exposure can be estimated to be approximately 6 µg/person per day from food, 2 µg/person per day from drinking-water, and 2 µg/person per day from the ambient air. Thus, the total exposure of the general population could be approximately 10 µg/person per day (exclusive of exposure to consumer products), which is far below the intake based on the ADI proposed by the US National Academy of Science of 180 µg/person per day. On the basis of available data, this exposure is not likely to constitute a health hazard.

However, the diffuse contamination of the environment with technical PCP must be considered as an important source of environmental PCDDs and PCDFs.

10.2 Evaluation of Effects on the Environment

The widespread use of technical PCP and its physical and chemical properties (water solubility, n-octanol/water partition coefficient, volatility) lead to ubiquitous contamination of air, soil, water, sediments, and environmental organisms.

Depending on the soil type, PCP can be very mobile, potentially leading to contamination of groundwater and hence, of drinking-water. Because applications in agriculture have been reduced, soil contamination will, for the most part, be confined to treatment areas.

Photodecomposition and biodegradation processes may not be adequate to eliminate PCP from the different compartments. Unfavourable temperature, pH, and other environmental conditions may retard degradation of PCP allowing it to persist in the environment. Biological decomposition may also be limited in waste-treatment factories resulting in high concentrations in the final effluents. PCP has also been used in aquatic environments as a molluscicide and an algicide.

PCP concentrations in surface waters are usually in the range of 0.1 - 1 µg/litre, though much higher levels can be found near point sources or after accidental spills (section 5.1.2).

PCP is highly toxic for aquatic organisms. Apart from very sensitive or resistant species, there is apparently no difference in the sensitivity to PCP of the different taxonomic groups (section 7.2). Invertebrates (annelids, molluscs, crustaceans) and fish are adversely affected by PCP concentrations below 1 mg/litre in acute toxicity tests. Sublethal concentrations are in the low µg/litre range.

As little as 1 µg PCP/litre can have adverse effects on very sensitive algal species. Moreover, low concentrations (µg/litre) may lead to substantial alterations in community structures, as seen in model ecosystem studies.

10.3 Conclusions

In this subsection, PCP and Na-PCP are referred to as PCP.

1. Human exposure to PCP is usually from technical products that contain several toxic microcontaminants, including PCDDs and PCDFs.

2. The acute health effects of exposure to high concentrations of technical PCP are generally the result of the biological action of the PCP molecule itself. Sub-chronic effects and the effects of long-term exposure to technical PCP are most probably largely related to the biological action of the PCDDs and PCDFs.

3. A dose-effect relationship for the acute or chronic toxicity of technical PCP for human beings cannot be derived from available data. Derivation of this relationship is confounded by variations in individual susceptibility, social and environmental influences, concomitant exposure to other chemical substances, a lack of accurate exposure estimates, and inadequate toxicity data.

4. Occupational exposure to technical PCP can lead to adverse health effects.

5. Non-occupationally exposed persons (using products containing technical PCP and/or those living in buildings treated with wood preservatives or paints containing PCP) can be exposed to concentrations of PCP in air that can have adverse health effects.

6. The exposure of the general population to diffuse sources of PCP (via food, drinking-water, ambient air, consumer products, chlorinated compounds that can be metabolized to PCP) is very low and, on the basis of available data, it is not likely to constitute a health hazard.

7. Epidemiological investigations and animal studies, conducted to date, are insufficient for an evaluation of the carcinogenicity of technical PCP. Uncertainties also exist over the genotoxic and fetotoxic effects of technical PCP.

8. PCP is rather persistent, quite mobile, and found in all environmental compartments. At the higher concentrations found in the surface water near point sources or discharges (mg/litre), aquatic life is adversely affected. Ambient concentrations of PCP commonly found in surface waters (0.1 -

1 µg/litre) may adversely affect very sensitive organisms and may lead to alterations in the ecosystem.

9. Use of technical PCP and its improper disposal (landfill and low-temperature combustion) can contribute significantly to the contamination of the environment with PCP, PCDDs, and PCDFs.

11. RECOMMENDATIONS

In this section, PCP and Na-PCP are referred to as PCP.

11.1 Environmental Contamination and Human Exposure

(a) Concentrations of microcontaminants in technical PCP, especially PCDDs and PCDFs, must be reduced by improving the quality in production processes.

(b) There is a need for specification of a technical PCP.

(c) Disposal of technical PCP and associated waste should preferably involve high-temperature combustion or, where this is not possible, the use of secure land-fill sites.

(d) In order to reduce contamination of surface waters and the hazards for the aquatic ecosystem, manufacturers and users of technical PCP should prevent releases into the environment.

(e) Protective measures should be provided for non-target aquatic organisms in cases where PCP is used as molluscicide or algicide.

(f) Occupational exposure to technical PCP must be reduced to a minimum. Reduction in exposure can be achieved by:

- explicit product labelling;
- employee instruction on product handling;
- lowering airborne concentrations; and
- use of effective protective equipment.

(g) Industries handling technical PCP should ensure adequate routine monitoring and health surveillance of all potentially exposed employees.

(h) The indoor application of PCP-based wood preservatives and wood stains and the use of PCP-treated wood products in the interior of buildings should cease.

(i) The availability and use of consumer products containing PCP should be reduced and controlled.

(k) The following commercial uses of PCP-based products should be eliminated, in order to reduce contamination of food and the environment:

- application as wood preservatives on wooden food containers, horticultural lumber, wood and tools in mushroom houses, and above-ground interior wood of farm buildings;
- application during the curing of hides;
- application as a herbicide or soil sterilant;
- application as a slimicide in wood pulp and paper operations; and
- application as a molluscicide in surface water if another control chemical or measure is available that is less toxic for man and the aquatic ecosystem.

11.2 Future Research

11.2.1 Human exposure and effects

(a) Reliable estimates of human absorption of airborne PCP via the lung and skin are required.

(b) The importance of the biotransformation of hexachlorobenzene and related compounds as contributors to human body burdens of PCP needs to be quantified.

(c) It is necessary to determine the intake and accumulation by human beings of the lipophilic microcontaminants (especially the PCDDs and PCDFs) resulting from exposure to technical PCP.

(d) Development of reliable estimates of biochemical and reproductive no-observed-adverse-effect levels is desirable.

(e) Studies on persons occupationally exposed to technical PCP should be conducted using a large enough cohort or sufficient numbers of cases to provide the statistical power necessary to determine the relationships between exposure to PCP and morbidity, mortality in general, and cancer. Such studies should include quantitative estimates of concentrations and duration of exposure to PCP, whereever possible.

11.2.2 Effects on experimental animals and in vitro test systems

(a) New data on the carcinogenicity of technical and pure PCP in both sexes of 2 mammalian species are required.

(b) There is a need for a long-term inhalation study on the effects of both technical and pure PCP.

(c) Studies should be undertaken to clearly determine the teratogenic effects of pure and technical PCP. The potential effects of PCP induced maternal hyperthermia on embryological development and fetal growth warrant investigation.

(d) More research on the genotoxic and mutagenic activity of pure and technical PCP is required.

11.2.3 Effects on the ecosystem

(a) Studies are needed to clarify the fate of sediment-bound PCP and its effects on the environment.

(b) Studies of the effects of long-term, low-level exposure on fresh-water aquatic communities are required to establish no-observed-adverse-effect levels.

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Environmental Health Criteria 71

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and group C was 'known to be exposed' (with chloracne). Fifty cells were examined from each subject. Chromosomal aberrations (in preparations from 48-h cultures) were scored in 124 individuals (31 in group A, 55 in group B, and 38 in group C). SCEs were scored in 40 individuals (8 in group A, 20 in group B, and 12 in group C). No significant difference was found between the groups either as regards chromosomal damage or SCEs. The mean number of chromosomal aberrations per cell was 0.0755 in group A, 0.0807 in group B and 0.0858 in group C. The mean number of SCEs per cell was 8.0 in group A, 8.5 in group B and 8.1 in group C. [The Working Group noted that the number of aberrant cells was not given nor was the type of aberration described.]

3.3 Case reports and epidemiological studies of carcinogenicity to humans

(*a*) *Cohort studies*

Mortality was reported for a small cohort of 204 workers involved in the manufacture of 2,4,5-T between 1950 and 1971 (Ott *et al.*, 1980) and followed up to 1976, where reported exposures included 2,4,5-trichlorophenol. There were five deaths (7.0 expected) among those with one or more years of exposure, including one from cancer (1.3 expected).

Zack and Gaffey (1983) reported the mortality status of 884 white men employed for at least one year between 1955-1977 by a chemical plant in Nitro, WV, USA, involved in the production of trichlorophenol and 2,4,5-T. 4-Aminobiphenyl, a human bladder carcinogen (see IARC, 1982e), was produced from 1941-1952 in this plant. There were nine cases of bladder cancer, with 0.91 expected; deaths from cancer other than of the bladder were not in excess. One case of liposarcoma was reported among workers assigned to 2,4,5-T operations. An accident during trichlorophenol production which took place in this plant was reported by Zack and Suskind (1980) (see below).

In a cohort study of workers in two Danish chemical plants (Lynge, 1985) (described in the monograph on occupational exposure to chlorophenoxy herbicides, p. 388), the only potential exposure to 2,4,5-trichlorophenol was between 1951 and 1959, when small amounts were produced or purchased to make 2,4,5-T. No overall increase in cancer incidence rate was observed, but there were statistically significantly increased risks of soft-tissue sarcoma and lung cancer in different subcohorts. [The Working Group noted that 2,4-dichlorophenol is an intermediate in the production of 2,4-D, which was produced by the larger of the two plants.]

Cook *et al.* (1986) examined mortality between 1940 and 1979 for 2189 men involved in the manufacture of 2,4,5-trichlorophenol and 2,4,5-T; work histories were classified according to exposure to TCDD. There were 298 deaths observed (standardized mortality ratio [SMR], 91) and 61 cases of cancer (SMR, 96). Five cases of non-Hodgkin's lymphoma were seen (SMR, 238; 95% confidence interval [CI], 77-556), but there was no evidence of a dose-response relationship for TCDD exposure. [The Working Group noted that no account was taken of latency in the analysis.]

Three studies have described cancer occurrence among workers following accidents in trichlorophenol-producing plants, with peak exposures to TCDD. A high proportion of

persons developed chloracne or acne-like lesions. Cook *et al.* (1980) observed three cancer deaths (1.6 expected) among 61 male employees involved in a 1964 accident in Michigan and followed up to the end of 1978. One death was reported to be from a fibrosarcoma. In the Federal Republic of Germany (Thiess *et al.*, 1982), 74 workers were involved in an accident in 1953 in a plant producing 2,4,5-trichlorophenol. Follow-up through 1980 revealed three deaths from stomach cancer, with relative risks of the order of 4-5 depending on the comparison group; there was no excess of cancers at other sites combined. Zack and Suskind (1980) reported cancer outcomes of a cohort of 121 males involved in a 1949 accident in a 2,4,5-trichlorophenol plant in West Virginia, USA. Between 1949-1978, follow-up revealed nine cancer deaths, with 9.04 expected. Three of these were lymphatic or haematopoietic in origin (0.88 expected [$p = 0.047$]), and one was a primary dermal fibrous histiocytoma (0.15 expected).

Exposure to chlorophenols and chlorophenoxy herbicides in humans and death from soft-tissue sarcoma

[The Working Group noted that it is difficult to evaluate mortality from soft-tissue sarcoma in relation to exposure to chlorophenols and chlorophenoxy herbicides from cohort studies and case reports, as reviewed by Fingerhut *et al.* (1984).

[A pathology review of histological specimens confirmed only five of seven cases as soft-tissue sarcomas, indicating possible overascertainment of soft-tissue sarcomas in mortality studies. Underascertainment is also a possibility, as shown by Fingerhut *et al.* (1984) and by Lynge (1985), for employees of a chemical plant producing chlorophenoxy herbicides. The limited validity of death certificates of soft-tissue sarcoma has been documented in the USA (Percy *et al.*, 1981).

[The Working Group also noted that revision of diagnosis for observed cases in mortality studies without identical revision of reference rates increases the complexity of interpreting results of such investigations.]

(*b*) *Case-control studies*

(i) *Soft-tissue sarcoma*

A Swedish case-control study of soft-tissue sarcoma and exposure to chlorophenoxy herbicides and chlorophenols (Hardell & Sandström, 1979) is described in the monograph on occupational exposures to chlorophenoxy herbicides (p. 390). When patients and controls with exposure to chlorophenoxy herbicides were excluded, the relative risk estimate for chlorophenol exposure was 6.6 ($p < 0.001$), with seven cases and six controls exposed [95% CI, 2.1-20.6].

A study in southern Sweden (also described in the monograph on occupational exposures to chlorophenoxy herbicides, p. 390) found a relative risk estimate for exposure to chlorophenols of 3.3 (95% CI, 1.3-8.1) (with 11 cases and eight controls exposed), when patients and controls with exposure to chlorophenoxy herbicides were excluded (Eriksson *et al.*, 1981).

19

A New Zealand study of soft-tissue sarcoma (referred to in the monograph on occupational exposures to chlorophenoxy herbicides, p. 391) found an odds ratio of 1.6 (90% CI, 0.5-5.2) for potential exposure to chlorophenols for five days or more, more than ten years prior to diagnosis (Smith *et al.*, 1984). Work in pelt-treatment departments (where 2,4,6-trichlorophenol has been used) or in tanneries (where pentachlorophenol and 2,4,6-trichlorophenol are used) yielded an odds ratio of 7.2 (six exposed cases; $p = 0.04$). When meat works and tanneries were contacted, it was found that two of the cases could not have been exposed to chlorophenols and exposure of a third was unlikely, while two could have been exposed to 2,4,6-trichlorophenol and one to pentachlorophenol.

(ii) *Malignant lymphoma*

A case-control study of exposure to chlorophenols, chlorophenoxy herbicides and other chemicals among 169 cases of malignant lymphoma and 338 controls has been reported in Sweden (Hardell *et al.*, 1981). The study design, including ascertainment of exposure, was similar to that of the Swedish soft-tissue sarcoma studies described in the monograph on occupational exposures to chlorophenoxy herbicides (p. 392). Relative risk estimates of 2.2 [95% CI, 1.1-4.4] for low-grade chlorophenol exposure and 7.6 [95% CI, 3.5-17.4] for high-grade exposure were found, after excluding those exposed to chlorophenoxy herbicides. The low-grade classification involved continuous exposure for not more than one week, or repeated brief exposures for not more than one month; longer exposures were classified as high-grade. No 'noticeable difference' in excess risk could be demonstrated between Hodgkin's disease and non-Hodgkin's lymphoma.

A New Zealand case-control study of non-Hodgkin's lymphoma involving 83 cases, 168 controls with other cancer and 228 general population controls, found an odds ratio of 1.2 (90% CI, 0.5-2.9) for potential exposure to chlorophenols when using other cancer patients as controls, and an odds ratio of 1.4 (90% CI, 0.5-3.7) when using general population controls (Pearce *et al.*, 1986). The odds ratio for fencing work, which involves exposure to chemicals such as copper-chrome arsenate as well as pentachlorophenol, was 2.0 (90% CI, 1.3-3.0). The odds ratio for slaughterhouse employment, which involves potential exposure to 2,4,6-trichlorophenol, was 1.8 (90% CI, 1.1-3.1); however, only four of the 19 cases who had worked in the plant reported working in the pelt department, where 2,4,6-trichlorophenol is used.

(iii) *Nasal and nasopharyngeal cancer*

Hardell *et al.* studied 44 cases of nasal cancer and 27 cases of nasopharyngeal cancer in northern Sweden and compared the reported frequency of exposure to chlorophenol (and other chemicals) with that of the combined 541 referents from earlier studies (Hardell & Sandström, 1979; Eriksson *et al.*, 1981) from the Umeå region. Exposure was assessed in the same way as in the previous studies (see above). A relative risk estimate of 6.7 (95% CI, 2.8-16.2) was found for exposure to chlorophenols of more than one week, continuously or intermittently for more than one month. The most frequent occupations in which exposure occurred were sawmilling and carpentery. After controlling for exposure to wood dust, an odds ratio of 6.7 (95% CI, 2.9-15.6) was obtained.

A study of 167 sinonasal cancer cases and 167 colorectal cancer controls carried out in Denmark, Finland and Sweden found an association with woodwork (Hernberg *et al.*, 1983). Two cases and no referent had probably been exposed to chlorophenols in addition to wood dust. A study of 839 cases of sinonasal cancer and 2465 controls from the Danish Cancer Registry classified these according to wood dust and chlorophenol exposure. A relative risk of 0.6 (95% CI, 0.3-1.2) was seen after adjustment for exposure to wood dust (Olsen & Møller-Jensen, 1984). [The Working Group noted that classification of chlorophenol exposure was based on occupational title and might not have been accurate.]

(iv) *Colon and liver cancer*

A study on colon cancer (described in the monograph on occupational exposures to chlorophenoxy herbicides, p. 393; Hardell, 1981) found a relative risk estimate of 1.8 (95% CI, 0.6-5.3) for high-grade chlorophenol exposure, based on six exposed cases and 13 (out of 541) exposed referents.

In a case-control study on primary liver cancer and several chemical exposures (Hardell *et al.*, 1984; described in the monograph on occupational exposures to chlorophenoxy herbicides, p. 393), the risk ratio for high-grade exposure to chlorophenols was 2.2 (95% CI, 0.7-7.3).

4. Summary of Data Reported and Evaluation

4.1 Exposure data

Several chlorophenols and their salts have been widely produced since the 1950s and used as wood preservatives, fungicides, slimicides, weed-killers and as precursors for chlorophenoxy herbicides. Widespread occupational exposure to chlorophenols and their chlorinated dibenzodioxin and dibenzofuran impurities is known to have occurred, especially in manufacturing plants and in wood-treatment applications. Increased urinary levels of chlorophenols and increased concentrations in adipose tissue of some chlorinated dibenzodioxins and dibenzofurans have been measured in workers exposed in sawmills and tanneries and in the textile industry. Skin absorption is believed to be a major route of exposure in these occupations. Burning of chlorophenol-containing materials in industrial or municipal incinerators may lead to the formation of various dibenzodioxin and dibenzofuran congeners.

4.2 Experimental data

Previous IARC evaluations of the carcinogenicity to experimental animals of several individual chlorophenols and of their impurity, 2,3,7,8-tetrachloro-*para*-dibenzodioxin (TCDD), are summarized in section 3.1.

4.3 Human data

Two studies among the wives of the workers at two chemical plants did not show an association between pregnancy outcomes and paternal exposure to 2,4,5-trichlorophenol, pentachlorophenol and TCDD and other dioxins.

Three studies have been published in which cytogenetic effects were investigated in workers exposed occupationally to chlorophenols. In two of the studies, no difference was seen between exposed and control subjects; but in one of these studies the persons were examined ten years after exposure. The other study showed increased incidences of dicentric and acentric chromosomal aberrations, but not of gaps, chromatid breaks or sister chromatid exchanges.

Several cohort studies have been conducted among chemical industry workers with potential exposure to 2,4,5-trichlorophenol, TCDD and other chemicals. Mortality rates for all cancers combined were not elevated. In a Danish cohort study, there may have been exposure to chlorophenols, present as intermediates in the production of chlorophenoxy herbicides. No increase in the incidence of cancers at all sites combined was observed, but there were statistically significantly increased risks of soft-tissue sarcoma and lung cancer in different subcohorts.

Two case-control studies conducted in different regions of Sweden showed a statistically significant association between exposure to chlorophenols and soft-tissue sarcoma; a study from New Zealand did not.

A statistically significant association between malignant lymphoma and exposure to chlorophenols was identified in a Swedish case-control study. A case-control study of non-Hodgkin's lymphoma in New Zealand suggested a possible association with fencing work, but not with other occupational exposures to chlorophenols.

A case-control study in Sweden detected a significant association between nasal and nasopharyngeal cancer and exposure to chlorophenols, independent of exposure to wood dust.

4.4 Evaluation[1]

There is *limited evidence* for the carcinogenicity of occupational exposure to chlorophenols to humans.

5. References

Ahlborg, U.G. & Thunberg, T.M. (1980) Chlorinated phenols: occurrence, toxicity, metabolism and environmental impact. *Crit. Rev. Toxicol.*, *7*, 1-35

[1]For definition of the italicized term, see Preamble, p. 22.

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23