CHAPTER 9C

Occupational exposure

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9C.1. Introduction

Reports of illness associated with exposure to chlorinated organic chemicals of the type discussed in this book date back to the latter part of the 19th century (Herxheimer, 1899) and the early part of the 20th century (Bettmann, 1901; Wauer, 1918; Lehmann, 1905).

Extensive outbreaks following exposure to chlorinated naphthalenes occurred during World War I, but it was not until the middle of the 20th century that occupational illness from exposure to the other compounds has become a problem. Review of the available literature suggests a clinical syndrome that is produced by the halogenated biphenyls, naphthalenes, dibenzodioxins and dibenzofurans. It is presently not known whether halogenated terphenyls may cause similar problems. Some of the signs and symptoms observed following exposure to toxic levels of these compounds have been noted frequently (Table 9C.1). In all instances, the skin lesion, *chloracne*, was usually one of the first signs noted. Signs and symptoms such as weight loss, general malaise, nausea, loss of appetite, impairment of liver function, hepatic prophyria (porphyria cutanea tarda) (see Chapters 7, 8) and sensory neuropathy were less frequently reported. Other effects were occasionally associated with some outbreaks of occupational illness, but their significance is not well understood. Not all of the observed signs have been reported for all of the chemicals under discussion. Chloracne, weight loss and impaired liver function have been most frequently associated with exposure to toxic levels of these chemicals.

As outlined in Chapter 7, 2,4,5-trichlorophenol and all chemicals made from it may be contaminated with 2,3,7,8-tetrachlorodibenzodioxin. Pentachlorophenol

Kimbrough (ed.) Halogenated biphenyls, terphenyls, naphthalenes, dibenzodioxins and related products

TABLE 9C.1
Symptoms and signs reported after occupational exposure.

System	Lesion	Chemical	Reference[a]
General	bloodshot eyes, lassitude, headache, abdominal pain, impotence, weight loss, insomnia, alopecia, disturbance in taste	chlorinated naphthalenes	Good and Persky, 1943
		technical pentachlorophenol	Bauer and Bauer, 1951; Behrbohm, 1959
		2,3,7,8-tetrachlorodibenzodioxin	Jirasek et al., 1974
		chlorinated biphenyls	Jones and Alden, 1936
Skin[b]	chloracne, pruritus	2,3,7,8-TCDD	Kimming and Schulz, 1957
		chlorinated biphenyls	Jones and Alden, 1936
		chlorinated naphthalenes	Good and Persky, 1943
		tech. pentachlorophenol	Behrbohm, 1959
		other tech. chlorinated phenols	Stingily, 1940; Dagois and Colomb, 1956
Liver	acute yellow atrophy, hepatocellular necrosis, mild fibrosis, fatty change, abnormal liver function, porphyria cutanea tarda	chlorinated naphthalenes (tetra-, penta-, hexa-)	Collier, 1943
		2,3,7,8-TCDD	Bauer et al., 1961; Bleiberg et al., 1964; Goldmann, 1972; Jirasek et al., 1974
		tech. pentachlorophenol	Truhaut et al., 1952; Gordon, 1956
		polychlorinated biphenyls (abnormal liver function tests)	Ouw et al., 1976
Digestive tract	anorexia, vomiting, hemorrhage	chlorinated naphthalenes	Good and Persky, 1943; Dwyer, 1946
		2,3,7,8-tetrachlorodibenzodioxin	Hofmann, 1957; Goldmann, 1972
Peripheral nervous system	sensory neuropathy, peripheral neuritis	2,3,7,8-tetrachlorodibenzodioxin	Goldmann, 1972; Jirasek et al., 1974
Respiratory system	bronchitis, reduced vital capacity	technical pentachlorophenol	Bauer and Bauer, 1951
		polychlorinated biphenyls	Warshaw et al., 1979

a. The symptoms and signs listed were observed by a number of other authors. The references listed serve merely as examples.
b. Depigmentation was reported in blacks for chlorinated naphthalenes by Collier (1944).

may be contaminated with more highly chlorinated dibenzodioxins, dibenzofurans and hexachlorobenzene. The polychlorinated biphenyls contain trace amounts of chlorinated dibenzofurans and chlorinated naphthalenes. Whether chlorinated naphthalenes are contaminated with chlorinated dibenzodioxins and chlorinated dibenzofurans has not been established. In fact, little is known about the complete composition of the technical products that have caused outbreaks of occupational illness in the past.

The cases of chloracne which Herxheimer reported (1899) occurred in a room where caustic potash was produced by the electrolysis of potassium chloride. The chlorine was reacted with calcium to give calcium chloride. Herxheimer initially assumed that nascent chlorine had caused the dermatitis. Crow (1970a) pointed out that, although many authors clung to the nascent chlorine theory, the cause was halogenated hydrocarbons which originated from the tar lining in the absorption towers, or the anodes of tar, bitumen and charcoal that were used in the electrolytic manufacture of hydrochloric acid and similar substances. These tars were the sources of the cyclic compounds which became halogenated. Thus far, it has not been unequivocally shown whether specific isomers in the mixtures of chlorinated naphthalenes and biphenyls are the acnegenic agents and also cause some of the systemic toxic effects. Most chlorinated biphenyl mixtures are contaminated with 2,3,7,8-tetrachlorodibenzofuran which may contribute to their toxicity. Certainly the contaminants in 2,4,5-trichlorophenol and related products are the agents responsible for chloracne (Kimming and Schulz, 1957). Most likely the contaminant hexachlorodibenzodioxin in pentachlorophenol causes chloracne.

9C.2. Chloracne

Depending on the severity of the exposure and the susceptibility of the individual workers, some will develop an occupational disease commonly referred to as chloracne after having had exposure to the halogenated cyclic compounds mentioned above for several weeks or months. Following exposure to high concentrations of 2,3,7,8-tetrachlorodibenzodioxins, the onset may be more rapid. Even after a single exposure to 2,3,7,8-tetrachlorodibenzodioxins, the onset of chloracne may be delayed for several weeks, but if the exposure is severe, it may appear in as little as 2–3 days. One, or repeated short-term, exposure to 2,3,7,8-tetrachlorodibenzodioxin usually occurs during the production of 2,4,5-trichlorophenol when the reaction overheats, resulting in the increased production of the unwanted contaminant 2,3,7,8-tetrachlorodibenzodioxin. This exothermic reaction may give rise to explosions (Milnes, 1971).

The clinical features of chloracne, regardless of the type of chemical that caused it, have been most consistent. The most distinctive cutaneous lesion is the chloracne cyst (Crow, 1970b). This lesion is skin-colored and measures from 1 to 10 mm in diameter with a central opening. The other dominant lesion is the comedo (Figs. 9C.1, 9C.2). Usually these lesions start over the maxillary bone, then involve the

Fig. 9C.1. Only mild chloracne over maxillary bone is noted.

entire face, the neck and ears. Often the nose and nasolabial folds are not as extensively involved. In males, the genitalia may be involved. Furthermore, lesions may be present on the back, arms and legs, and other areas of the body, particularly where garments are in close contact with the skin. Depending on the severity, the skin contains only a few lesions (Fig. 9C.1) or the lesions are so close together that they give the skin a rough, grayish-brown appearance. The comedones and cysts can become secondarily infected and large pustules may form. Cysts may rupture and cause foreign body granulomata.

The chloracne-type skin lesion may be preceded by a faint rash which, in some cases, itches severely. In areas exposed to the sunlight, a photosensitivity-type reaction may occur and conjunctivitis with swelling of the eyelids and the rest of the facial skin may precede the development of chloracne. Since the workers are often exposed to the chloracnegenic agent, such as TCDD, as well as other chemicals, such as 2,4,5-trichlorophenol, it is not entirely clear whether the early rash is produced by the TCDD or due to the irritating effect of the 2,4,5-trichlorophenol or other substances.

Once chloracne has developed, it may remain active for many years, and particularly when secondary infections occur, deep-pitted scars may remain as a residual effect. These scars can be quite disfiguring (Fig. 9C.3). No specific treatment is available and most palliative means have not been very effective. Treatment in the

Fig. 9C.2. A worker with acute extensive chloracne.

past has included Vitamin A acid, UV light, X-ray, lancing and expressing of pustules. However, the best treatment is prevention, although dermabrasion has also been effective (Crow, 1970a).

The manufacture of these chlorinated hydrocarbons and the coating of wires and condensers with insulating materials and other industrial processes should be done in enclosed systems. Protective clothing provided by and laundered by the company should be handed out fresh daily. Shower baths after work should be compulsory and supervised. Sufficient shower facilities should be available so that workers are not delayed. Schwartz and Peck (1943) suggested synthetic wetting agents instead of soap as cleanser. They also recommended monthly skin examinations and liver function tests. In the United States, recommendations for a lower polychlorinated biphenyl standard were made by the National Institute of Occupational Health in 1977 (NIOSH, 1977) which suggests proper hygiene procedures to avoid dermal contact and recommends that occupational exposure be controlled so that no worker is exposed to PCBs at a concentration greater than 1.0 $\mu g/m^3$ of air deter-

mined as a time-weighted average (NIOSH, 1977a). The existing standards for occupational exposure to PCBs in different countries have been summarized by the International Labour Office (1970). They range from 0.5 mg/m^3 to 1.0 mg/m^3 in many countries.

It is particularly important that no potentially contaminated clothes are taken home since chloracne has been transmitted by this vehicle to other members of the family.

A skin lesion exactly like chloracne can be produced on rabbit ears or hairless mice and the muzzle of rhesus monkeys. In cattle and horses, a microscopically slightly different skin lesion which is also called hyperkeratosis or X-disease develops following exposure to compounds that produce chloracne in humans. In cattle and horses, the skin lesion is usually accompanied by hair loss in the affected areas and the epidermis is covered by a thick layer of keratin (Kimbrough, 1974; Kimbrough et al., 1977). Prior to the ability to detect chloracnegenic compounds by chemical analysis, the rabbit ear test was utilized to screen technical products for their presence (Adams et al., 1941) (see also Chapter 5).

In rabbits, monkeys and men, the microscopic appearance of the skin lesion varies, depending on the interval between last exposure and the time the biopsy was obtained. Microscopic examination of human skin biopsies from chloracne cases or tissue sections from rabbit ears with hyperkeratosis show markedly dilated hair follicles that are filled with keratin. Eventually the entire follicular appendage becomes transformed into a sac of keratin (Figs. 9C.4 and 9C.5). The sebaceous glands involute partially or completely. The epithelial cells lining the follicles and adjacent to them proliferate. Acanthosis is present and the individual prickle cells become enlarged. Polymorphonuclear leukocytes aggregate around hair follicles. This is followed by intrafollicular collections of leukocytes, microvesicles and abcesses within the follicular wall. Subsequently the follicular wall is destroyed and an abcess may develop. According to Shelley and Kligman (1957), who induced chloracne experimentally in 31 male adults with chlorinated naphthalenes, the sebaceous glands returned gradually months after the last application. Eventually, the epithelium lining the keratin-filled follicles atrophies.

Although on casual examination, chloracne resembles juvenile acne, the distribution of chloracne is quite different as is frequently the age of onset. Juvenile acne is characterized by papular eruptions due to inflammation with the accumulation of secretion of the sebaceous glands. Hyperkeratosis and atrophy of sebaceous glands does not occur in juvenile acne.

In a few instances in which workers developed chloracne following exposure to 2,3,7,8-tetrachlorodibenzodioxin, hypertrichosis and hyperpigmentation was pronounced (Jirasek et al., 1976; Bleiberg et al., 1964).

For many years, it was believed that chloracne was due to external contact and not the result of systemic exposure to the acnegenic agents. However, this belief is refuted by two episodes of accidental poisoning following ingestion of the acnegenic compounds. In one episode, 'Yusho' rice bran oil became contaminated with a

Fig. 9C.3. Residual scars subsequent to chlorsene.

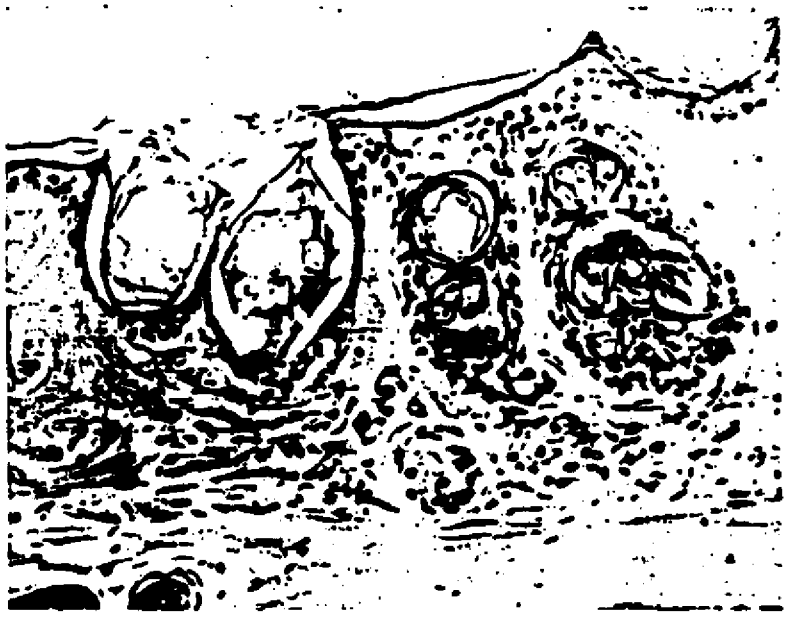

Fig. 9C.4. Follicular appendage of the skin from a normal rabbit ear.

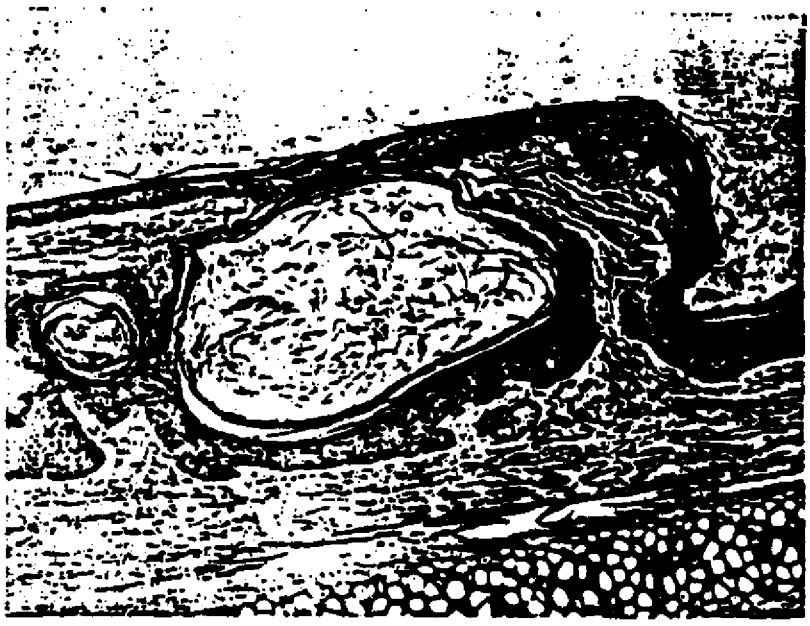

Fig. 9C.5. Follicular appendage from a rabbit ear affected by a chloracnegenic agent.

mixture of chlorinated biphenyls, quarterphenyls and dibenzofurans (Rappe et al., 1977; Miyata et al., 1978), and resulted in illness which included chloracne (Chapter 9B.1).

In 1945, six people fried vegetables in a fat-like substance thought to have been hexachloronaphthalene which they found in the bomb ruins of Berlin in Germany (Hertzberg, 1947) and subsequently developed chloracne. Similar skin lesions can also be produced in primates by oral exposure to chlorinated biphenyls or chlorinated dibenzodioxins (Barsotti and Allen, 1975; Allen et al., 1977). In rabbits, depending on the dose, application of acnegenic agents on the ear may either only result in local hyperkeratosis or at higher doses also produce a toxic effect on the liver (Kimbrough, 1977). Thus, local dermal application of these compounds, particularly the 2,3,7,8-tetrachlorodibenzodioxin may also lead to systemic disease. More recently, occupational exposure to 3,4-dichloroaniline and some herbicides made from it, such as propanil (*N*-(3,4-dichlorophenyl)propanamide) have also produced chloracne. In these instances, the toxic contaminant is tetrachloroazobenzene or tetrachloroazoxybenzene (Morse et al., 1979). These compounds are not as stable as the chemicals discussed in this book, and hence may be less of a problem.

9C.3. Presence of halogenated aromatics in human tissues and body fluids

Of all the chemicals discussed, only the chlorinated biphenyls have been measured with any frequency in human tissues. Chlorinated dibenzofurans were found in patients suffering from Yusho (Chapter 9B1) and in one instance, tissue was analyzed for 2,3,7,8-tetrachlorodibenzodioxin from a resident living in the Seveso area in Italy (Chapter 9B2). Brominated biphenyls are not as prevalent in human tissues as chlorinated biphenyls and are primarily found in the population of the state of Michigan, U.S.A. (Chapter 9A). Since the chlorinated biphenyls are lipophilic, the highest concentration is found in adipose tissue, although proportionally lower concentrations are present in other organs as well as blood. The different chlorinated biphenyl isomers are metabolized at different rates (Chapter 4) resulting in shifts in the gas-chromatographic pattern. The ratio of polychlorinated biphenyls between adipose tissue, other organs and blood varies somewhat, depending on whether exposure is current or took place in the past and whether the blood specimen was fasting. Pregnancy, weight loss and kidney disease may also affect this ratio. In order to determine the body burden of these compounds, adipose tissue would be the most suitable specimen for most of the halogenated aromatic compounds. Although appropriate for individual cases, it is usually not feasible to obtain adipose tissue samples in large population studies. In spite of the limited value of blood levels as an indicator of body burden, they can give some idea of the levels of exposure. A person with a polychlorinated biphenyl blood level of 10 ppb (μg/l) might at the most have adipose tissue levels of a few ppm (mg/kg) or less, while those with blood levels of 100 ppb (μg/l) might have adipose levels anywhere from 20 to 50 ppm (mg/kg). Since the chlorinated dibenzodioxins and chlorinated dibenzofurans, particularly the 2,3,7,8-tetra- isomer, are so extremely toxic, illness would be expected to be present at lower concentrations than for chlorinated bi-

TABLE 9C.2
Partial list of chemical companies where explosions or sudden accidental release of large quantities of TCDD has occurred during the production of 2,4,5-trichlorophenol and related products.[a]

Name of company	Place	Year	Reference
Monsanto	Nitro, W.Va., U.S.A.	1949	IARC, 1978
Badische Anilin und Soda Fabrik	Ludwigshafen, Rhein, G.F.R.	1953	Hofmann, 1957
Philips Duphar Ltd.	Amsterdam district, Harlem, The Netherlands	1963	Dalderup, 1974a, 1974b
	Grenoble, France	1966	Dugois and Colomb, 1956
Coalite and Chemical Products Ltd.	Bolsover, U.K.	1968	May, 1973
	Hamburg, G.F.R.	1954	Schulz, 1957; Kimming and Schulz, 1957
ICMESA	Seveso, Italy	1976	Hay, 1979

a. Additional companies are listed by Hay (1979).

phenyls. These chemicals are also more polar and it is possible that their concentration in the liver may be different relative to the concentration in adipose tissue. However, this was not the case for the one resident from Seveso, Italy, who was studied in this respect (Chapter 9B2).

Low background levels of PCBs can be found in blood and other tissues of the general population of industrialized nations (Chapter 9A). Such background levels need to be considered when occupational exposure is evaluated.

Since PCBs are mixtures of chemicals, quantitation is quite difficult and a number of different ways of quantitating them have been proposed, such as adding the PCB peak heights of the gas chromatograms and comparing it to a known amount of standard (see Chapter 2). Because of these differences in quantitation, the differences in isomeric composition of the different PCB mixtures, and differences in individual susceptibility, it can presently not be predicted with certainty what a toxic blood or adipose tissue level constitutes in each case. However, in some individuals, PCB concentrations of 50 ppb (ng/g) in blood were associated with abnormal liver function tests (MMWR, 1978), while in other studies (Karppanen and Kolho, 1973), this was not the case. In capacitor plants where PCBs are heated and, therefore, volitalized, considerable respiratory exposure occurs (Table 9C.4). If PCBs are handled at room temperature as in the production and repair of transformers, dermal exposure may predominate.

Very little information is available linking PCB air levels to PCB blood levels, PCB adipose tissue levels or symptoms (Table 9C.3). Since PCB air levels may fluctuate a great deal, air monitoring may not adequately reflect exposure.

No published information is available on the presence of halogenated naphthalenes and terphenyls in workers. Neither have the chlorinated dibenzodioxins or dibenzofurans been extensively measured in the occupational setting.

TABLE 9C.3
PCB concentrations in the occupational environment and in blood of workers exposed to PCBs.

Duration of PCB exposure	PCB levels		Effects reported	Reference
	Environmental (mg/m^3)	Blood (ppb)		
Not known	10	–	unbearable irritation	Elkins, 1959
4–8 mo.	5–7	–	chloracne	Puccinelli, 1954
<1–20 yr.	0.2–1.6	370, ave.	chloracne, hyperpigmentation, liver injury	Hasegawa et al., 1972
2.5 yr. ave.	not reported	820, ave.	chloracne	Kitamura et al., 1973
2.5–18 yr.	0.013–0.27	36–286	irritation, liver injury	Levy et al., 1977
14 mo.	0.1	–	chloracne, liver injury	Meigs et al., 1954
2–23 yr.	0.32–1.44	>200	chloracne, liver injury	Ouw et al., 1976
Up to 15 yr.	not reported	7–300	chloracne, elevated triglycerides	Hara et al., 1974 Hara et al., 1975
	<1	74–1,900	no effect	Karppanen and Kolho, 1973

9C.4. Polychlorinated biphenyls

Chlorinated biphenyls (PCBs) were introduced into industry around 1929 and in the early 1930s. They were primarily used as dielectric fluids in capacitors and transformers. In capacitor plants, the chances of being exposed to PCB vapors were greater than in transformer plants. Later, the use of polychlorinated biphenyls expanded to other areas (Chapter 1). One of the first reports on health effects of polychlorinated biphenyls was made by Jones and Alden (1936). These authors examined 17 of 23 workers that were engaged in the production of polychlorinated biphenyls. All of the workers had chloracne. The chloracne involved the face, genitalia, trunk and extremities in many of the workers. Prior to the outbreak of chloracne in the plant, the electrical property of the chlorinated biphenyls had fallen below specifications and the color of the product had deepened. It was not determined whether this was caused by a change in the chemical composition of the material. The symptoms of illness in the report were more extensively described in the first worker that presented himself with chloracne. This worker complained of lassitude, loss of appetite and loss of libido. Unfortunately, it is not clear from the report whether a more than cursory attempt was made to determine systemic health effects. In 1937, Drinker et al. reported their efforts to determine whether chlorinated biphenyls had systemic health effects. Their studies were prompted by three fatal cases of jaundice in workers who had been exposed to chlorinated naphthalenes and chlorinated biphenyls. In only one of these three cases is the presence of chloracne mentioned. Exposure in all three instances was to tetra- and pentachloronaphthalene and 10% chlorinated biphenyls. Drinker et al. (1937) mention and warn against the use of carbon tetrachloride as a solvent since it may have additive toxic effects on the liver. Following these studies, a tabulation of 14 chlorinated hydrocarbons with permissible safe concentrations in the air of work-rooms was made (Drinker, 1939). Over the years, other cases of chloracne following exposure to chlorinated biphenyls were reported in the literature. Most of these involved exposure to vapors which developed when polychlorinated biphenyls or mixtures of chlorinated terphenyls were heated (NIOSH, 1977).

At times, the skin rashes that workers developed were accompanied by pruritus. Some of these workers had other complaints, such as burning of the eyes, nose and throat, dry throat, nausea and dizziness. Many of the workers were also exposed to trichlorobenzene. Meigs et al. (1954) reported chloracne in workers who had had exposure to polychlorinated biphenyl vapors for 5–14 months. The concentration of polychlorinated biphenyls in the workers' breathing zone was determined to be 0.1 mg/m^3. Evidence of slight liver injury was also present in these workers. Air level determinations in the earlier outbreaks of chloracne were not reported. Only recently have better and more accurate methods of PCB quantitation been developed. Thus, Ouw et al. (1976) found air levels in a capacitor plant which ranged from 0.32 mg/m^3 Aroclor 1242 (PCBs) to 1.44 mg/m^3. Workers in this environment complained of burning of the eyes, face and skin, and persistent body

odor. Nineteen of the 34 workers were employed in an impregnating room and had heavy exposure while the remainder of the workers assembled Aroclor dipped capacitor components and had less exposure. One worker suffered from chloracne and five complained of eczematous rashes. A few of the workers had abnormal liver function tests, elevated serum protein levels and others showed low levels of serum α_1-globulin. These workers had a mean PCB blood level of about 400 ppb (μg/kg). The control group in this study had no detectable PCB blood levels. This lack of PCB background levels in the general population of New South Wales was explained by the fact that environmental pollution with PCBs in that part of the world is much lower.

In most studies of workers with chloracne, evidence of liver injury was also found and in one study, abnormal liver function tests were present in workers who did not have chloracne (NIOSH, 1977). Elevated serum triglycerides have been found in exposed workers in the United States (Fishbein et al., 1979) and in Japanese studies. Similarly, Smith et al. (1978) found slightly elevated triglyceride levels and lower high and low density lipoproteins in workers slightly and moderately exposed to PCBs when fasting plasma levels were compared to controls. Similarily, Sak and Ahlers (1977) observed significantly elevated serum concentrations of triglycerides, total cholesterol and phospholipids in workers occupationally exposed to polychlorinated biphenyls. Many factors can influence serum lipoprotein levels (Beaumont et al., 1970), such as diet, excessive alcohol consumption, pregnancy, exercise, emotional stress, smoking, estrogens, other hormones and medications, such as salicylates. In addition, hyperlipoproteinaemia also occurs in a number of common diseases, such as hypothyroidism, insulin-dependent uncontrolled diabetes, nephrotic syndrome, biliary obstruction, pancreatitis, dysglobulinemia, or auto-immune hyperlipoproteinemia. It would be of great importance to determine whether halogenated biphenyls and related compounds do generally also have such an effect as a few studies suggest, and at what exposure levels this effect occurs.

Animal studies suggest that lipid metabolism in the liver may be affected by halogenated biphenyls (Kimbrough et al., 1972).

Another effect of PCBs on the liver is the induction of *mixed-function oxidases*. This has been studied extensively in animals. Alvares et al. (1977) determined that in 5 workers occupationally exposed to Aroclor 1016, a PCB mixture primarily composed of di-, tri-, tetra- and pentachlorobiphenyls, plasma antipyrine half-life was significantly lower than in matched controls. These workers had been exposed to Aroclor 1016 for at least 2 years and had no obvious signs or symptoms of PCB poisoning, such as chloracne or abnormal clinical liver function test results. Other health effects that have been reported more recently are eye and upper respiratory irritation. Thus, Warshaw et al. (1979) studied a group of 326 workers in a capacitor plant with a mean employment of more than 15 years and a mean age of 41.1 years for males and 47.3 years for females. Work-related eye or upper respiratory irritation was reported by 48% of the workers, and 10% had experienced tightness in the chest. Spirometric studies were conducted on 309 workers; 66 of them were

dropped from the study because of exposure to talc, textile dust or asbestos, leaving 243 for analysis. In males, there were about twice as many smokers and exsmokers as nonsmokers. In females, the proportion of nonsmokers was higher. Thirty-four of the workers (14%) had a reduced vital capacity and 27 of these demonstrated a restrictive pattern of impairment (FEV/FVC >0.7). According to Warshaw et al. (1979), the prevalence of restrictive impairment in the capacitor workers is comparable only to that found in asbestos workers. The vital capacity in PCB workers that had no opportunity to be exposed to asbestos should be studied to confirm these findings.

No conclusive evidence has thus far been reported which demonstrates that occupational exposure to PCBs has caused an increased incidence of cancer.

Bahn et al. (1976) reported results of a preliminary investigation. This study consisted of a search of chart records of a group of 51 research and development employees and 41 refinery plant employees at a New Jersey petrochemical facility. Between 1949 and 1957, these workers had been exposed to Aroclor 1254, a PCB mixture composed of chlorinated biphenyl homologs from mono- to heptachlorobiphenyl. Three melanomas and two carcinomas of the pancreas were found. This incidence was significantly higher than the expected rates. Since exposure to other chemicals also occurred and since the cohort was small, further studies are necessary to determine whether PCBs have caused cancer in humans. A retrospective mortality study conducted by the U.S. National Institute of Occupational Health (CDC) may provide additional information in the near future.

9C.5. Chlorinated naphthalenes

Following the early reports of chloracne which were caused by chlorinated tar products (Herxheimer, 1899; Bettman, 1901), the second episode of outbreaks of occupational chloracne occurred during the first World War following exposure to the chlorinated naphthalenes. Chlorinated naphthalenes (halowaxes) were used in the production of gas masks. Wauer (1918) referred to chloracne as 'pernakrankheit'. The term 'perna' originated from '*per*chlor*na*phthalin'. The chlorinated naphthalenes were also used to impregnate fabric and to make soles for shoes (Teleky, 1927). After World War I, this use of chlorinated naphthalenes stopped. A few years later, the chlorinated naphthalenes were used in the mining industry as water and fire resistant insulating material for detonators. This resulted in outbreaks of chloracne in 1926 and 1927 among workers that produced such detonators (Teleky, 1927). Subsequently, around 1930, chlorinated naphthalenes (Mayers and Silverberg, 1938) and chlorinated diphenyls were used as insulating material for cables and condensers. In the United States, several hundred cases of illness following exposure to chlorinated naphthalenes were reported. Among them were several deaths due to acute yellow atrophy of the liver (Jones, 1941; Sulzberger et al., 1934, Flinn and Jarvik, 1936). However, such cases were isolated and it is possible that such additional factors as infectious viral hepatitis may have contri-

buted to the disease. Since workers in many instances were exposed to mixtures of chlorinated naphthalenes and biphenyls, it was not clear what actually caused the systemic illness. The industries concerned then initiated a study of the toxicity of these products (Drinker et al., 1937). This resulted in improved occupational hygiene and the establishment of exposure limits at the work place and the use of lower chlorinated substances which seemed to cause less health effects. During World War II, chlorinated naphthalenes and chlorinated biphenyls were extensively used in the ship-building industry. Painting the surface of the ships with these chemicals neutralized them against magnetic contact mines. Furthermore, the chlorinated naphthalenes were also used as insulating material for cables. In this industry, illness was observed not only in the workers who insulated the cables, but also in the workers who handled the cables after they had been manufactured. Although the use of chlorinated naphthalenes has declined, they are still used occasionally because of their low cost. Weber (1969) reported chloracne in the cable industry where chlorinated naphthalenes were used. Kleinfeld et al. (1972) described an episode in 1972 where 92 workers were exposed to a mixture of tetra- and pentachloronaphthalenes in the manufacture of insulated electrical coils. In many of the industrial processes, the chlorinated naphthalenes were heated, producing vapors to which the workers were exposed. Although the fact that these compounds caused chloracne had been known for years, the serious systemic effects were not generally recognized until the 1930s and 1940s. The first complaints of the workers were digestive disturbances, burning of the conjunctivae, and in some instances sexual impotence and haematuria (Von Wedel et al., 1943). Other complaints were bloodshot eyes, lassitude, headaches, abdominal pain, weight loss, insomnia, alopecia, and disturbances in taste (Good and Pensky, 1943). A number of case reports appeared in the literature in the '30s and '40s describing patients who worked with chlorinated naphthalenes, developed acute yellow atrophy of the liver and died (Greenburg et al., 1939). Cotter (1944) described a number of such cases. Most of these patients were exposed to chlorinated naphthalenes for several weeks to several months before they became ill. In many instances, chloracne was not recorded in the case reports, and in some instances it was pointed out that it was not present. The following account by McLetchie and Robertson (1942) gives a description of the typical clinical course of these workers:

"This 41-year-old female was admitted with a history of nausea, vomiting, and jaundice of four weeks duration. She had been employed for the past six months at a process which exposed her to fumes of chlorinated naphthalenes. A number of her coworkers had developed an acneform dermatitis, but there was no other case of jaundice. About 8 weeks before admission, the patient began not to feel well and noticed that in the evening, her feet and ankles became swollen. Permanent puffiness developed around the eyes. Two weeks later, she became breathless on slight exertion, jaundice developed four weeks prior to admission. Shortly after onset of jaundice, troublesome nausea developed. However, she did not lose any weight. Vomiting also occasionally occurred. The patient noticed that her urine was

becoming darker while her stools were grayish in color. Physical examination on admission revealed a well-nourished patient which showed no signs of any great discomfort and was mentally alert. A definite but not deep icteric tinge of the skin and conjunctivae was present and a faint purpuric rash was noted on the legs and lower abdomen. There was also slight edema around the ankles and puffiness of the tissues around the eyes. The physical findings were essentially negative except for a slight increase in the area of cardiac dullness and a slightly diminished liver dullness. The urine was dark brown and contained bile. On the third day after admission, the patient became drowsy and the jaundice increased in intensity. Muscular twitching of all limbs developed. A patchy-brown discoloration of the skin over the arms and the chest was noted. The patient continued in coma, the pulse rapidly increased in rate, and she died on the fifth day after admission. On post-mortem examination, two pints of straw-colored fluid were found in the peritoneal cavity and there was marked edema of the loose retroperitoneal tissues. The liver was very small, shapeless, collapsed under a wrinkled capsule, soft in consistency with few firm nodules scattered throughout. The nodules varied in size from a few millimeters to 2.5 cm in diameter. The liver weighed 650 grams (normal 1,500 grams). On section, the nodules were of a dull-yellow color. The intervening soft tissue was mainly red. The gallbladder was normal; the stomach contained much dark-brown mucus. The kidneys were stained deep green, and the heart revealed moderate hypertrophy and slight dilitation of the right ventricle. The cardiac valves showed chronic rheumatic endocarditis. On histologic examination, the liver showed a varying picture of acute damage, fibrous proliferation and regeneration. Large areas of autolyzed, necrotic, hepatic parenchyma were noted. Islets of surviving epithelial tissue in areas with collapsed sinusoids where dead hepatocytes had been resorbed were noted. In these areas, congestion, hemorrhage, and round cell infiltration was also present. Furthermore, small areas of liver parenchyma were surrounded by bands of young connective tissue which contained many poorly formed bile ducts. The pancreas showed minute ares of necrosis in the pancreatic fat. No other findings of note were made."

The livers of the fatal cases reported by Cotter (1944) showed in many areas complete absence of hepatic cells, bile duct proliferation, hemorrhage, and an inflammatory reaction. None of his cases showed typical chloracne although one patient had a papular rash of the forearms. Cotter points out that in blacks, depigmentation of the skin may be one of the early manifestations of illness. Another interesting observation among the seven cases reported by Cotter was the fact that one worker became jaundiced after a year of working with chloronaphthalenes. He was transferred to a department where he did not come in contact with these chemicals and his jaundice subsided, but recurred when he was put back on his original job. Although in most of these instances, the workers were exposed to vapors of chlorinated naphthalenes, Peck (1944) noted an increasing incidence of acne-like lesions in electricians who were installing cables on ships during the second world war. These cables had been coated with chlorinated naphthalenes and chloro-

diphenyls. The chloracne was usually found in electricians engaged in stripping (the coated cables). The halowax which was stripped off was impregnated in asbestos which was wrapped around the wires as insulation.

Experimental studies were carried out with the chlorinated naphthalenes which caused outbreaks in different working situations. These mixtures were composed of chlorinated naphthalenes with various percentages of chlorination. Teleky (1927) pointed out that in factories where the substances used contained only 14% chlorine, the incidence of chloracne was much reduced. In one of the companies, the health status of the workers was greatly improved when naphthalenes with only 7–8% of chlorine were substituted for those with higher percentages of chlorine. A number of experimental studies stimulated by the health problems observed in workers exposed to these chlorinated naphthalenes demonstrated that the penta- and hexachloronaphthalenes seemed to be the most toxic. This experimental work also indicated that mixtures of chlorinated naphthalenes with chlorinated diphenyls increased the toxicity of these materials (Von Wedel et al., 1943). During that time, the most extensive studies were done by Bennett et al. (1938). In these studies, the trichlornaphthalenes were less hepatotoxic than the higher chlorinated compounds and the chlorinated diphenyls were considered to be the most toxic of all. However, no chemical analyses for any of these compounds were performed at the time to determine whether any toxic impurities might be present. Similarly, Shelley and Kligman (1957) tested a number of halowaxes for acnegenic potential in humans. The following mixtures of chlorinated naphthalenes were tested:

Mono- and dichloronaphthalenes (Halowax 1000), tri- and tetrachlornaphthalenes (Halowax 1001), penta- and hexachlornaphthalene (Halowax 1014), heptachlornaphthalene (Halowax 1052) and octachlornaphthalene (Halowax 1051). Of these, only the mixture of penta- and hexachlornaphthalene produced chloracne. The other four chlorinated naphthalene mixtures were without effect. However, Mayers and Silverberg (1938) reported a series of patients who had developed chloracne after being exposed to a mixture of tri- and tetrachlornaphthalenes. Again, no chemical analysis of this particular mixture was done. On the other hand, studies in rabbits injected with mixtures of tri- and tetrachlornaphthalene, or tetra- and pentachlornaphthalene or penta- and hexachlornaphthalene only showed liver damage when they were given the penta- and hexachlornaphthalenes, but not when they were given the mixtures of the other chlorinated naphthalenes. Thus, most of the clinical observations as well as the available experimental data seem to indicate that the penta- and hexachloronaphthalenes are the most toxic components of the mixtures of chlorinated naphthalenes.

9C.6. Contaminants (chlorinated dibenzodioxins and chlorinated dibenzofurans)

Chlorinated dibenzodioxins and chlorinated dibenzofurans are contaminants of a number of commercial products (Chapters 1, 2). The only documented episode of substantial exposure of humans to chlorinated dibenzofurans occurred in Japan,

and these subjects were also exposed to polychlorinated biphenyls (Chapter 9B1). It is known that products such as pentachlorophenol are contaminated with chlorinated dibenzodioxins and chlorinated dibenzofurans, but in the published reports dealing with occupational exposure to technical pentachlorophenol no efforts have been made to distinguish the effects of these trace contaminants from those of pentachlorophenol per se. Through the efforts of Kimming and Schulz (1957), it is known, however, that to a large extent, illness caused by technical 2,4,5-trichlorophenol and all products made from 2,4,5-trichlorophenol is actually caused by TCDD. TCDD is the most toxic isomer of the group of chlorinated dibenzodioxins (Chapter 5).

Occupational exposure to TCDD may occur in the production of 2,4,5-trichlorophenol and all products for which 2,4,5-trichlorophenol is used as starting material. In addition, exposure to commercial products contaminated with TCDD may also result in illness.

Two types of exposures have occurred in these occupational settings. Workers may be exposed daily to TCDD during normal production of 2,4,5-trichlorophenol and its end products. In this type of setting, chloracne developed gradually in some workers after they have been exposed for several weeks or months. In addition, these workers may also show systemic illness.

The other type of occupational illness has a more sudden onset. When 2,4,5-trichlorophenol is produced from tetrachlorobenzene, unless the reaction is carefully controlled, it may overheat and result in an explosion of the reaction vessel. Once the temperature of the reaction exceeds 160°C, increasing amounts of TCDD are also formed. Exposure of workers to TCDD during the explosion and subsequently during clean-up operations has often been quite heavy and has resulted in the onset of chloracne in a week or two, sometimes accompanied by systemic illness. A number of such episodes have been published in the literature and some are listed in Table 9C.2. Clean-up crews and maintenance men are particularly endangered.

Acute symptoms occurring after such accidents have consisted of headaches, nausea and dizziness. Rarely, severe itching, redness and swelling of the face or other areas of the skin may develop, and swelling of the eyelids with conjunctivitis may also be present. Within two or three weeks chloracne develops and systemic illness, such as weight loss, easy fatigueability and aching muscles, particularly in the lower extremities and chest, may be present. Other complaints often recorded were insomnia, irritability and loss of libido. The liver may become tender and enlarged, and sensory changes, particularly in the lower extremities, have been observed. Total serum lipids may be increased and the prothrombin time may be prolonged. Symptoms may be quite persistent, particularly the severe aches and pains which are manifestations of peripheral neuropathy and the fatigueability (IARC, 1978; Bauer et al., 1961; Bleiberg et al., 1964; May, 1973; Jensen and Walker, 1972; Oliver, 1975). Unfortunately, since chloracne is the most obvious manifestation of TCDD poisoning, the systemic effects have been less well studied

and reported. While in some episodes, chloracne seems to be the only significant health effect (May, 1973) in most episodes, systemic illness was also noted. Unfortunately, a number of these episodes either have not been published at all or have only been insufficiently reported, such as the accident which occurred in Nitro, West Virginia, in 1949 or the health effects observed in the Philips Duphar Co. in the Netherlands. The reports made by Bauer et al. (1961), Schulz (1957), Bleiberg et al. (1964), Oliver (1975), Goldman (1972) and Jirasek et al. (1976) describe systemic effects in more detail. Most of the persons exposed in industrial settings were exposed to a mixture of chemicals, such as 2,4,5-trichlorophenol, TCDD, 2,4,5-trichlorophenoxyacetic acid, and, in the episode reported by Jirasek (1976), also to pentachlorophenol. It is, therefore, not clear whether all effects were solely caused by TCDD. Only the two laboratory workers studied by Oliver (1975) had exposure to pure TCDD.

Systemic illness is usually reported only in workers with chloracne. However, Jirasek et al. (1976) cite 4 workers with systemic illness without chloracne. From the other published reports, it is not clear whether all exposed workers were examined for systemic illness or whether they were selected on the basis of chloracne which may have led to the prhaps erroneous assumption that in humans, illness caused by TCDD must always be accompanied by chloracne.

Jirasek et al. (1976) found that a number of their patients had porphyria cutanea tarda. In addition to the chloracne, hypertrichosis and hyperpigmentation were noted. Abnormal liver function test results (elevated SGOT and SGPT) were obtained for 11 of 80 patients. In more than half of the workers, total cholesterol, total lipids, and phospholipids were elevated. Urinary uroporphyrins were elevated in 23 workers. Thin layer chromatography showed that urinary 8- and 4-carboxyporphyrin were increased. Both liver and urine fluoresced under UV light. A peripheral neuropathy was documented in 17 of these workers. In 4 workers, localized effects on the central nervous system were also observed. In the outbreak reported by Bleiberg et al. (1964), a number of workers had, in addition to chloracne, abnormal excretion of urinary uroporphyrins, hirsutism, and hyperpigmentation. Six years later, in a followup study of the same plant, only one worker had persistent uroporphyrinuria (Poland et al., 1971). In addition, a number of authors (Schulz, 1957; Bauer et al., 1961; Jirasek et al., 1976; Oliver, 1975) observed a neurasthenic syndrome characterized by a lack of drive and vigor, sleep disorders, emotional instability and diminished libido or potency (Kleu and Goltz 1971).

Bauer et al. (1961) studied three groups of workers in Germany who had developed chloracne and/or systemic illness after working in the production of chlorinated phenols. Liver biopsies of three workers showed in one instance a fatty liver with slight fibrosis and an inflammatory reaction, and in two instances, 'perihepatic' changes and a brown pigment which stained partially positive for iron. A liver biopsy from another showed a gray pigment which was not positive for iron.

Among the long-term followup studies reported thus far in workers exposed to

TCDD is one by Thiess and Goldmann (1976). Of the 53 original workers exposed to TCDD in 1953, 22 were still employed by BASF in 1976; 3 workers received partial compensation – 1 for persistent chloracne, 1 for residual paresis of the left leg, and 1 because of deafness. Apart from residual scars, the other 18 workers had no persistent skin lesions in 1976. Causes of death were as follows: 2 – myocardial infarct, 4 – cardiovascular decompensation, 4 – carcinoma of different sites, 1 – mitral stenosis, 2 – suicide, 1 – bleeding of the esophagus. As mentioned, one worker had died earlier (Goldmann et al., 1972). No information was given on the 16 retired workers. This study illustrates how persistent the chloracne may be in some individuals.

Recently, a followup study was also conducted on the workers in Nitro, West Virginia (Zack and Suskind, 1980) in which the acute symptoms initially suffered by the workers were described. Aside from the symptoms and signs already mentioned, 4 of 6 workers who were examined in 1949 and 1950 had an enlarged liver and a delayed prothrombin time at that time. A regression of symptoms and signs was observed in these workers when they were reexamined in 1953. The mortality experience of 121 of these workers who had developed chloracne following the explosion in 1949 was also reported. Among this group of workers, 32 deaths were recorded against 46.41 expected. There were 9 deaths from malignant neoplasms with 9.04 expected. There were 5 lung cancer deaths versus 3.02 expected, 1 skin cancer death with 0.15 expected, and 3 deaths from neoplasms of lymphatic and hematopoietic tissue.

A followup examination of 11 of 23 workers who had first become sick in 1953/1954 following exposure to TCDD were reexamined in 1976 (Krause and Brassow, 1978). The chloracne had completely disappeared in only 2 workers. Seven of the 11 still complained of epigastric pain, nausea and intolerance of alcohol. Six of the 11 had an enlarged liver which was not present when they were examined in the 1950s and 6 of the 11 had at least one abnormal liver function test. Furthermore, Hardell and Sandström (1979) have reported an increased incidence of mesenchymal tumors in workers who were either exposed to technical 2,4,5-trichlorophenol or 2,4,5-trichlorophenoxiacetic acid. The problem with all of these studies is that the number of cases examined is small. Hardell and Sandström tried to control for that by conducting a case control study where they matched 4 controls to each case by age, sex and locality. However, by excluding all control cases with cancer, they may have biased their study.

Another chlorinated phenol, pentachlorophenol, is used extensively as a wood preservative and fungicide. This product is contaminated with chlorinated dibenzodioxins and chlorinated dibenzofurans, but usually with the hexa-, hepta- and octa-homologs (Chapter 2). Occasionally, workers engaged in the production of pentachlorophenol have also developed chloracne (Baader and Bauer, 1951) and complaints such as neuralgic pain in the lower extremities, persistent bronchitis and eye irritation (Behrbohm, 1959). The bronchitis seems to be more prevalent in workers exposed to technical pentachlorophenol than to the other technical products

discussed in this chapter. Workers dealing with wood preservatives again experience mixed chemical exposure. Other chemicals used in such industries include organic arsenic and tin compounds, copper derivatives and creosotes. Pentachlorophenol per se is an uncoupler of oxidative phosphorylation and, like 2,4-dinitrophenol, increases the metabolic rate, resulting in hyperthermia, profuse sweating and weight loss. A number of fatalities following exposure to pentachlorophenol have been described (Mason et al., 1965, Bergner et al., 1965). In these cases, absorption of several hundred mg of pentachlorophenol has usually occurred in severe or fatal poisoning and pentachlorophenol blood levels as high as 10–20 ppm (μg/g) have been measured soon after exposure. On the other hand, workers in wood-treating plants may reach pentachlorophenol blood and urine concentrations as high as 10–20 ppm without symptoms of toxicity (Casarett et al., 1969). Simultaneous exposure to heat may make workers more susceptible to the toxic effects of pentachlorophenol. Since pentachlorophenol is used extensively, detection of ppb (ng/g) concentrations of pentachlorophenol in blood or urine must be considered to represent background levels which are frequently detected in the general population (Bevenue et al., 1967; Casarett et al., 1969). In some fatal human cases, hepatocellular necrosis was observed (Truhaut et al., 1952; Gordon, 1956). Whether these effects resulted from the simultaneous exposure to toxic contaminants in pentachlorophenol has never been investigated (see also Chapters 2 and 5). Vacuolation of hepatocytes was also noted in livers of infants who were accidentally exposed to technical-grade pentachlorophenol in a nursery (Robson et al., 1969).

9C.7. Chlorinated terphenyls and brominated compounds

Essentially no information is presently available on halogenated terphenyls and only one preliminary study on workers exposed to brominated biphenyls has been conducted (Kay, 1977). In addition, Bahn et al. (1980) examined 35 workers of a total cohort of 86 men who had been engaged in the manufacture of decabromobiphenyl and decabromobiphenyl oxide. A total of 89 control subjects were chosen from steel workers and wire men. Studies of thyroid function revealed four cases of primary hypothyroidism in the 35 exposed workers and in none of the controls. This represented a prevalence of 11.4% which is statistically significantly higher than the background incidence of 2.8% found in males in the United Kingdom. Since the group of subjects studied was small, additional studies will have to be done to determine how prevalent hypothyroidism is following exposure to these types of compounds.

Summary

The occupational diseases caused by halogenated biphenyls, terphenyls, naphthalenes, dibenzodioxins and dibenzofurans were reviewed. Occupational illness has primarily occurred following exposure to 2,3,7,8-tetrachlorodibenzodioxin, chlorin-

ated biphenyls and chlorinated naphthalenes. The health problems associated with exposure to these compounds include chloracne, liver disease, porphyria cutanea tarda, and neuropathies. Not much is known about the other compounds mentioned.

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