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Pentachlorophenol in Drinking-water

Background document for development of
WHO *Guidelines for Drinking-water Quality*

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Preface

One of the primary goals of WHO and its member states is that "all people, whatever their stage of development and their social and economic conditions, have the right to have access to an adequate supply of safe drinking water." A major WHO function to achieve such goals is the responsibility "to propose regulations, and to make recommendations with respect to international health matters ...."

The first WHO document dealing specifically with public drinking-water quality was published in 1958 as International Standards for Drinking-Water. It was subsequently revised in 1963 and in 1971 under the same title. In 1984–1985, the first edition of the WHO Guidelines for drinking-water quality (GDWQ) was published in three volumes: Volume 1, Recommendations; Volume 2, Health criteria and other supporting information; and Volume 3, Surveillance and control of community supplies. Second editions of these volumes were published in 1993, 1996 and 1997, respectively. Addenda to Volumes 1 and 2 of the second edition were published in 1998, addressing selected chemicals. An addendum on microbiological aspects reviewing selected microorganisms was published in 2002.

The GDWQ are subject to a rolling revision process. Through this process, microbial, chemical and radiological aspects of drinking-water are subject to periodic review, and documentation related to aspects of protection and control of public drinking-water quality is accordingly prepared/updated.

Since the first edition of the GDWQ, WHO has published information on health criteria and other supporting information to the GDWQ, describing the approaches used in deriving guideline values and presenting critical reviews and evaluations of the effects on human health of the substances or contaminants examined in drinking-water.

For each chemical contaminant or substance considered, a lead institution prepared a health criteria document evaluating the risks for human health from exposure to the particular chemical in drinking-water. Institutions from Canada, Denmark, Finland, France, Germany, Italy, Japan, Netherlands, Norway, Poland, Sweden, United Kingdom and United States of America prepared the requested health criteria documents.

Under the responsibility of the coordinators for a group of chemicals considered in the guidelines, the draft health criteria documents were submitted to a number of scientific institutions and selected experts for peer review. Comments were taken into consideration by the coordinators and authors before the documents were submitted for final evaluation by the experts meetings. A "final task force" meeting reviewed the health risk assessments and public and peer review comments and, where appropriate, decided upon guideline values. During preparation of the third edition of the GDWQ, it was decided to include a public review via the world wide web in the process of development of the health criteria documents.

During the preparation of health criteria documents and at experts meetings, careful consideration was given to information available in previous risk assessments carried out by the International Programme on Chemical Safety, in its Environmental Health

Criteria monographs and Concise International Chemical Assessment Documents, the International Agency for Research on Cancer, the joint FAO/WHO Meetings on Pesticide Residues, and the joint FAO/WHO Expert Committee on Food Additives (which evaluates contaminants such as lead, cadmium, nitrate and nitrite in addition to food additives).

Further up-to-date information on the GDWQ and the process of their development is available on the WHO internet site and in the current edition of the GDWQ.

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The work of the following coordinators was crucial in the development of this document and others in the Addendum:

P. Chambon, Health Environment Hygiene Laboratory of Lyon, Lyon, France (inorganic constituents)
U. Lund, Water Quality Institute, Horsholm, Denmark (organic constituents)
H. Galal-Gorchev, Urban Environmental Health, World Health Organization, Geneva, Switzerland (pesticides)
E. Ohanian, Environmental Protection Agency, Washington, DC, USA (disinfectants and disinfection by-products)

The coordinators for the overall administrative and technical aspects of this document were, respectively, J. Kenny and H. Galal-Gorchev, Urban Environmental Health, WHO, Geneva, Switzerland.

Ms Marla Sheffer of Ottawa, Canada, was responsible for the scientific editing of the document.

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GENERAL DESCRIPTION

Identity

CAS no.: 87-86-5
Molecular formula: C_6HCl_5O

Unpurified technical pentachlorophenol (PCP) contains other chlorophenols and chlorophenoxyphenols, as well as several microcontaminants, particularly polychlorinated dibenzo-*p*-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs). Because of attempts to reduce toxic impurities, various technical preparations may be quite different both temporally and geographically. Chlorophenol preparations in various countries have varied from almost pure PCP to those in which 2,3,4,6-tetrachlorophenol was the main component, 2,4,6-trichlorophenol concentrations were significant, and PCP accounted for as little as 5–10% (IARC, 1986).

Physicochemical properties *(WHO, 1987)*

Property	*Value*
Physical state	light tan to white needle-like crystals
Water solubility (at 20°C)	14 mg/litre (pH 5) 2 g/litre (pH 7) 8 g/litre (pH 8)
Log octanol–water partition coefficient	3.56 (pH 6.5) 3.32 (pH 7.2)
Vapour pressure	2×10^{-6} kPa at 20°C
Melting point	191°C
Boiling point	310°C (decomposition)
Density	1.987 g/cm^3
pK_a	4.7 at 25°C

Organoleptic properties

The odour threshold of PCP in water has been given as 0.86 mg/litre at 30°C (ATSDR, 1994) and 1.6 mg/litre (temperature not specified) (WHO, 1987). The taste threshold is 0.03 mg/litre (temperature not specified) (WHO, 1987). In cold water, the taste threshold is increased (Lamp et al., 1990).

Major uses

PCP and other chlorophenols are used primarily for protecting wood from fungal growth. Their use is in decline, and they have been abandoned from most other applications, such as indoor disinfectant, leather and textile application, and herbicide uses. In several countries, their use has been totally discontinued (e.g. Sweden, Germany, Finland) or practically abandoned as a result of severe restrictions (e.g. Denmark). However, PCP is still an important pesticide in some developing countries because of its low cost and broad spectrum. In some developed countries (e.g. France, USA), several thousand tonnes are produced annually (IARC, 1991; McConnell et al., 1991). Even in those countries where PCP use has been abandoned, PCP continues to be an important environmental contaminant, because it is imported via various materials treated with it.

Environmental fate

PCP and other chlorophenols can be metabolized by numerous aquatic and soil microorganisms, but environmental conditions are usually unfavourable for biodegradation (Salkinoja-Salonen et al., 1989; Bajpai & Banerji, 1992; Orser & Lange, 1994; Laine & Jørgensen, 1996). Slow elimination in surface waters, high persistence in sediments, formation of stable metabolites, and the limited adaptation of microorganisms to chlorophenols owing to their high microbial toxicity imply that chlorophenols are practically non-biodegradable in the aquatic environment (UBA, 1996). In addition, the trace contaminants, especially PCDDs and PCDFs, are not metabolized.

Chlorophenols are relatively water soluble in the anionic form. At pH 6.7, 99% of PCP is ionized and in easily leachable form. Therefore, soil contamination may lead to the contamination of groundwater as well. The solubility of the dioxin/furan contaminants is very low (in the order of 10^{-8} g/litre), and these contaminants are readily sorbed onto soil particles and other surfaces; hence, the risk of contamination of finished drinking-water is not great. In surface waters, organic or clay particles easily transport dioxins/furans to distant sites from their origin (Koistinen et al., 1995).

PCP is accumulated by aquatic organisms through uptake from the surrounding water or along the food-chain (WHO, 1987).

ANALYTICAL METHODS

A capillary gas chromatographic method with electron capture detection is the most widely applied method of assaying PCP (usually methylated or acetylated) after acid extraction to diethyl ether or another organic solvent (WHO, 1987; IARC, 1991; Jorens & Schepens, 1993). The detection limit is 0.005–0.01 µg/litre. Recently, other methods have been advocated, such as gas chromatography with atomic emission detection (Turnes et al., 1994), gas chromatography–mass spectrometry using selected ion monitoring (Kontsas et al., 1995), and high-performance liquid chromatography (Frebortova & Tatarkovicova, 1994).

ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

Air

Because of its high vapour pressure, PCP easily evaporates from treated wood surfaces, and the loss may be as high as 30–80% a year (WHO, 1987). Its indoor use in buildings is highly inadvisable (Jorens & Schepens, 1993; Liebl et al., 1995) and has caused a number of poisonings. Volatilization from water is pH dependent, and only the un-ionized form seems to be volatile (WHO, 1987). Although PCP is ubiquitous, there is little information on its concentrations in ambient air (WHO, 1987; Thompson & Treble, 1995). Fallout as calculated from Finnish snow samples ranged from 1.49 to 136.0 µg/m^2 (Paasivirta et al., 1985).

Water

In the past, PCP concentrations as high as 25 000–150 000 µg/litre in industrial effluent were reported; at one time, 30–40 t were calculated to be transported by the Rhine per year (WHO, 1987). Concentrations up to 10 500 µg/litre have been reported locally in a river (Fountaine et al., 1976), but concentrations in water samples are usually below 10 µg/litre (WHO, 1987). Monitoring data showed that PCP concentrations generally decreased (from 0.07–0.14 µg/litre in 1988 to 0.01–0.02 µg/litre in 1993) in the River Elbe after PCP production was stopped in Germany in 1986 and its use was banned in 1989. Such a trend was not seen in the Rhine and its tributaries, where concentrations were even higher in 1990–1991 than in 1980–

1989 (maximum levels up to 0.23 µg/litre); the cause is not known (UBA, 1996), but it indicates continuing environmental contamination.

Under special conditions, PCP may accumulate to very high concentrations in groundwater. In the spring water of a Finnish village, concentrations of 70–140 µg/litre were found, and investigation of the groundwater reservoir revealed extremely high concentrations of 56 000–190 000 µg/litre in the deep parts of the reservoir (Lampi et al., 1990). The obvious source was a local sawmill using chlorophenols since 1940s.

Bottom sediments usually contain higher concentrations of PCP than the overlying waters. In Canadian water samples, PCP concentrations ranged from non-detectable to 7.3 µg/litre; in the respective sediments, concentrations ranged from non-detectable to 590 µg/kg (WHO, 1987). In a lake downstream of the above-mentioned Finnish village, total chlorophenol concentrations of 2.6–11.0 µg/litre were detected (Lampi et al., 1990), whereas the concentration in sediment was 100 µg/kg dry weight or more (Lampi et al., 1992a). In New Zealand, the highest PCP concentrations (3.6 µg/litre in surface water and 400 µg/kg dry weight in sediments) were found downstream from a sawmill (Gifford et al., 1996).

PCP concentrations in drinking-water are usually in the range of 0.01–0.1 µg/litre (WHO, 1987). It has been thought that PCP's odour threshold is low and should render water unpalatable, but a recent episode in Finland demonstrated that people may drink water containing up to 100 µg/litre of chlorophenols with few complaints (Lampi et al., 1990). As stated above, evaporation depends on pH and temperature, and detection in cold water is unreliable.

Food

In Canada, analysis of 881 pork liver tissue samples revealed a gradual decline in PCP levels in 1988–1989 from those in earlier years. Some 6.6% of the samples contained levels in excess of 0.1 mg/kg, the highest level being 0.72 mg/kg. Of 51 beef liver samples, 2.0% had levels in excess of 0.1 mg/kg, the maximum level being 0.35 mg/kg. Examination of 214 chicken and 68 turkey liver samples showed only one with a level above 0.1 mg/kg; this incident was traced to the use of wood shavings as bedding (Agriculture Canada, 1989). Another study in Slovakia found detectable PCP concentrations in 79% of food samples from school kitchens; the average PCP concentration in positive samples was 6.3 µg/kg (Veningerová et al., 1994).

Estimated total exposure and relative contribution of drinking-water

Daily net intake of PCP in the general population has been estimated to be 5–35 µg/day (Reigner et al., 1992a). The long-term average daily intake of PCP by the general population in the USA was estimated to be 16 µg/day using six-compartment environmental partitioning models; food, especially fruits, vegetables, and grains, accounted for 99.9% of the total exposure (Hattemer-Frey & Travis, 1989). In Canada, the estimated daily intake is 0.05 µg/kg of body weight per day, mostly via food or indoor air (Coad & Newhook, 1992). It seems likely that food accounts for the majority of intake unless there is specific local chlorophenol contamination causing increased concentrations in drinking-water or exposure from log homes treated with PCP.

KINETICS AND MATABOLISM IN LABORATORY ANIMALS AND HUMANS

The kinetics of PCP have been reviewed on a number of occasions (Ahlborg & Thunberg, 1980; WHO, 1987; IARC, 1991), and only a general overview and a few recently emphasized points are presented here. PCP is probably well absorbed orally (Reigner et al., 1992a),

although bioavailability may be influenced by food (Yuan et al., 1994). During occupational exposure, PCP is well absorbed via the dermal and pulmonary routes (IARC, 1991). Good oral (WHO, 1987; Reigner et al., 1992b; Yuan et al., 1994) and dermal (Wester et al., 1993) absorption is supported by animal studies. It is likely that most PCP is conjugated to glucuronic acid and excreted into urine, although the rate of glucuronidation has been controversial (Reigner et al., 1992a). It is somewhat debatable whether an important rodent metabolite, tetrachloro-1,4-hydroquinone, is formed in humans, but at most it is a minor metabolite (Reigner et al., 1992a).

PCP is avidly bound (99.5%) to plasma proteins in humans (Reigner et al., 1993). There is some uncertainty as to the elimination rate of PCP, and half-lives from 33 hours to 16 days have been reported (Reigner et al., 1992a). Both protein binding and urinary pH could cause variation, but there may also be methodological reasons for the differences found. One may safely assume that the half-life is a few days. The bioconcentration factor for PCP is rather low, and steady-state levels in human adipose tissue amount to only 2–4 times the average daily intake (Geyer et al., 1986).

EFFECTS ON EXPERIMENTAL ANIMALS AND *IN VITRO* TEST SYSTEMS

Acute exposure

Oral LD_{50} values range from 36 to 177 mg/kg of body weight in mice and from 27 to 175 mg/kg of body weight in rats (IARC, 1991).

Short-term exposure

A number of toxic effects in short-term tests have been attributed to impurities present in technical-grade PCP preparations. Rats receiving technical-grade PCP at 500 mg/kg of feed (equivalent to 25 mg/kg of body weight per day) for 8 months had slow growth rates, liver enlargement, porphyria, and increased activities of some liver microsomal enzymes (Goldstein et al., 1977; Kimbrough & Linder, 1978). These were not seen when purified PCP was used, and in fact they are typical effects of tetrachlorodibenzo-*p*-dioxin (TCDD)-like compounds (Pohjanvirta & Tuomisto, 1994). Some effects on enzyme activity, such as strong inhibition of sulfotransferase activity, are due to PCP itself (Boberg et al., 1983).

A number of effects on immune systems have been noted: reduced humoral immunity and impairment of T-cell cytolytic activity in mice (Kerkvliet et al., 1982a,b) and decreased cell-mediated and humoral immunity in rats (Exon & Koller, 1983). The effects are attributed to dioxin/furan impurities (Kerkvliet et al., 1985).

Thyroid hormones were decreased in female Wistar rats after 4-week dosing by gavage with pure PCP at 30 mg/kg of body weight per day without a consequent increase in thyroid-stimulating hormone (Jekat et al., 1994), suggesting a hypophyseal or hypothalamic action. It is of some interest that PCP decreased the uptake of thyroxin into cerebrospinal fluid and the brain (van Raaij et al., 1994).

Male Wistar rats (number per group unspecified) administered PCP (purity unspecified) at 1.0 or 3.0 mmol/litre in drinking-water *ad libitum* for 3–4 months showed degenerative changes in peripheral nerves, including degeneration of myelin sheath and loss of neurotubules and neurofilaments and other axoplasmic components in A- and B- but not C-type fibres. Hepatocyte swelling and vacuolar degeneration were also seen, as well as some proximal tubular damage in the kidneys (Villena et al., 1992).

Reproductive and developmental toxicity

PCP is not teratogenic in rats, but it is embryo/fetotoxic at high doses (Schwetz et al., 1978; Exon & Koller, 1982; Welsh et al., 1987).

Rats were administered 3 or 30 mg/kg of body weight of purified PCP 62 days before mating, during mating, and to females during gestation and lactation. The high dose caused reductions in the number of offspring, neonatal body weight, neonatal survival, and growth of weanlings. The NOAEL was 3 mg/kg of body weight per day (Schwetz et al., 1978).

Developmental effects of purified (98% purity) and technical-grade (88.4% purity) PCP in rats were investigated by administering PCP orally at doses ranging from 5 to 50 mg/kg of body weight per day from day 6 to day 15 of gestation. Purified PCP caused delayed fetal development without simultaneous maternal toxicity at 5 mg/kg of body weight per day. Technical-grade PCP did not have any effects on the mother or fetus at 5 mg/kg of body weight per day (Schwetz et al., 1974).

Female Sprague-Dawley rats were exposed to PCP (95% pure) at 0, 5, 50, or 500 mg/kg of feed (equivalent to 0, 0.25, 2.5, or 25 mg/kg of body weight per day). This study was designed to produce progeny that were exposed to PCP both pre- and postnatally. Decreased litter sizes and increased number of stillborn were observed at the highest dose (Exon & Koller, 1982).
Male and female Sprague-Dawley rats were fed purified PCP (>99% pure) at doses of 0, 4, 13, or 43 mg/kg of body weight per day for 181 days, through mating and pregnancy. PCP was embryolethal and maternally toxic at the highest dose tested (Welsh et al., 1987).

Mutagenicity and related end-points

The genetic toxicology of PCP was thoroughly reviewed by Seiler (1991). PCP does not seem to produce DNA damage, and the few scattered observations of mutagenic activity were attributed to oxygen radical formation by its metabolite. This seems to be supported by later studies that implicate the rodent metabolite of PCP, tetrachloro-1,4-hydroquinone (Jansson & Jansson, 1992a; Dahlhaus et al., 1994, 1995; Naito et al., 1994; Waidyanatha et al., 1994; Sai-Kato et al., 1995; Wang & Lin, 1995). There is some evidence of weak clastogenic effects in chromosomal aberration assays *in vitro* and in lymphocytes of exposed persons *in vivo* (Bauchinger et al., 1982; Seiler, 1991). Also, 2,4,6-trichlorophenol caused chromosome malsegregation rather than mutations in Chinese hamster ovary cells (Jansson & Jansson, 1992b; Armstrong et al., 1993).

Carcinogenicity

Early carcinogenicity studies on PCP were negative or equivocal (Innes et al., 1969; Schwetz et al., 1978), but there were deficiencies in these studies (IARC, 1991). In a carefully executed study of the US NTP (McConnell et al., 1991), both a generic technical-grade PCP and a preparation with lower levels of impurities (about 2 orders lower with respect to PCDDs and PCDFs) were fed to $B6C3F_1$ mice (50 per sex per group) for 2 years at average doses of 0, 18, or 35 mg/kg of body weight per day (technical grade) and 0, 18, 35, or 116 mg/kg of body weight per day (purer grade). Dose-dependent and significantly elevated levels of hepatocellular adenomas and carcinomas, phaeochromocytomas, and haemangiosarcomas were observed. Overall, the purer preparation was not less tumorigenic than the technical-grade PCP. Hepatic tumours and phaeochromocytomas were more common in males, whereas haemangiosarcomas were seen only in females. McConnell et al. (1991) came to a plausible conclusion that tumours are caused primarily by PCP itself and not by impurities, although hexachlorodibenzo-*p*-dioxin may play a small part in accentuating the effect. IARC (1991) concluded that there is sufficient evidence for the carcinogenicity of PCP in experimental

animals. The US NTP is conducting a 2-year feeding study in F344 rats (as cited by Yuan et al., 1994).

There is a paucity of carcinogenicity data on 2,3,4,6-tetrachlorophenol. 2,4,6-Trichlorophenol was found to cause hepatocellular carcinomas or adenomas in mice of both sexes and lymphomas and leukaemias in male rats (National Cancer Institute, 1979). This was considered to provide sufficient evidence for its carcinogenicity in experimental animals (IARC, 1982).

EFFECTS ON HUMANS

The paramount difficulty in interpreting human studies, especially long-term studies, has been simultaneous exposure to other chemicals (Johnson, 1990; Saracci et al., 1991). Those working in chemical industries are often simultaneously exposed to chlorophenols, solvents, dibenzodioxins, dibenzofurans, and the chemical being synthesized. Those working in forestry or agriculture are often simultaneously exposed to chlorophenols, chlorophenoxy acids, dibenzodioxins and dibenzofurans, as well as other pesticides.

Owing to the extreme toxicity and high carcinogenic potency of TCDD in laboratory animals, there has been a tendency to attribute most of the toxicity to dioxins and furans. However, as dioxins and furans exist only as impurities, any exposure to them means perhaps close to a million-fold higher exposure to the main chemical (McConnell et al., 1991; Vartiainen et al., 1995a). An exception is early years of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) production, which caused remarkably high TCDD exposure (Flesch-Janys et al., 1995).

In addition, the vapour pressure and water solubility of chlorophenols are substantially higher than those of dioxins and furans, favouring higher exposure via air and water. Also, absorption of chlorophenols through skin is probably better than that of dioxins (Wester et al., 1993; Pohjanvirta & Tuomisto, 1994). Therefore, the primary relevance of the measured concentrations of kinetically persistent dioxins/furans may be that they indicate past exposure to the main chemical, especially if the exposure is long-lasting.

The slow pattern of the kinetics of dioxins and furans dictates that, for their own toxicity, a steady gradual exposure is more important than an occasional short exposure, unless this is very large. In fact, the long half-life of dioxins (5–10 years or more) (Pirkle et al., 1989; Wolfe et al., 1992; Flesch-Janys et al., 1994; Needham et al., 1994) means that a steady-state level will be achieved only in 30–40 years at a constant intake. This renders it unlikely that an occasional exposure, such as in forestry and agriculture, would significantly change the body balance, even if the concentrations of the main chemical increase dramatically during spraying or handling. The situation is quite different in chemical industries. If the workers are exposed continuously for years or decades (Fingerhut et al., 1991; Flesch-Janys et al., 1995), then extremely high dioxin levels (thousands of pg/g fat) may be accumulated.

PCP poisoning

PCP and other higher chlorinated phenols act cellularly to uncouple oxidative phosphorylation and to inhibit ATPase and several other enzymes (Jorens & Schepens, 1993). This leads to excessive heat production and fever. Symptoms of acute poisoning include central nervous system disorders, dyspnoea, and hyperpyrexia, leading to cardiac arrest. Marked rigor mortis is typical (IARC, 1991). In general, acute human poisoning is seen only after large accidental or suicidal doses. The estimated minimal lethal dose in humans has been calculated to be 29 mg/kg of body weight (IARC, 1991).

The human toxicology of PCP was recently reviewed by Jorens & Schepens (1993). In addition to metabolic, respiratory, and central nervous system effects (see above) seen only

after an acute large oral dose, they classified the clinical features as effects on skin and haematopoietic tissue, renal effects, and gastrointestinal effects. Some of these effects, notably chloracne, are probably due to dioxin/furan impurities. These effects have occasionally been seen after heavy occupational exposure. In a Chinese PCP production plant, high prevalence of chloracne, increased urinary porphyrin excretion, and decreased motor nerve conduction velocities were observed in the high-exposure area (Cheng et al., 1993; Coenraads et al., 1994). These are likely due to dioxin-like impurities. Drinking-water exposure was associated with gastrointestinal symptoms (nausea, pains, diarrhoea) and mild skin disorders (itching, eczema) (Lampi et al., 1993). The latter findings can be assumed to be due to chlorophenols, as no dioxin exposure was noted (Vartiainen et al., 1995b).

Immunological effects

Immunological abnormalities suggested in one study were T-cell activation and autoimmunity, functional immunodepression, and B-cell dysregulation (McConnachie & Zahalsky, 1991). These were found among 38 individuals living in log houses treated with PCP; hence, if true, the effects are more plausibly due to volatile PCP than to non-volatile impurities. T-lymphocyte dysfunction was also implied in 188 patients who were exposed to PCP (Daniel et al., 1995). In another study, no major clinical or laboratory signs of immune deficiency were found (Colosio et al., 1993).

Cancer

A number of studies since the 1970s implicated the group of chemicals including chlorophenols, chlorophenoxy acids, chlorinated dibenzo-*p*-dioxins, and chlorinated dibenzofurans in the causation of cancer, especially soft-tissue sarcoma and non-Hodgkin lymphoma (Lilienfeld & Gallo, 1989; Johnson, 1990; IARC, 1991). Owing to several inconsistencies, the case remained debatable.

Several important contributions were published during the 1990s that give further information on such an association (Eriksson et al., 1990; Wigle et al., 1990; Zahm et al., 1990; Zober et al., 1990; Coggon et al., 1991; Fingerhut et al., 1991; Green, 1991; Manz et al., 1991; Saracci et al., 1991; Lampi et al., 1992b; Scherr et al., 1992; Smith & Christophers, 1992; Bertazzi et al., 1993; Bueno de Mesquita et al., 1993; Kogevinas et al., 1993, 1995; Lynge, 1993; Hardell et al., 1994; Mikoczy et al., 1994; Flesch-Janys et al., 1995). There is a tendency for the risk to be non-significant or borderline in many well-executed studies. This results from small numbers of very rare cancers, but it may also be an indication of the difficulties of accurate exposure assessment. Although individual studies are not always convincing, there is certain coherence in the results incriminating this group of chemicals in the risk of soft-tissue sarcoma, less so with non-Hodgkin lymphoma.

The relative contribution of each particular chemical is even less clear, as several chemicals among the group are animal carcinogens and as there is a paucity of information on others. There was no indication in a large international multicentre cohort of a difference in soft-tissue sarcoma risk between those workers who were probably exposed to TCDD and those who were exposed only to the main chemical (Saracci et al., 1991). A similar observation has been made in several other studies (Pearce & Bethwaite, 1992; Zahm & Blair, 1992; Lynge, 1993). In nested case–control studies (Kogevinas et al., 1995) within the previous cohort (Saracci et al., 1991), relatively high odds ratios were noted for soft-tissue sarcoma by exposure to both phenoxy acids and dioxins/furans. Again, risks were not specifically associated with those herbicides contaminated with TCDD. Individuals with PCP exposure were too few for conclusions to be drawn (Kogevinas et al., 1995).

Generally, the role of chlorophenols remains more elusive than that of other chemicals of the group, because the exposed groups are smaller and therefore the number of cases of these

relatively rare cancers is often only from zero to five. This decreases the statistical power in cohorts and increases the possibility of chance findings. In a relatively large case–control study (105 cases and 335 controls) on non-Hodgkin lymphoma, Hardell et al. (1994) observed an odds ratio of 4.8 (CI 2.7–8.8) for chlorophenols, with PCP being the most common type. There seemed to be a higher risk in those exposed for a longer time. In a similar case–control study on soft-tissue sarcoma (237 cases and 237 controls), a risk ratio of 5.25 (95% CI 1.69–16.34) was observed in a high-exposure chlorophenol group (Eriksson et al., 1990).

In a large US multicentre occupational cohort, there was a significant correlation between long-term exposure to dioxins/furans and soft-tissue sarcoma (based on three cases), but again there is no certainty on whether the causative agent (provided the correlation indicates a true causal relationship) was dioxins/furans or the bulk chemicals (Fingerhut et al., 1991). A more detailed picture was obtained in a German cohort in a herbicide-producing plant where the exposure of each worker during a 33-year period was modelled (Flesch-Janys et al., 1995), but still 2,4,5-trichlorophenol or 2,4,5-T exposure occurred simultaneously with dioxins. In this study, a dose-related increase was observed in total mortality, cancer mortality, and ischaemic heart disease mortality. The effect was seen especially in the highest quintile, and the estimated highest dioxin equivalent concentrations were extremely high, over 4000 pg/g blood fat (normal young population in Europe, 10–30 pg/g fat; older people, up to 100 pg/g fat) (WHO, 1989, 1996; Vartiainen et al., 1995b). Viewed against these concentrations, the dioxin concentrations in the studies of Eriksson et al. (1990) and Hardell et al. (1994) cannot be even close to those found in chemical industries; if their observations are true, the cancers are more likely due to chlorophenols/phenoxy acids than to contaminant dioxins.

Some light may be thrown on the discussion of the roles of chlorophenols and their impurities by an episode in Finland, where 3500 inhabitants were potentially exposed to chlorophenols but not dioxins/furans for at least 15 years through contaminated groundwater (Lampi et al., 1990, 1992a; Vartiainen et al., 1995a,b). In this cohort, increased incidences of soft-tissue sarcoma (six cases) and non-Hodgkin lymphoma (12 cases) were observed during three successive 5-year periods (Lampi et al., 1992b). In a case–control study, a significantly elevated risk ratio was observed for non-Hodgkin lymphomas among persons who consumed fish from the downstream lake or drinking-water from the village waterworks (Lampi et al., 1992b). This implies that chlorophenols alone without the contribution of the minor dioxin/furan impurities may be associated with cancer at relevant exposure levels.
In conclusion, there is some, although not irrefutable, evidence that chlorophenol preparations, including PCP, may cause cancer in humans. There seems to be no reason to believe that the problem could be overcome by advocating more purified preparations. In fact, there is little evidence that minor carcinogenic impurities, such as TCDD and other chlorinated dioxins and furans, would be more important than the main chemical, and there is limited direct evidence on the basis of both animal experiments and epidemiological studies that pure chlorophenols may, at relevant concentrations, pose a risk of cancer in humans. As far as water is concerned, only the risk of chlorophenols is plausible, as the PCDD/PCDF impurities are practically non-soluble in drinking-water.

PROVISIONAL GUIDELINE VALUE

IARC (1990) classified PCP in Group 2B — the agent is possibly carcinogenic to humans, because of inadequate evidence of carcinogenicity in humans and sufficient evidence in experimental animals. There is suggestive, although inconclusive, evidence of the carcinogenicity of PCP from epidemiological studies of populations exposed to mixtures including PCP. There is conclusive evidence of carcinogenicity in one animal species, although there are notable variations in metabolism between experimental animals and humans. It was therefore considered prudent to treat PCP as a potential carcinogen.

Adequate dose–response data for carcinogenicity are available only from toxicological studies in animals. Based on multistage modelling of tumour incidence in the US NTP bioassay without incorporation of a body surface area correction, although recognizing that there are interspecies differences in metabolism, the concentration of PCP associated with a 10^{-5} excess lifetime cancer risk is similar to the current guideline value. The current provisional guideline value of 9 µg/litre is therefore retained.

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