Occupational exposure to polychlorinated biphenyls in electrical workers. II Health effects

M MARONI,¹ A COLOMBI,¹ G ARBOSTI,¹ SUSANNA CANTONI,² AND V FOA¹

From Clinico del Lavoro "L. Devoto,"¹ University of Milan, and Occupational Preventive Medicine Service,² Municipality of Milan, Italy

ABSTRACT Health conditions were evaluated in 80 electrical workers exposed for many years to polychlorinated biphenyl (PCB) mixtures with a 42% mean chlorine content, who had blood PCB concentrations from 41 to 1319 $\mu\text{g/kg}$. The clinical study was based on personal history data, physical examination, and laboratory tests (red cell and leukocyte count; determination of haemoglobin, packed cell volume, bilirubin, serum protein electrophoretic fractions, pseudocholinesterase, AST, ALT, GGT, and OCT). Fifteen workers were found to have skin diseases—chloracne (4), folliculitis (4), oil dermatitis (1), juvenile acne (1), and dermatitis due to irritative or allergic agents (5). Sixteen workers showed more or less pronounced hepatic involvement, consisting most often of hepatomegaly with an increase in serum GGT, AST, ALT, and OCT values. In two workers bleeding cavernous haemangiomas were discovered, in one case associated with chronic myelocytic leukaemia. All the workers with chloracne were employed on electric capacitor impregnation with PCBs, and no definite association was found between chloracne and blood PCB concentrations. Conversely, a significant positive association was found between the abnormal liver findings and blood PCB concentrations, particularly trichlorobiphenyl blood concentrations.

The abnormal hepatic findings observed are similar to those reported in experimental animals given PCBs, and in some workers such findings should probably be considered as clinical signs of hepatic microsomal enzyme induction.

The toxicity of polychlorinated biphenyls (PCBs) has been studied in several animal species: high oral doses of PCBs induce liver damage in non-human primates and in rodents.¹⁻⁴ In monkeys, depending on dose and mode of administration, acne, alopecia, hyperpigmentation of the skin, thymic atrophy, ocular lesions, and subcutaneous oedema have been also observed.⁵⁻⁷ In rodents, however, low doses of PCBs, not sufficient to cause macroscopically evident organic disease, can alter several biochemical functions: after chronic oral or parenteral PCB administration it was possible to show an increase in the smooth endoplasmic reticulum of liver cells with induction of microsomal enzyme activity,⁸⁻¹⁰ hepatic porphyria,

⁹⁻¹¹ and an altered metabolism of steroids and vitamin A.^{12,13} Despite the numerous studies on PCB toxicity in animals, few data are available on adverse effects on man.

This gap is particularly evident for chronic low-dose effects, such as those that may occur in occupational and environmental exposure, since acute toxic damage after oral poisoning in man was widely reported in connection with yusho, an epidemic that in 1968 affected over 1000 Japanese people who ate rice oil heavily contaminated with Kanechlor 400.^{14,15}

Only a few data are available on the effects on man of occupational exposure to PCBs, but chloracne and possibly liver damage were reported many years ago.¹⁶⁻¹⁸ Commercial mixtures of PCBs are known to contain small amounts of chlorinated dibenzofurans, and some of the toxic effects attributed to PCBs may be due to these compounds.

We report the results of a study on the health of workers with long occupational exposure to PCBs in electric capacitor manufacture and testing plants.

Requests for reprints to: Marco Maroni, MD, Department of Occupational Hygiene and Toxicology, Clinica del Lavoro "L. Devoto," University of Milan, via S Barnaba 8, 20122 Milan.

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Materials and methods

SUBJECTS AND PLANTS

Eighty workers (40 female, 40 male) were studied, 67 of whom were exposed to Piralene 3010* (a PCB mixture with 42% chlorine content) in a plant (A) manufacturing electric capacitors and transformers and 13 exposed to Apirolio† (a PCB mixture with the 42% chlorine) in a plant (B) testing electric capacitors.

The mean age ($\pm$ SD) and duration of employment of the 80 workers was 37 ± 8 and 12 ± 6 years.

The exposure levels of the workers were assessed by liquid gas chromatographic determination of the PCBs in the workrooms and in the blood. For a more detailed description of plants, analytical methods, and results of exposure level evaluation see the previous paper.

CLINICAL METHODS

The workers underwent routine physical examination and a detailed clinical history was obtained; all subjects with suspected skin complaints were also examined by a dermatologist. The following laboratory tests were performed on blood and serum samples from fasting subjects: red cell and leukocyte count; determinations of haemoglobin and packed cell volume; serum bilirubin (total and indirect); serum protein electrophoretic fractions; serum alkaline phosphatase; serum pseudocholinesterase, serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT), serum gamma-glutamyl-transpeptidase (GGT), and serum ornithin-carbamoyl transferase (OCT) activities. Complete routine analysis was performed on morning urine samples.

*Prodelec, France.

†Caffaro, Italy.

Results

Several abnormal findings affecting mainly the skin and liver were detected in the workers.

Skin lesions

In the 80 workers studied 10 cases of acne and folliculitis and five cases of dermatitis due to primary irritative or allergic sensitising agents were detected. Table 1 summarises the clinical features of the cases of chloracne and folliculitis. The first three cases showed the simultaneous presence of active skin lesions (comedones, suppurative folliculitis, and superficial cysts) and repair processes (vermicular scars), while there were no active skin lesions in the fourth case. Cases 5 and 6 were not diagnosed with certainty because the morphology of the skin damage was not very typical for chloracne, neither were the regions affected entirely typical, the most characteristic areas—that is, the malar region, ear, and other parts of the face—being spared.

In the other cases reported in table 1 the key to the diagnosis was the clinical history and the morphology of the lesions.

The workers affected with chloracne were all working in plant A, where they had been employed for many years on capacitor impregnation with PCBs; after the onset of the disease they continued working in the same department of the plant but were less often employed on capacitor impregnation. At the time of the study their blood PCB concentrations were rather high (mean blood PCB concentration = $450 \mu\text{g/kg}$, range $310\text{--}495 \mu\text{g/kg}$), but did not differ significantly from the concentrations of the other five unaffected workers employed on the same job.

ABNORMAL LIVER FINDINGS

Sixteen workers were observed with more or less pronounced hepatic involvement, as deduced from

Table 1 Clinical features of workers with chloracne and folliculitis

Case No	Age (yr)	Age at 1st PCB exposure	Skin lesions		Affected regions	Diagnosis
			Age at onset	Current findings		
1	49	27	39	Vermicular scars, comedones, superficial cysts, and suppurative folliculitis	Abdomen, thighs	Chloracne
2	26	16	22	Vermicular scars, comedones, superficial cysts, and suppurative folliculitis	Face, neck	Chloracne
3	50	20	23	Vermicular scars, comedones, superficial cysts, and suppurative folliculitis	Neck, shoulders, arms, back	Chloracne
4	43	28	40	Vermicular scars	Arms, back, legs	Past chloracne
5	38	24	37	Folliculitis	Scrotum	Folliculitis (possibly chloracne)
6	49	42	45	Comedones with erythema	Neck, sternum	Folliculitis (possibly chloracne)
7	31	23	21	Non-vermicular scars of folliculitis	Neck	Folliculitis
8	40	37	33	Non-vermicular hypopigmented scars of folliculitis	Forearms	Folliculitis
9	38	29	27	Scars of oil-dermatitis	Left forearm	Oil-dermatitis
10	44	25	16	Non-vermicular scars of acne	Back	Juvenile acne

Table 2 Clinical and laboratory findings in workers with liver abnormalities

Case No	Age (yr)	Duration of exposure index*	Hepatomegaly	Laboratory tests†					Blood chlorobiphenyls			
				AST	ALT	SGGT	SOCT	SPCH	TRI-CB	PENTA-CB	TOTAL-CB	
				nr < 12	nr < 12	nr 6-28	nr 0.5-10	nr 18-36	(µg/kg)	(µg/kg)	(µg/kg)	
Plant A workers												
11	52	10.9	+				11		211	480	691	
12	50	13.7	+						355	964	1319	
13	44	6.2	++			34			227	384	611	
14	51	2.6	++ +				10.2		269	403	672	
15	39	2.5	+	20	13	49	17.2	39	269	374	643	
16	26	0.3	+				15		227	1032	1259	
17	52	1.0	++					16	246	249	495	
18	31	1.3	—			39	11.7		105	172	277	
19	38	3.1	—	13			13.7		141	297	438	
				2.20	2.17	6.22	0.3-4.7	18.36				
Plant B workers												
20	30	4.0	+		21.8	33			407	63	470	
21	30	2.5	++			53			328	49	377	
22	56	11.0	++		20				147	33	180	
23	24	2.5	++						77	54	131	
24	26	2.5	++		23.6	49			200	176	376	
25	30	4.0	+		18.2	48			135	155	290	
26	31	2.0	+	25.4	36.4	91			104	48	152	

AST = Serum aspartate aminotransferase; ALT = Serum alanine aminotransferase; SGGT = Serum gamma glutamyltranspeptidase; SOCT = Serum ornithin-carbamoyltransferase; SPCH = Serum pseudocholinesterase; TRI-CB = Trichlorobiphenyl mixture components; PENTA-CB = Pentachlorobiphenyl mixture components; TOTAL-CB = Total chlorobiphenyls.

— = Absent; + = Mild; ++ = Moderate; +++ = Pronounced.

*Duration of exposure index was calculated as follows: duration of exposure index = $\text{yr}_E \times \frac{\text{hr}_{\text{PCB}}}{\text{hr}_{\text{tot}}} \times 100$, where yr_E is the duration of employment in years and hr_{PCB} and hr_{tot} are respectively the annual working hours with exposure to PCBs and the total annual working hours. †Only results outside normal ranges are reported. In plants A and B workers enzymatic assays were performed with different analytical methods. nr = Normal range.

Table 3 Blood PCB concentrations in workers with and without abnormal liver findings

	Age (yr)	Duration of exposure index*	Blood trichlorobiphenyl compounds (µg/kg)	Blood pentachlorobiphenyl compounds (µg/kg)	Blood total chlorobiphenyls (µg/kg)
	Mean ± SD range	Mean ± SD range	Mean ± SD range	Mean ± SD range	Mean ± SD range
Workers with abnormal liver findings (n = 16)	38 ± 11 24-56	4.4 ± 4.0 0.3-13.7	215 ± 95 77-407	308 ± 306 33-1032	524 ± 349 131-1319
Workers without abnormal liver findings (n = 64)	37 ± 8 22-55	3.2 ± 3.0 0.1-12.9	92 ± 64 13-345	176 ± 108 15-489	296 ± 160 41-562
Student <i>t</i> test:	p > 0.1	p > 0.1	p < 0.001	p < 0.01	p < 0.001

*See table 2.

symptoms, clinical examination of the liver, and laboratory tests. They were all men (nine in plant A and seven in plant B) and none had a history of excessive intake of alcohol or drugs.

Eight workers complained of symptoms related to digestive difficulties, such as postprandial epigastric distress, epigastric pain with or without burning, postprandial headache, intolerance to fatty foods, bad taste in the mouth first thing in the morning; in case 20 these symptoms were also accompanied by decreased libido (table 2).

At examination all but two asymptomatic workers showed various degrees of hepatomegaly, in several cases the liver was unusually firm on palpation and in one case facial spider angiomas were present.

The most frequently altered laboratory test results were serum GGT activity (8 cases), transaminases (7), and OCT (6). Blood count, bilirubin, alkaline phosphatase activity, serum electrophoretic fractions, and urine analysis were within the normal range in all workers. None of these workers was suffering from chloracne at the time of the study nor had they been affected in the past.

Affections possibly related to the currently observed liver findings were found in the histories of three workers. Case 17 had suffered six years previously from acute ischaemic heart disease followed by aortocoronary bypass implantation and serum infectious hepatitis. Case 18 had suffered from cholelithiasis in the past, but at the time of the study he

Fig 1 Frequency of workers with abnormal liver findings for increasing levels of blood trichlorobiphenyl concentrations. χ^2 trend = $p < 0.001$ (for statistical analysis workers with blood trichlorobiphenyl concentrations below 150 µg/kg and above 300 µg/kg were collected only into two groups).

Fig 2 Frequency of workers with abnormal liver findings for increasing levels of blood pentachlorobiphenyl concentrations. χ^2 trend = $p < 0.05$ (for statistical analysis all the workers with blood pentachlorobiphenyl concentrations above 450 µg/kg were collected into a single group).

Fig 3 Frequency of workers with abnormal liver findings for increasing levels of blood total chlorobiphenyl concentrations. χ^2 trend = $p < 0.001$ (for statistical analysis all workers with blood total chlorobiphenyl concentrations above 600 µg/kg were collected into a single group).

had not had any symptoms for several months. Lastly, case 25 had had a transitory drug-related icterus about ten years previously after treatment for pulmonary tuberculosis: he quickly recovered from the icterus and had been well ever since. Evaluating the jobs of the workers with liver complaints in plant A, four workers were employed on capacitor impregnation, two on low-power capacitor assembling and machine servicing, and one on high-power capacitor welding; in plant B all the workers were employed on capacitor testing.

In table 3 the mean age, length of exposure to PCBs, and blood PCB concentrations are reported for the workers with and without hepatic involvement. Statistical analysis indicated a significant difference for blood PCB concentrations, but no significant difference was found for age and duration of exposure. Figures 1, 2, and 3 show the frequencies of workers with liver involvement for increasing blood PCB concentrations. Statistical analysis (χ^2 trend¹⁹) indicated the presence of a significant positive association between prevalence of liver involvement and blood chlorobiphenyl concentrations.

OTHER DISORDERS

In addition to the dermatological and hepatic abnormalities, two cases of bleeding haemangioma and one case of leukaemia were observed.

The first case of haemangioma occurred in the only worker employed in plant A on high-power capacitor welding, who also showed a mild asymptomatic hepatomegaly (case 16 in table 2). This worker had had from birth a skin haemangioma of 3-4 cm diameter on the forehead; it had not troubled him in the past but after a few months' working at the present job, it had begun to expand and bleed and surgical excision was necessary.

The second case of haemangioma occurred in the worker who also had leukaemia. This man had been employed in the high-power capacitor department of plant A since the age of 30 and for 16 years after had always been well. Six months before the beginning of the present study, he complained of bleeding from the tongue and was admitted to hospital. A cavernous haemangioma of the tongue was found and surgically treated. Laboratory tests performed in hospital showed a chronic myelocytic leukaemia, since when the patient has been undergoing treatment.

Discussion

The workers studied here had been exposed to PCBs for a long time, and had blood PCB concentrations from 41 to 1319 µg/kg (see table 3); a large proportion were found to have abnormalities of the skin or

the liver (tables 1 and 2).

As regards the skin, some cases of chloracne observed were attributable to PCB exposure. This disease was diagnosed and distinguished from simple folliculitis by the pathognomonic morphology of the skin lesions and from the "spontaneous" acne due to the atypically affected regions (arms, legs, abdomen, scrotum, etc). In two cases the distinction was not certain because of the concomitant presence of typical and atypical diagnostic features of chloracne. All the four cases of chloracne observed had developed several years ago in workers with long service, and in three cases, despite the decrease in intensity of exposure, still active skin lesions were found indicating the progressing nature of this disease. The mechanism by which chloroarylhydrocarbons induce chloracne is not known: it was suggested that the sebaceous gland damage might be due to the local contact of these substances,²⁰ but according to Puccinelli²¹ the skin lesions' PCB is transported by the blood to the site of lesion after both gastrointestinal and cutaneous absorption. Congenital predisposition has been considered important in the pathogenesis of acne, and a tendency to seborrhoea probably also favours the onset of chloroacne.

Conventional liver function tests and clinical investigation gave abnormal results in 16 workers. The findings were mainly hepatomegaly of various extent and dysfunction indicated by increase in serum enzymatic activities but only in a few cases was a well-defined mild liver failure (presence of symptoms, hepatomegaly, and abnormal laboratory findings) present.

As suggested by the data reported in table 3 and in figs 1, 2, and 3 the liver involvement seems to be connected with the internal dose (body burden) of PCBs. Testing the frequency of hepatic involvement against blood PCB concentration, a significant trend ($p < 0.001$) was clearly observed for blood trichlorobiphenyls, but not for pentachlorobiphenyls ($0.01 < p < 0.05$). As the blood concentration of trichlorobiphenyls may reflect the current PCB exposure level more closely than that of pentachlorobiphenyls, the correlation between liver involvement and occupational PCB exposure seems to be more likely.

Some abnormal results in liver function tests (since the mean of each test for the whole group was within normal limits) were found by Ouw *et al*²² in 34 workers with a mean blood Aroclor 1242 concentration of 400 $\mu\text{g/kg}$ (range from trace to 4510 $\mu\text{g/kg}$). In that study no association was observed between BSP retention values and blood Aroclor concentrations or duration of exposure. Also, no signs of toxicity were evident in 11 Finnish workers exposed to Aroclor 1242, whose blood PCB concentrations were from 75 to 1900 $\mu\text{g/kg}$.²³ In our study the number of

workers and the limited liver screening methods did not allow a precise dose-response relationship to be set between internal PCB dose and liver functions. Nevertheless, if the tentative biological limit of 200 $\mu\text{g/kg}$ of PCBs in blood suggested by Ouw *et al*²² is applied to our results, 20% of the cases with abnormal hepatic findings had lower blood PCB concentrations: this could mean that the efficacy of this limit needs to be further evaluated.

The carcinogenicity of PCBs has been tested in several animal species and in the opinion of the IARC²⁴ there is experimental evidence for carcinogenic effects of some PCBs in rodents. In man evidence suggestive of a relation between exposure to PCBs and the development of malignant melanoma was recently reported.^{25, 26} Moreover, in a study of 73 Finnish necropsies, the highest concentrations of PCBs were found in the liver and adipose tissue of three people who had died of cancer (lung, liver cancer, and leukaemia).²⁷ Among our workers two fast-developing cavernous haemangiomas and one myelocytic chronic leukaemia were discovered: these observations have induced us to plan a retrospective epidemiological study on cancer incidence among these workers.

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