Pentachlorophenol and the peripheral nervous system: a longitudinal study in exposed workers

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ABSTRACT A longitudinal study was performed to examine whether chronic occupational exposure to pentachlorophenol (PCP) or its compounds causes measurable alterations in the conduction velocity in peripheral nerves as an "adverse effect." In total, the results of nerve conduction velocity (NCV) determinations in 1980 and 1984 in 10 subjects (7 men, 3 women) who had been exposed for an average of 16 years (range 4-24) were available. The concentrations of PCP in the air at the workplace varied between 0.3 and 180 $\mu\text{g}/\text{m}^3$ and were thus below the maximum allowed concentration (MAK value) of 500 $\mu\text{g}/\text{m}^3$. The biological monitoring carried out showed the following results: PCP in the serum: 38-1270 $\mu\text{g}/\text{l}$; PCP in the urine: 8-1224 $\mu\text{g}/\text{l}$. Compared with the upper normal limits (PCP in the serum 150 $\mu\text{g}/\text{l}$, PCP in the urine 60 $\mu\text{g}/\text{l}$), distinct internal exposure to PCP has resulted in some of the employees. Determinations of the NCV of motor and sensory nerve fibres (ulnar, median, peroneal, and sural nerve) were always in the normal range. A significant difference in the NCV for the period 1980-4 could not be detected. In addition, the correlation analyses did not show any hints of "dose-effect relations." It is concluded that occupational exposure to PCP over several years in the concentrations observed probably do not lead to any adverse effects on the peripheral nervous system.

Pentachlorophenol (PCP) and its sodium salt are attaining increasing importance in industrial medicine and in environmental hygiene because of their wide distribution in preservatives and pesticides.

Investigations on the toxicity of PCP were carried out more than 40 years ago.¹ In connection with the manufacture and processing of products containing PCP acute and chronic PCP intoxications have occasionally been observed.²⁻⁵ A fatal PCP intoxication has also recently been described.⁶ Despite comprehensive knowledge on its kinetics, metabolism, and toxicology,⁷⁻¹¹ the question of possible peripheral neurotoxic effects in man has not yet been adequately clarified.¹² In 1951 Baader and Bauer reported on neurological disorders in the context of a PCP intoxication.¹³

On the basis of its chemical structure, pentachlorophenol belongs to the group of polychlorinated aromatic hydrocarbons. In other compounds of this class such as hexachlorocyclohexane,¹⁴ poly-

chlorinated biphenyls,¹⁵ trichlorophenoxyacid,¹⁶ and chlorinated dioxins,¹⁷ neurotoxicity for man has been shown in some cases, so that such effects may also be assumed as a hypothesis for PCP.

For this reason, we have examined by means of sensitive neurophysiological technique whether occupational exposure to PCP over several years caused adverse effects on the peripheral nervous system.¹⁸ Furthermore, the results could be compared with those of an earlier cross sectional investigation from 1980¹⁹ in order to detect any alterations that may have occurred during this time.

Subject selection and methods

The subjects investigated from a chemical company were 15 men and three women in 1980 and 12 men and three women in 1984. A total of only 10 employees (7 men, 3 women) aged from 29 to 52 (median 41) were available for the longitudinal study. All employees had contact with PCP and PCP-containing substances for an average of 16 years (duration of employment 4-24 years). Three areas with different

levels of PCP exposure could be defined on the basis of the production procedure:

- (1) Production (high exposure).
- (2) Filling (moderate exposure).
- (3) Depot (low exposure).

The diagnostic procedure comprised the following single steps:

(1) Recording of the case history by means of a standardised questionnaire.

(2) Physical examination including initial neurological status.

(3) Determination of motor and sensory nerve conduction velocity of the ulnar, median, peroneal, and sural nerves.

(4) Biomonitoring (PCP in the serum, PCP in the urine).

PCP was determined in biological material using a sensitive gas chromatographic method as previously described.^{20 21}

Furthermore, an "ambient air monitoring" with personal active sampling using impingers was carried out in five subjects. The neurophysiological findings were evaluated on the basis of our own reference values²² and published data.²³

Results

Table 1 shows data on the concentrations of PCP in the air at various workplaces in 1980 and 1984. The MAK value of 500 $\mu\text{g}/\text{m}^3$, valid since 1978, is not reached on average by a factor of 10 (production), 50 (filling), and 10 (depot). Furthermore, the results of measurements of air concentrations of tetrachlorophenols (TCP), γ hexachlorocyclohexane (lindan), and aldrin from 1977 and in some cases from 1984 were available. These chlorinated hydrocarbons could only be detected in traces in the range of 5 ppb in 1977. The concentrations of TCP in the air varied between 1 and 291 $\mu\text{g}/\text{m}^3$ in 1984.

The results of biological monitoring are shown in table 2. The PCP concentrations in the serum vary

Table 2 Results of pentachlorophenol in serum and urine of 10 exposed workers in 1980 and 1984

PCP in serum ($\mu\text{g}/\text{l}$)	1980	1984
Production (n = 4)	150, 200, 1100, 1270	133, 337, 521, 1259
Filling (n = 4/3)	80, 100, 110, 460	105, 124, 463
Depot (n = 2)	90, 120	38, 135
PCP in urine ($\mu\text{g}/\text{l}$)		
Production (n = 4)	13, 24, 141, 477	20, 104, 188, 268
Filling (n = 4)	13, 19, 587, 1224	4, 12, 12, 55
Depot (n = 2)	78, 557	8, 48

between a minimum of 38 $\mu\text{g}/\text{l}$ and a maximum of 1270 $\mu\text{g}/\text{l}$ and show an increased PCP exposure compared with our upper normal limit of 150 $\mu\text{g}/\text{l}$.^{20 21}

Lindan or TCP in serum varies between less than 1.5 $\mu\text{g}/\text{l}$ and a maximum of 3 $\mu\text{g}/\text{l}$ (upper normal limit less than 1.5 $\mu\text{g}/\text{l}$) or less than 9 $\mu\text{g}/\text{l}$ and a maximum of 156 $\mu\text{g}/\text{l}$ respectively. In the urine the TCP concentrations range from less than 7 $\mu\text{g}/\text{l}$ to 223 $\mu\text{g}/\text{l}$ (normally undetectable).

An occupational exposure to other chemicals at the workplace known to have a peripheral neurotoxicity such as n-hexane, methyl-n-butylketone, and certain solvent mixtures could be ruled out from the history.

On the basis of the history and the laboratory results obtained in preventive medical examinations by one of us (HJK) there was no hint of a possible non-occupational risk of a polyneuropathy such as former neurological diseases, diabetes mellitus, excessive alcohol consumption (over 80 g of alcohol daily), or the intake of certain drugs.

Symptoms in the form of distal paresthesias or muscular weakness, which might indicate a peripheral neuropathy, were reported by one subject only. The physical neurological examinations showed no signs of polyneuropathy such as paresis, hypaesthesia or pathological reflexes in any case. The findings of 1980 can thus be confirmed.¹⁹

Table 3 shows the results of the determinations of the nerve conduction velocity in the form of the

Table 1 Results of pentachlorophenol (PCP) in air at three different workplaces in 1980 and 1984 after stationary and personal sampling

PCP in air ($\mu\text{g}/\text{m}^3$) (stationary sampling)	1980	1984
Production	2–50	2, 2 and 134
Filling	0.3–8	1 and 8
Depot	—	29 and 180
PCP in air (personal sampling)		
Production	—	5, 32 and 44
Filling	—	—
Depot	—	13 and 67

Table 3 Results of the nerve conduction velocity measurements in 10 PCP exposed workers in 1980 and 1984. The ranges and medians are shown. The nerve conduction velocity values are corrected for a skin temperature of 32°C

Parameter	Nerve	Nerve conduction velocity m/s		Lower value of normal
		1980	1984	
MCV max	Ulnar	46–65 (59)	51–64 (56)	51
pSCV	Ulnar	40–50 (46)	38–52 (50)	40
pSCV	Median	43–55 (45)	38–52 (48)	40
MCV max	Peroneal	—	49–63 (58)	45
pSCV	Sural	—	39–50 (45)	40

ranges and medians for 1980 and 1984. There were no significant changes in either the ranges or the medians. A delayed nerve conduction velocity due to age is not manifested, since this generally amounts to only about 1–2 m/sec for one decade.²³ Even considering the individual courses of the three neurophysiological parameters, no consistent or directional alterations are shown if a realistic interindividual variation of about 10% is taken as a basis. This is most evident for the sensory nervous conduction velocity of the median nerve, which is the measurement with the best reproducibility (fig 1).

To examine the presence of possible dose effect relations, we have plotted the sensory nervous conduction velocity of the median nerve and the sural nerve in relation to the exposure index (product of years of exposure and serum PCP concentration) (fig 2). This does not show a significant slowing of the nerve conduction velocity with increasing exposure.

Fig 1 Individual sensory nerve conduction velocities of median nerve in 10 PCP exposed workers in 1980 and 1984.

Fig 2 Individual sensory nerve conduction velocities of median and sural nerves of 10 subjects in relation to PCP exposure index. (For details see text.)

Discussion

According to the knowledge available so far, the clinical picture of chronic PCP intoxication is variable. In addition to symptoms affecting the central, peripheral, and vegetative nervous systems, mucosal irritations, alterations in the blood count, and hepatotoxic effects have been described.^{2–5} On the basis of recent reports, contaminations of technical PCP products by hexachlorodibenzodioxins, heptachlorodibenzodioxins, and octachlorodibenzodioxins, should be discussed in addition to PCP as a cause for the adverse health effects.²⁴ In the air samples investigated tetrachlorophenols (TCP) could be detected at a level of up to 291 $\mu\text{g}/\text{m}^3$. Tetra-chlorodibenzo-p-dioxin (TCDD), however, could not be detected in the technical PCP product (detection limit: 1 ppb). On the basis of these results, possible neurotoxic effects of TCDD could largely be ruled out. The chlorinated hydrocarbons lindane and aldrin could be detected only in traces up to 5 ppb in air samples, so that a relevant neurotoxic effect could not result from this.

The employees included in the study have had an average of 16 years contact with working materials containing TCP or PCP. A comparison of the results of biological monitoring of the years 1980 and 1984 shows good agreements with regard to the serum PCP values.¹⁹ It is important in this connection that alterations in the production technique have not been made in past years, so that retrospectively one may assume relatively constant exposure conditions in this period. Lauwerys suggests a urinary limit value of 1 mg free PCP/g creatinine²⁵; there was only one case bordering on this both in 1980 and in 1984, the other values were always below the limit. We have not found a recommended limit value for PCP in serum. The evaluation of a biological tolerance value for working materials (BAT value) for PCP by the Commission of the German Research Society is at present in preparation (tentative values: 1000 μg PCP/l serum and 300 μg PCP/l urine).²⁶

In some cases values at the workplaces investigated are considerably less than the current MAK value²⁷ of 500 μg PCP/ m^3 air. Because of the known percutaneous absorption of PCP, biological monitoring has a greater significance for the surveillance of exposed workers than ambient air monitoring.

The neurophysiological findings do not show any negative effects of a chronic exposure to PCP for both 1980 and 1984 or over time. There are thus no relevant indications for the presence of adverse effects on the peripheral nervous system. This observation is supported by the results of correlation analyses using the exposure duration and exposure index respectively. Overall, no correlations were calculated

in the sense of dose effect relations. We have found no corresponding published neurophysiological studies for employees exposed to PCP. The longitudinal study essentially confirms the results of the earlier investigation.¹⁹ The indications for a correlation between the altered pattern of neurophysiological results and long term PCP exposure detected at that time in three out of 18 subjects cannot be confirmed in the longitudinal study.

The lack of any peripheral neurotoxicity of PCP shown by these results is also explained pathophysiologically. PCP is more readily soluble in water than other chlorinated hydrocarbons (hexachlorocyclohexane, for instance) and thus does not have a pronounced affinity for the high lipid tissues of the nervous system.

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