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HUMAN HEALTH EFFECTS OF POLYCHLORINATED BIPHENYLS (PCBs) AND POLYBROMINATED BIPHENYLS (PBBs)¹

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INTRODUCTION

Polychlorinated biphenyls (PCBs) are chemical compounds with the empirical formula $C_{12}H_{10-n}Cl_n$, with $n = 1-10$. They are a mixture of chlorinated biphenyl congeners. Theoretically, 209 such congeners are possible, but at least 20 congeners have never been identified in commercial products. In addition, PCBs may contain polychlorinated dibenzofurans and chlorinated quaterphenyls as impurities. PCBs were discovered before the turn of the century, and the useful industrial properties of mixtures obtained by chlorination of biphenyl were recognized early. In 1966 the discovery of PCBs in environmental samples (1) spurred renewed interest in the analysis and toxicity of these compounds.

In recent years many industrial nations have taken steps to control the flow of PCBs into the environment. PCBs and PCB-containing formulations are restricted (an exception is sometimes made for mono- and dichloro-PCB) for most uses, except for categories such as closed-system electrical equipment and hydraulic fluids in mining equipment.

Commercial production of PCBs began in the United States in the late 1920s. In 1971, Monsanto Chemical Company voluntarily stopped open-ended uses of PCBs, and subsequently only the lower chlorinated biphenyls

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were produced (Aroclor 1242 and 1016). In 1977 the company ceased production entirely (2). Many PCBs manufactured in the past (3) are still in use in old transformers, but even this use is decreasing. The estimated cumulative production and consumption of PCBs in the United States in the period 1930-1975 (in millions of pounds) was as follows: total production, 1400; imports, 3; domestic sales, 1253; exports, 150.

PCBs are inert chemicals that are fairly resistant to degradation. Because of their stability and lipophilicity, they have accumulated in the environment and in organisms. They have been identified in indoor air (4) at concentrations of $0.1 \mu\text{g}/\text{m}^3$ (5), in fish (6, 7) and other food products, and in sediments from lakes and rivers (8, 9). PCBs have also been identified at varying concentrations in soil ($0.01 \text{ mg}/\text{kg}$ - $100 \text{ mg}/\text{kg}$) (10). They do not occur naturally. Thus, their presence in the environment is linked with human activities, and concentrations are higher in urban and heavily industrialized areas than in rural and remote areas. However, trace amounts are also found in remote areas, since the air may transport such chemicals over large distances.

Although PCBs are no longer used commercially in the United States because of their persistence, they are still present in our environment. A number of transformers and capacitors that contain PCBs, however, are still in use. Results of laboratory experiments showed that pyrolysis of PCBs at temperatures of 200 - 600°C could result in the formation of significant amounts of the more toxic polychlorinated dibenzofurans (PCDFs) (11).

In February 1981, an electrical fire occurred in a New York State office building in Binghamton, N.Y. The fire, which originated in a switch gear in the basement, caused the bushings to crack on a nearby transformer. About 180 gallons of PCB dielectric fluid Pyralon (65% Aroclor 1254, 35% chlorinated benzenes and trace additives) were lost. A fine layer of oily soot covered many of the internal surfaces of the 18 floors of the building. Analysis of a soot sample showed that it contained various isomers of chlorinated dibenzofurans, 2,3,7,8-tetrachlorodibenzodioxin, other chlorinated dibenzodioxins, and chlorinated biphenylenes. Some of these chemicals are much more toxic than the PCBs. Because of these findings the Binghamton state office building was closed, and workers wearing respirators and protective clothing began an extensive cleanup of the building. The cleanup operations lasted four years, and the cost has been enormous (12). Since then several other transformer fires have occurred. These fires have not resulted in as much contamination as the one in Binghamton, partly because the transformers in the other fires were usually located in a separate vault (13).

The problems with polybrominated biphenyls (PBBs), which are also a mixture of chemicals, have been quite different. In 1970 a chemical company in Michigan manufactured polybrominated biphenyls as flame retardants. The same company also produced magnesium oxide, a chemical commonly mixed

into feed for livestock. The flame retardant was called Firemaster and the magnesium oxide, Nutrimaster. In 1973 some bags of Firemaster were accidentally sold as Nutrimaster and mixed into animal feed. This resulted in widespread contamination in the state of Michigan (14). Since 1974 PBBs have not been produced in the United States. At the time of the exposure little was known about the toxic effects of PBBs. Ten years after the Michigan residents were exposed, no clinical illness has been causally linked to PBB exposure in this group, although chloracne was apparently noted in some workers who manufactured PBB.

HUMAN EXPOSURE

Because PCBs are ubiquitous and very persistent in the environment, humans have been and will continue to be exposed to them, particularly in industrialized countries. PCBs may be inhaled in small amounts through the air or ingested through food. In the United States today, people are primarily exposed to PCBs by consuming fish from contaminated waters (9). In the past, some farm families were exposed to PCBs from dairy products; these PCBs originated from coating material used in the inside of silos (15). In addition, workers who repair transformers and workers who handle toxic wastes may also be exposed (16).

The PCB products that were manufactured by Monsanto in the United States had the trade name "Aroclor." The particular kind of Aroclor is identified by a four-digit number. The first two digits refer to the 12 carbon atoms, and the second two refer to the percent, by weight, of chlorine in the mixture. Thus, Aroclor 1254 contains about 54% chlorine, and Aroclor 1260, about 60% chlorine.

The composition of this mixture of chemicals, with different properties, changes once it gets into the environment and into organisms. Some components of the mixture are more easily degraded in the environment than others. As a result the PCBs identified in the environment resemble Aroclor 1254 but are not identical to it. Similarly, the PCB mixtures found in humans usually resemble Aroclor 1254 if exposure occurred primarily through the environment. A different composition of the PCBs may be found in serum or adipose tissue samples from occupationally exposed workers. For instance, if the workers are primarily exposed to Aroclor 1016 or Aroclor 1242, which contain much less of the more highly chlorinated homologs, then their gas-chromatographic patterns resemble a combination of Aroclor 1016 or 1242 and Aroclor 1254. For this reason Smith et al (17), in evaluating occupational exposure, divided PCBs into high and low chlorinated biphenyls. The gas-chromatographic pattern of the PCB mixture present in humans can be used to determine whether the exposure occurred primarily

through occupation or through the environment, or, in the case of occupational situations, whether most of the exposure was recent or occurred many years ago.

Although 93% of the US population eats fish, the average annual per capita consumption is small: 15 lbs. per year (6, 7). If PCBs are to be quantitated in fish, the edible portion rather than the whole fish must be examined. Because of their lipophilicity, PCBs are preferentially stored in the hepatopancreas of the fish, giving erroneously high levels if the whole fish is analyzed. Similarly, levels in cooked fish are lower (6).

Generally, PBBs are not found in the environment because they have had less commercial use than PCBs. PBB contamination is essentially restricted to Michigan's lower peninsula. Most persons who lived in Michigan during the 1973-1974 period have low-level PBB body burdens (18). The greatest degree of contamination occurred mainly in areas with contaminated farms; this segment of the population still has appreciable body burdens (19).

Since PBBs and PCBs are lipophilic, they are preferentially stored in adipose tissue. They are also present, to a smaller extent, in serum and other organs and in human milk. The concentration of these materials in different organs depends upon the lipid content of such organs, with the exception of the brain where the concentration is lower than the lipid content would indicate. PCBs and PBBs pass the placenta and are primarily excreted through bile and milk. In addition to lipid content, the ratios between adipose tissue, blood, and vital organs are influenced by exposure level, sex, age, length of exposure, and also by whether exposure is current. At very low concentrations an analytical imprecision influences the ratios much more than at higher concentrations (19). Since human milk is relatively easy to obtain, it has been used to monitor human exposure. Jensen (20) recently summarized results of such monitoring studies. Average levels of PCBs below 2 ppm (mg/kg) in milk fat have normally been found, although women living in heavily industrialized urban areas may have higher levels. The fat concentration in human milk averages 2.6-4.5% (21). At 2% fat, 1 liter (l) of milk would contain 0.04 mg or 40 μ g if the PCBs were present in milk fat at a concentration of 1 ppm. If an infant weighed 5 kg and imbibed 750 ml of milk per day, it would take in about 6 μ g/kg, a dose that exceeds the 1.5 μ g/kg dose calculated as acceptable by Cordle et al (6). At 1% milk fat this dose would be reduced to 3 μ g/kg. As the infant gains weight, the dose on a kilogram body weight basis will be reduced to some extent, however; milk is the sole food source for only about six months. After the first week, the daily milk intake is estimated to be 150 ml/kg body weight per day. This consumption gradually falls after two months and declines to 120 ml/kg body weight at four-to-six months. Finally, the amount of PCBs and other halogenated organic chemicals declines with time. However, at low concentrations this

may not be obvious because of continued exposure of the mother and the variability of the analytical results. In addition to PCBs, human milk contains trace amounts of many other persistent chemicals. Whether the infant's consumption of such chemicals has any adverse health effects is not known.

Most persons, particularly in industrialized countries, have had some exposure to polychlorinated biphenyls even if they do not eat fish. The concentrations at which such exposure presents a risk are not clear. Recently, Cordle et al (6, 7) calculated the dose of PCBs to people consuming fish from Lake Michigan. They concluded that persons eating Lake Michigan fish ingested an average of 46.5 mg of PCBs per year; this amount ranged from 14.17 to 114.31 mg/year/person. The calculated mean daily dose received by the exposed group was 1.7 μ g/kg/day and ranged from 0.09 to 3.94 μ g/kg/day. Thus, the average sports fisherman consuming contaminated fish would receive a total PCB dose equal to 200 mg in about 4.3 years. No adverse health effects or groups of symptoms clearly related to PCB exposure could be identified in this exposed group. The presence of PCBs in the exposed persons has not caused any observable adverse health effects similar to those observed in the Yusho population (see below). However, this finding does not exclude the possibility that the effects are too subtle for detection or that they require long-term observation.

Similarly, in Michigan an analysis of 1,075 human milk samples showed that all contained PCB residues and that the residues ranged from trace amounts to 5 ppm (mg/kg) based on fat level. The public health significance of PCB residues in human breast milk and their effects on breast-fed infants are unclear. Since there are no human data on which to base public health policy, risk predictions for PCBs have been based on results from animal studies, particularly the positive bioassay studies. Reviewing these data, Cordle et al (6, 7) concluded that a 2-ppm (mg/kg) tolerance for PCB in fish be established, since a 1-ppm (mg/kg) tolerance does not greatly reduce the estimated risk.

As previously mentioned, some of the isomers of the PCBs and PBBs are much more easily degraded or metabolized. Because they can be metabolized, they are more easily excreted. Others may be retained in the body for long periods; in general, the PBBs appear to be more persistent in human tissues than the PCBs (19, 22).

POLYCHLORINATED BIPHENYLS

Background

When PCBs were first used industrially some workers developed chloracne. Results of early animal studies seemed to suggest that PCBs might have some toxic effects on the liver. Beyond that observation no information was avail-

able. Because PCBs were so inert chemically, they were not considered to cause a great deal of toxicity. In 1968 a poisoning outbreak occurred in Japan (23) that affected over 1,000 persons. These individuals had purchased rice oil, in large drums, from a single source and had used this rice oil for cooking. Chloracne was one of the leading signs in those who became ill. It was soon discovered that PCBs had been used as a heat-exchange fluid in the factory where the rice oil originated. PCBs had leaked out of the columns in which they were contained into the rice oil when the rice oil was heated. Since the disease was caused by ingesting contaminated rice oil, it was called Yusho (rice-oil disease). When the outbreak first occurred, its association with exposure to PCBs was not clear. At that time the capabilities for measuring these types of chemicals in tissues and body fluids were limited, particularly in Japan. Therefore, early in the investigation total chlorine, rather than PCBs, was measured. Retrospectively determining the precise dose these patients received is difficult. Whether the consumed oil was uniformly contaminated is also not clear. However, a relationship between the amount of rice oil ingested and some symptoms could be established (24). Because of this poisoning outbreak and other environmental problems, animal studies were started in Japan, in the United States, and in other countries to elucidate the toxic effects of PCBs. These data are summarized in several detailed reviews (16, 25, 26).

Animal Studies

This article addresses primarily the human health effects of PCBs and PBBs. Therefore we highlight only recent results from animal studies that might give a better understanding of implemented public health policies and potential human health effects. One of the difficulties in using animal data to predict human health effects for PCBs and related compounds is that animal species vary greatly in their responses. Further, many of the animal studies use relatively high doses. Therefore, determining how such animal studies relate to the human situation is difficult. Some animal species, such as the subhuman primates, the guinea pig, and the mink, are much more sensitive to the toxic effects of PCBs than the rat or the mouse; also the types of toxic effects and morphological changes in the organs of different species vary.

Most animal studies conducted during the 1970s used mixtures of PCBs. In general, PCBs were found to affect reproduction and the immune response, and to cause liver tumors in rodents (16). When different mixtures of PCBs were studied, however, the results were inconsistent. For instance, the mixture Aroclor 1254 affects reproduction in rats at much lower doses than does Aroclor 1260 (27).

More recently some of the isomers of the PCB mixture were found to be much more toxic than others (28-32). The more toxic isomers constitute only

a very small portion of the mixture, particularly those with less chlorine by weight, such as Aroclor 1242 or Aroclor 1016. Recently, Schaeffer et al (33) found that a German PCB mixture—Clophen A-30, with an average composition of 1% monochlorobiphenyl, 20.7% dichlorobiphenyl, 57.4% trichlorobiphenyl, 17.3% tetrachlorobiphenyl, 1.8% pentachlorobiphenyl, 1.0% hexachlorobiphenyl, 0.6% heptachlorobiphenyl, and 0.1% octachlorobiphenyl—produced a 3% incidence of hepatocellular carcinoma, whereas Clophen A-60 produced a 61% incidence of hepatocellular carcinoma in Wistar rats. The incidence of the disease in the controls was 2%. The Clophen A-60 had an average composition of 0.2% monochlorobiphenyl, 1.1% dichlorobiphenyl, 2.2% trichlorobiphenyl, 3.1% tetrachlorobiphenyl, 19.8% pentachlorobiphenyl, 43.2% hexachlorobiphenyl, 25.3% heptachlorobiphenyl, 4.7% octachlorobiphenyl, and 0.3% nonachlorobiphenyl. Similarly, Norback & Weltman (34) and Kimbrough et al (35) were able to produce hepatocellular carcinomas in rats with Aroclor 1260, the more highly chlorinated Monsanto product.

When Aroclor 1254 was fed to rats, fewer liver tumors developed in exposed rats (36); however, the incidence of gastric intestinal metaplasia and adenocarcinoma of the stomach increased (37, 38). Whether PCB fractions without hexachlorobiphenyls, heptachlorobiphenyls, and octachlorobiphenyls produce hepatocellular carcinomas in rodents should be explored.

Particularly in the United States, mixtures such as Aroclor 1242, 1254, and 1016 were used more than Aroclor 1260. Because of these differences in potency, the PCBs in heavily contaminated areas of our environment should be characterized according to their isomeric composition. For instance, whether the PCBs in Lake Michigan are of the same composition as those found in New Bedford Harbor, Massachusetts, is not clear.

Aside from tumor formation, PCBs cause a variety of other biological effects, such as the induction of enzymes (39). In some species they may cause atrophy of the thymus, intrahepatic bile duct hyperplasia, hyperplasia of the epithelial lining of the urinary bladder, atrophy of the sebaceous glands, and hyperkeratosis of the ducts (40). Some isomers are fetotoxic, and some produce metaplasia of the sebaceous glands, nailbeds, ameloblasts, thymus corpuscles, and gastric mucosa (28, 41). Subhuman primates, mink, and guinea pigs are particularly sensitive to the toxic effects of PCBs; other species, such as the rat, the mouse, and the dog, can tolerate much higher doses. From empirical observations, humans also appear to be less sensitive to the toxic effects of PCBs. The ability to store these chemicals in adipose tissue may be protective. Generally, the subhuman primates and mink have less adipose tissue than humans. Animals with greater ability to store vitamin A on a quantitative basis, such as the hamster and the rat, are somewhat less susceptible to the toxic effects of these types of compounds (42). The

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mechanism by which these types of chemicals affect hepatic retinoids is not clear. Apparently, the duration of the reduction of hepatic retinoids does not correlate with the induced aryl hydrocarbon hydroxylase (AHH) activity (43).

Body Burdens

Many investigators have reported PCBs in human tissues (44, 45). In the United States, according to data from the Centers for Disease Control (CDC), mean PCB serum levels are about 5–7 ng/ml (ppb), although some patients may have higher serum levels without any documented unusual exposure. These data were also summarized by Kreiss (46). Levels in adipose tissue and in human milk fat are 100–200 times as high, since PCBs are highly lipid soluble (20). Mes et al (47) reported that PCB levels in adipose tissue of accident victims ranged from 0.9–9.4 mg/kg.

Sahl et al (48) surveyed PCB blood levels in 738 pre-employed and 1,058 currently employed workers of a utility company. The median blood level before employment was 4 mg/l and the range, 1–37 mg/l. These levels were quite similar to those in the currently employed group.

Patients who died of cancer in Denmark had somewhat higher levels of PCBs in their adipose tissue (49). Since terminal cancer patients have usually lost a great deal of weight, bioconcentration may have occurred. Similarly, in patients with highly impaired liver function, tissue concentrations of xenobiotics may be slightly higher than those in healthy persons. However, levels remained higher if parameters such as weight, height, occupation, and residence were considered (50), whereas levels of PCBs in breast fat tissue from patients with breast cancer were similar to those of controls (51).

Furthermore, Lawton et al (52) demonstrated that random errors and interlaboratory variations in procedure and methods of data reporting can influence serum and adipose PCB levels. Unless an interlaboratory quality-control system is set up, measured levels between laboratories are not necessarily comparable. For instance, Lawton et al (52) found that the results of repeated analyses on serum samples of known composition showed the 95% prediction interval for an individual measurement to be about $\pm 42\%$. This interval depends on the method of extraction, the procedure used, and the means of quantitation.

Summary of Human Epidemiology Studies

Recently, investigators studied the predominantly black population of Triana, a small rural town in the southern United States (53). This population was excessively exposed to DDT residues by consuming contaminated fish. The residents also had PCB body burdens. Fish consumption correlated positively with PCB blood levels; no other source of PCB exposure could be established. These researchers noted that PCB serum levels increased with age and that

levels were lower in females of each age group. Similar findings were made for DDT residues. The serum cholesterol level was positively associated with the log PCB level, independent of age, sex, fish consumption, body-mass index, and alcohol consumption. Rates of borderline and definite hypertension for study participants were 30% higher than those expected on the basis of national rates (54). Log PCB serum values contributed significantly to explaining the variability of log systolic and diastolic blood pressure in multiple regression analysis (55). Median total cholesterol levels of individuals in the United States increase with age from about 150 to 160 mg/dl at age 20 to over 200 mg/dl at age 50. PCBs in blood are influenced by serum lipid content, and populations with inherently lower total serum cholesterol levels appear to have a different PCB serum to adipose tissue ratio. The age-associated increase in blood PCB levels could be related to the long half-life of some PCB isomers that are preferentially retained in mammals (29); as long as exposure continues, a true steady state between intake and excretion is never reached. Other variables affecting body burdens may be differences in metabolism with age. In the Triana studies, the blood levels of total DDT residues also increased with age, and others have made similar observations (56, 57). Lawton et al (58) studied workers who had been exposed to electrical-grade Aroclor 1016, 1242, and/or 1254; the study covered the period from before the workers were exposed to two years after PCB exposure ceased. Serum levels for the lower chlorinated PCBs in 1977 ranged from 57–2270 ppb and in 1979, from 12–392 ppb; for the higher chlorinated PCBs serum levels ranged from 6–142 ppb in 1977 and from 4–108 ppb in 1979. These findings again illustrate the preferential excretion of lower chlorinated PCB. Lawton et al (58) also found that cholesterol levels correlated with log serum PCBs. Similar associations with log serum PCBs were found for log gamma glutamyl transpeptidase (GGTP) and, in some cases, for log alanine aminotransferase. When the PCB concentrations were expressed as levels in serum lipids, all the associations between serum lipids or enzymes and log serum PCBs disappeared except for those between log GGTP and log PCBs. Similarly, Chase et al (59) found no significant correlation between either serum triglycerides or aminotransferases and the PCB levels in adipose tissue. How age and length of exposure affect these parameters is not adequately explained in the article. Finally, Akagi & Okumura (60) were not able to confirm a positive association between PCB blood levels and elevated blood pressure in Yusho patients.

Thus, as Brown (61) has suggested, the positive association between PCB serum levels and elevated triglycerides and serum cholesterol can be explained by the increased solubility of PCB in serum with higher lipid content.

In several cross-sectional studies of exposed workers, only minor abnormalities not necessarily related to PCB exposure have been detected

(62-66). In cross-sectional studies, however, the ability to evaluate chronic health effects is limited. In several studies, a positive association between results of one liver function test—the test for γ -glutamyltranspeptidase—and PCB blood levels has been found. Kimbrough (67) has summarized earlier studies on the health effects of PCBs observed in workers.

In 1930 and 1940, chloracne, a disfiguring skin disease, was reported among workers exposed to PCBs. One of the clinical features of chloracne is the chloracne cyst, which is skin colored and measures from 1-10 mm in diameter, with a central opening. The other dominant lesion is the comedo. The skin lesions may only involve the face, but many also extend to other parts of the body. Microscopic examination of human skin biopsies from chloracne cases shows markedly dilated hair follicles filled with keratin. The sebaceous glands involute partially or completely. The epithelial cells lining the hair follicles and the adjacent surface epithelium proliferate, and acanthosis is present. In old lesions, the epithelial lining of the greatly dilated hair follicles becomes atrophic.

Jones & Alden (68) examined 17 of 23 workers engaged in the production of PCBs. The workers had chloracne involving the face, genitalia, trunk, and extremities. Before the outbreak of chloracne in the plant, the electrical property of the PCBs had fallen below specifications, and the color had deepened. In the report, symptoms of illness were extensively described for the first worker who was diagnosed as having chloracne. This worker complained of lassitude, loss of appetite, and loss of libido. Over the years, other cases of chloracne following exposure to PCBs have been reported. Most of these involved exposure to vapors that developed when PCBs were heated (69).

At times, the skin rashes that developed in workers were accompanied by pruritus. Some workers also complained of burning of the eyes, nose, and throat; dry throat; nausea; and dizziness. Meigs et al (70) reported chloracne in workers who had been exposed to PCB vapors for 5-14 months. The concentration of PCBs in the workers' breathing zone was 0.1 mg/m³. Evidence of slight liver injury was also present. Ouw et al (71) found air levels in a capacitor plant that ranged from 0.32-1.44 mg/m³ Aroclor 1242 (PCB). Here workers complained of burning eyes, face, and skin in general, and persistent body odor. One worker suffered from chloracne, five complained of eczematous rashes, and a few had abnormal liver function tests. These workers had a mean PCB blood level of about 400 ppb (μ g/kg). In most studies of workers with chloracne, evidence of liver injury was also found; in one study, workers who did not have chloracne were found to have abnormal liver function (69).

PCBs also affect the liver by inducing mixed-function oxidases. Alvares et

al (72) determined that in five workers occupationally exposed to Aroclor 1016—a PCB mixture primarily composed of dichlorobiphenyls, trichlorobiphenyls, tetrachlorobiphenyls, and pentachlorobiphenyls—plasma antipyrine half-life was significantly lower than that in matched controls, suggesting the induction of mixed-function oxidases in the liver. These workers had been exposed to Aroclor 1016 for at least two years and had no obvious symptoms of PCB poisoning.

Other health effects are eye and upper respiratory irritation. Warshaw et al (65) studied a group of 326 workers in a capacitor plant with a mean employment of more than 15 years and mean employee ages 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 they had been exposed to talc, textile dust, or asbestos. Thus, 243 men were available 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. Because of additional variables such as smoking and asbestos exposure, these findings are difficult to interpret.

Taylor et al (73), in an attempt to determine whether the fetus would be affected in capacitor workers, examined pregnancy outcome and birth weight, and found that the gestation period was reduced by one week. The infants weighed slightly less than the controls; this finding could be explained by the reduced gestation period. Smoking and alcohol consumption were not controlled, however; furthermore, whether the socioeconomic status of this group of women was similar to that of the control group is not clear. Thus, until other studies confirm these findings, they should be viewed with caution.

In several papers Jacobson and his associates reported behavioral changes and a reduced gestation period in association with higher fish intake or higher intake of PCBs (9, 74-76). Furthermore, Jacobson et al (74) reported that intrauterine PCB exposure may have a delayed effect on central nervous system functioning. Since genetic makeup, the mother's lifestyle, and acute illness also affect these parameters, these findings are difficult to interpret. Furthermore, many other chemicals are also excreted in human milk (20). Rogan & Gladen (77), for instance, found that mothers with high levels of DDE [1,1'-(2,2-dichloroethenylidene)-bis-4-chlorobenzene] in their milk tended to wean their infants earlier, as they did not thrive. Apparently, PCB levels in milk were higher in older women, women who drank alcohol regularly, and primiparas (78).

Whether high levels of DDE affect lactation is not clear. In animals, DDT

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homologs, but not specifically DDE, have been shown to have estrogenic effects (79). Before these findings can be clarified, additional studies must be done.

No conclusive evidence thus far reported shows that occupational exposure to PCBs causes an increased incidence of cancer. Bahn et al (80) reported results of a preliminary study 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. Three melanomas and two carcinomas of the pancreas were found. This incidence was significantly higher than expected. Exposure to other chemicals also occurred, however, and the cohort was small.

Brown & Jones (81) conducted a retrospective mortality study of 2,567 workers in two capacitor plants. The relatively few deaths (163) severely limited the statistical power of the study, and the average follow-up was only 15 years, whereas latency periods of 20–30 years are not uncommon for cancer. Over 50% of the sample had exposure to PCBs for two years or less. Deaths from liver cancer, cirrhosis of the liver, and rectal cancer were slightly higher than expected, but not significantly for both sites combined. The observed increase for cancer of the rectum was statistically significant among females at one of the plants. In a follow up study (82) no additional cancers of the rectum were noted, and the standardized mortality ratio (SMR) dropped from 336 to 211. However, two additional cancers of the liver and biliary tract were observed, bringing the total of these tumors to five as reported on the death certificates. However, a review of the medical records raises questions about at least one of these tumors.

Bertazzi et al (83) reviewed the mortality of 290 males and 1,020 females who had worked for six months or more in capacitor production. Males had a statistically significant increased number of deaths from all neoplasms. When deaths were analyzed by organ system, deaths from neoplasms of the digestive system, the peritoneum, and the lymphatic and hematopoietic tissues were higher. Among females, all causes of deaths were significantly elevated. The actual numbers in this study, however, were small.

Yusho and Yucheng

Two outbreaks of poisoning have been reported that followed the ingestion of rice oil contaminated with polychlorinated dibenzofurans, biphenyls, and quaterphenyls (PCQs). The first outbreak occurred in Japan in the summer of 1968 and the second outbreak, in Taiwan in 1979. Ironically, the outbreak in Taiwan repeated what had occurred 10 years earlier in Japan. Many studies of these two outbreaks have been published in Japanese or Chinese. In 1984 some of the information in these reports was published in English in the

American Journal of Industrial Medicine 5:1–153; the information is also summarized in volumes 59 and 60 of *Environmental Health Perspectives*.

In Japan and Taiwan the disease was first recognized because chloracne developed in the affected patients (84). In Japan, members of all of the affected households had purchased rice oil from a specific company, and the toxic rice oil produced or shipped on February 5 and 6 of 1968 contained large amounts of Kanechlor 400, a brand of PCB with a chlorine content of 48%. At the time of the outbreak, no analytical methods specific for PCBs were available in Japan; the concentration of Kanechlor 400 in the oil was therefore estimated from the organic chlorine content to be 2,000–3,000 ppm. Kanechlor 400 had been used for heating the rice oil in a metal container at over 200°C, at a reduced pressure of 3–44 mm Hg, to remove odorous material from it. Kanechlor (K) must have leaked from the heating pipe into the processed oil, but the actual mechanism of the contamination has apparently not been determined. The reanalysis of the K-rice oil, once the methods were developed, showed that some of the oil samples contained 1,000 ppm (mg/kg) PCB. This concentration was much lower than had originally been estimated. Therefore, other chlorine-containing compounds were assumed to be in the oil, and additional samples were analyzed. The oil was found to contain an average of 5-ppm polychlorinated dibenzofurans (85). According to Buser et al (86), the Yusho oil contained more than 40 polychlorinated dibenzofuran isomers, including the highly toxic 2,3,7,8-tetrachlorodibenzofuran (TCDF) and 2,3,4,7,8-pentachlorodibenzofuran (PCDF). In addition, the oil contained PCQs at a concentration of 866 ppm (87, 88).

According to estimates made by Kuratsune (89), the total amount of PCB, PCDF, and PCQs consumed by the patients was, on the average, 633 mg of PCB, 3.4 mg of PCDF, and 596 mg of PCQ. This calculates to roughly 157 µg/kg body weight/d. PCB, 0.9 µg/kg body weight/d. PCDF, and 148 µg/kg body weight/d. PCQ. At this dose the length of the latent period between exposure and onset of clinical illness was roughly 71 days, with a range from 20 to 190 days. Some of the oil the patients consumed may have contained higher or lower levels because in such situations contamination is usually not uniform. Furthermore, the patients consumed different amounts of contaminated rice oil. The severity of symptoms was positively associated with the amount of contaminated rice oil consumed (24).

Early in the outbreak the patients had chloracne, dark-brown pigmentation of the nails, itching, pigmentation of the skin, swelling of the limbs, pigmented mucous membranes, eye discharge, hyperemic conjunctivae, jaundice, swelling of the upper eyelids, a feeling of weakness, numbness of the limbs, and fever. Over 1,000 people were affected. Thirty-six babies showed fetal PCB syndrome, which consists primarily of a dark-brown pigmentation

of the skin (Cola babies). The cutaneous pigmentation was caused by an increase in melanin pigment in the epidermis (90). The mucous membranes were also pigmented. In all cases, the pigmentation disappeared by the time the babies were between two and five months old. In affected infants, the face was edematous, and spotty calcifications were noticed in the parietal and occipital areas of the skull. In a few of the infants, the teeth had erupted at birth. Subsequently, the adult patients with clinical disease complained of having to expectorate a great deal and, on auscultation, wheezing was noted; however, on examination, there was no evidence of bronchial asthma or pulmonary emphysema. In many of these patients, the respiratory symptoms have persisted, and the patients have chronically infected airways. In the early 1970s, some changes were noted in the patients' serum immunoglobulin levels, but the levels returned to normal. Over time the severity and the extent of the skin lesions improved considerably in the exposed population. Fifteen years after the accident, only a very few patients had extensive chloracne (91).

About five years after the outbreak of Yusho, tissue and body fluids of Yusho patients were analyzed for various congeners of PCB and PCDF. At this time, the PCB levels in adipose tissue were 1.9 ± 1.4 ppm (mg/kg). In the liver they were 0.08 ± 0.06 ppm and in blood, 6.7 ± 5.3 ppb ($\mu\text{g/kg}$); thus, they were not very different from levels in the general population in Japan. On the other hand, the isomeric distribution for the PCBs in the Yusho patients varied from that in the control population in the same area (92). About 40 PCDF congeners were identified in the rice oil that the Yusho patients ingested. Only some PCDF congeners were retained in the body for a long time; they included 2,3,6,8-TCDF, 2,3,7,8-TCDF, 1,2,4,7,8-PCDF, 2,3,4,7,8-PCDF, and 1,2,3,4,7,8-hexachlorinated dibenzofurans. Since these congeners do not have free adjacent carbon atoms, they are not as easily metabolized and excreted. More of the 2,3,4,7,8-PCDF than the other isomers was retained in the patients' tissues. In the five patients studied, the concentration of this isomer ranged from 6.9 ppb ($\mu\text{g/kg}$) in a specimen obtained in 1969 to 0.1 ppb ($\mu\text{g/kg}$) in a specimen collected in 1977. Measurable concentrations of TCDFs were only detected in the earlier years. Although not the most toxic isomer, the 2,3,4,7,8-PCDF caused mixed-function oxidase induction at a dose of 1 $\mu\text{g/kg}$ in rats, and atrophy of the thymus, suggesting toxicity at a very low dosage level. Thus, the clinical manifestations observed in these patients were primarily caused by the PCDFs, specifically by the more toxic isomers.

In the Yucheng episode, it was never determined with certainty how the rice oil was contaminated (93). In 1979 a school for blind persons informed a local health bureau in Taichung County that a strange disease characterized by an acnelike skin eruption had been occurring frequently among students and

staff since the end of March. At the same time, 85 of 150 workers in a nearby plastic shoe factory had the same symptoms. Later that year, this outbreak was also reported to a local health bureau. Victims in both outbreaks had consumed the same brand of cooking rice oil, which had been manufactured by the same company and which had been purchased in the same store. For this reason the rice oil was the prime suspect in the outbreak. In additional reports of outbreaks in other companies and in the general population, all victims had consumed the same type of C-rice oil.

Finally, because the disease resembled the Yusho disease in Japan, samples of C-rice oil and patients' blood were analyzed in Japan and were found to contain either a Kanechlor-400 or a Kanechlor-500 mixture at concentrations as high as 65 and 108 ppm (mg/kg), respectively. Over 2,000 patients were finally identified as having been poisoned by contaminated rice oil. Oil samples collected from other outbreaks contained PCBs at concentrations of 31–300 ppm (mg/kg). Retrospective studies determined that the period of PCB intake ranged from 3 to 9 months. The average total intake for each person varied from 0.77 to 1.8 mg of PCB. Within the first year of the outbreak, the blood levels of PCB in 13 patients ranged from 3 ppb to 1,156 ppb. Most of the patients had blood levels between 11 and 150 ppb ($\mu\text{g/kg}$). The symptoms observed in these patients were quite similar to those already described for the patients in the 1968 Yusho outbreak in Japan.

The rice oil was not only contaminated with PCBs but also with PCDFs and polychlorinated quaterphenyls. It contained the same major components of PCDFs observed in the rice oil in Japan—namely, 2,3,4,6,7-PCDF and 2,3,4,7,8-PCDF. Relatively high concentrations of 2,3,4,5,3',4'-hexachlorobiphenyl were found in the blood and adipose tissue of the Yucheng patients. This particular PCB isomer is biologically quite active, and the concentration of 2,3,4,3'4'-pentachlorobiphenyl was also elevated in these patients. Furthermore, as in the Yusho patients, the concentration of 2,3,7,8-TCDF was comparatively low (92). Chen et al (94) analyzed additional samples of the oil, blood, and adipose tissue of the Yucheng patients. These investigators identified several TCDF and PCDF isomers. Apparently, 2,3,7,8-TCDF was only a minor component in the oil; the major component was 2,3,4,8-TCDF. One of the major furans in the toxic oil was 2,3,4,7,8-PCDF.

The concentrations of the PCDFs in different oil samples ranged from 0.21 to 1.68 ppm. Polychlorinated quaterphenyls were present in concentrations ranging from 25 to 53 ppm (mg/kg). Overall, the concentrations of PCDFs and PCQs were lower in these oil samples than in the oil samples that had caused the Yusho outbreak. Whether these oil samples were representative is not really known. The 3,4,3'4'-tetrachlorobiphenyl was also identified in the oil that caused Yucheng disease in Taiwan. This isomer is considered to be

the most toxic PCB isomer present in commercial PCB preparations (95); it was present at a concentration of about 1%. Most other commercial PCB preparations, such as the Aroclors, in the United States have not been shown to contain this particular isomer.

In addition to the epidemiological studies, some disease-specific investigations were also conducted. The blood pressure of the Yucheng and Yusho patients was not affected (60). Although some of the patients in the Yusho cohort have died of cancer (90), the number has been small; because the latency period may be long, the population should be followed for a longer period to determine whether the cancer incidence will increase.

Although PCBs and related compounds are known to affect reproduction in animals, and although they affected some fetuses and neonates in the Yusho and Yucheng episodes, the information on reproduction and fetal toxicity in general is very limited. In one such study, Hara (96) examined women working in a capacitor plant who also nursed their infants and who themselves had mild chloracne and erythema of the skin. The human milk of some of these women contained, on a whole milk basis, PCB levels that ranged from below 50 ppb ($\mu\text{g/kg}$) to about 400 ppb ($\mu\text{g/kg}$). Forty children of these mothers were followed for a five-year period. Some children were found to have "decayed" nails, gingival pigmentation, mottled enamel, and dental caries. No relationships between these changes or symptoms to PCB blood levels, however, were observed. The general population in the United States and other countries also has body burdens of PCBs, PCDFs, and polychlorinated dibenzodioxins (97, 98). However, these background concentrations—particularly for the biologically active isomers—are far lower than they were in the Yusho and Yucheng patients, even several years after exposure.

Chang et al (99) examined the delayed immune response in 30 Yucheng patients and compared their responses with those of 50 controls. The mean age of patients in both groups was about 14 years. The authors injected a solution of streptokinase and streptodornase subcutaneously into the flexor side of the forearm. The response was read at 24 hours (hr) and again at 48 hr after injection. Eighty percent of the controls had an induration of 5 mm or more in diameter 24 or 48 hr after they were injected; only 43% of the exposed group responded similarly. All of the poisoned patients had dermal lesions, and the percentage of patients with a positive response decreased with increasing severity of the skin lesions (chloracne). Furthermore, the degree of the dermal lesions appeared to be associated with the whole blood PCB concentrations. Patients with minor skin lesions that were classified as grade 1 appeared to have a normal skin response. The same authors found that PCBs caused a decreased concentration of IgA and IgM, but not of IgG, in serum.

Furthermore, the percentages of total T cells, active T cells, and T mu cells decreased, whereas the percentage of B cells and T gamma cells were not

affected (100). These two reports are the first in which the effect on the immune response was actually correlated with body burdens of PCBs and in which only severely poisoned patients showed this effect. This finding is consistent with the findings from animal studies in which relatively high doses of PCBs affected the immune response and also caused some other adverse effects.

In the Japanese and the Taiwanese Yusho and Yucheng poisoning outbreaks, sensory neuropathy was reported in a number of patients for whom nerve conduction velocities were measured (101, 102). The blood levels of the various chemicals (PCBs, PCDFs, PCQs) were negatively correlated with the lowered nerve conduction velocity, suggesting that these types of chemicals affect nerve conduction velocity. (It is not quite clear why most investigators measure nerve conduction velocity to detect sensory neuropathy. Other tests that would measure the detection of vibration, touch, and temperature would be more useful from a clinical perspective.)

Seppalainen et al (103) examined 16 men working in a cardboard plant who were exposed to fumes that resulted from the explosion of 15 capacitors containing Clophen A-30. The first PCB air concentrations, measured 5.5 hr after the explosion, were 8,000 to 16,000 $\mu\text{g/m}^3$ air. PCDFs were also formed. The soot samples contained tetrachlorodibenzofuran up to 90 $\mu\text{g/g}$, of which 6.5 $\mu\text{g/g}$ was 2,3,7,8-tetrachlorodibenzofuran. In addition, monochloropyrenes and dichloropyrenes were found. Most of the men had a transient sensory neuropathy in their lower extremities.

Chang et al (104) reported increased urinary δ -aminolevulinic acid uroporphyrin excretion in 69 Yucheng patients over that of 20 controls. No information on the patients' clinical conditions or on how these findings related to degree of exposure was given. No such observations have been reported from Japan.

POLYBROMINATED BIPHENYLS

Since the toxicity of PBBs both in laboratory animals and livestock was recently reviewed (105), we do not review it here in detail. In laboratory animals, PBBs generally cause effects similar to those that the PCBs cause. They produce morphological changes in the liver, affect reproduction, and promote biochemical changes, such as hepatic porphyria and induction of mixed-function oxidases. Teratogenic effects have also been noted. In addition, atrophy of the thymus has been reported, and hepatocellular carcinomas have been produced in both rats and mice. The overall findings reported in animal studies are similar to those that have been reported for PCBs.

Although the PCB contamination of the environment is a more general problem, the PBB contamination primarily affects certain areas within the state of Michigan. Most persons living within the lower peninsula of Michi-

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gan have had slight exposure, since the contamination resulted from dairy products and since normal marketing channels for these products involved the mixing of milk from many producers in relatively few processing facilities. In addition, most cull dairy cattle are used for hamburgers and processed meat products that would also receive wide distribution. Thus, the marketing system diluted the degree of exposure for the individual; however, it increased the number of those exposed. In 1978, the distribution of PBBs was comprehensively studied in a probability sample of 1,738 persons. PBB levels in serum were determined, and 844 adipose tissue samples were also analyzed for PBBs. PBBs were detected in 97.3% of the adipose tissue samples, in 68% of the adult serum samples, and in 72.7% of the serum samples from children. The mean PBB concentration in adipose tissue was 400 ppb ($\mu\text{g/kg}$); in serum it was 1.3 ppb ($\mu\text{g/kg}$) for adults and 1.8 ppb ($\mu\text{g/kg}$) for children. The highest adipose tissue concentration was 37 ppm (mg/kg) (18). In additional studies, when cohorts of PBB-exposed residents of Michigan were compared with residents of the state of Wisconsin, a higher prevalence of a variety of symptoms and complaints was noted in the Michigan residents (106). Similarly, in comparative neurobehavioral studies, the Michigan population was found to be affected more than that in Wisconsin (107).

Since the findings were not correlated with body burdens of PBB in any of these studies, determining whether other factors may be responsible for these differences is difficult. In 1976, the Michigan Department of Public Health established a cohort of farmers who had been exposed to varying concentrations of PBBs in their products and their environment. A total of 3,877 persons were enrolled. They included farm residents, direct recipients of farm products, chemical workers and their families, and a few persons who had been originally studied in a smaller previous study.

The serum PBB levels in this entire group ranged from no detectable levels to 1,900 ppb ($\mu\text{g/l}$), with a mean of 21.2 ppb ($\mu\text{g/l}$) and a median of 3 ppb ($\mu\text{g/l}$). Because of the wide range of exposure and because results could be analyzed by regression analyses with exposure as a variable, a comparison group for acute health effects was not included. This cohort was found to have various symptoms and conditions; however, these symptoms did not correlate with PBB body burdens. Symptom prevalence rates were slightly higher in persons with no detectable PBBs in serum than in those with measurable quantities. In all groups, including chemical workers and quarantined farm residents, the highest prevalence rates were in persons with the lowest serum PBB levels (22).

Similarly, in this study and in a previous immunologic study (108) no dose-related depression of lymphocyte function in persons exposed to PBBs could be demonstrated. All these findings suggest that there may be no causal

relationship between the abnormal lymphocyte functions observed in some persons or the prevalence of other symptoms and exposure to PBBs. This cohort of Michigan residents is still being followed by the Michigan Department of Health in collaboration with the Centers for Disease Control. Several studies of subgroups of this population and surveys for chronic health effects have been conducted since the cohort was first assembled (109, 19). When serum and adipose tissue concentrations were compared, a significant correlation was found. The serum:adipose tissue concentration ratios ranged from 1 to 140 to 1 to 260 for pregnant women and male chemical workers, respectively. Males from farms had a significantly different ratio of 1 to 325 to 329. Potential transplacental passage of PBBs was demonstrated, since they could also be found in the fetus and newborn. Cord blood contained one-tenth of the concentration found in the maternal serum, which indicated partial placental passage. Human milk contained PBBs at 107–119 times the quantity found in maternal serum. PBBs were also detected in bile and feces, which indicates that these materials can be transferred into the intestinal tract. All of these concentrations were measured long after the population had first been exposed to PBBs (19). Concentrations of PBBs observed in bile and feces were about one half to seven-tenths of the serum levels and are probably about 0.5% of the adipose tissue levels. These findings indicate that PBBs are very slowly excreted, which is consistent with the findings of Tuey & Matthews in rats (110). The estimated half-life for PBB is 6.5 years.

More recently, two groups of Michigan residents—those with high PBB serum levels and those with PBB serum levels around 1 ppb—were matched for age, sex, and smoking. For both groups, various clinical laboratory tests were conducted, blood pressure was measured, and height and weight were determined. In this study, 83 participants had PBB serum levels of 50 ppb ($\mu\text{g/l}$) or more. In the middle group, 83 had PBB levels of 5–49 ppb and 96 had PBB levels of 0–44 ppb ($\mu\text{g/l}$) in serum. Urinary porphyrins were also measured in all of the participants. Thus far, the final results of this study have not been reported. For most of the parameters studied—which included serum glucose, triglycerides, high-density lipoproteins, various liver functions, creatinine, uric acid, thyroid function, proteins, calcium and phosphorus in serum, and also measurement of various porphyrins—no differences of clinical significance were found among different groups (M. Barone, personal communication). (Note: Even though significantly more women in the high PBB group used birth-control pills than women in the low PBB group, too few were using them to affect urine porphyrin levels.) In none of a variety of other studies conducted on this population as well as other groups in Michigan did any findings indicate that exposure to PBB had impaired the health of the exposed group. All of these studies have been reviewed by Fries (105).

Although this population was exposed during a 9-month period in 1973 and 1974, whether it will have chronic health effects is unknown. This particular cohort needs to be followed for 30 to 40 years before the question of chronic health effects can be intelligently addressed. Two problems with assessing chronic health effects are that the cohort, in spite of its size, is still relatively small and that the amount of exposure it has received varied widely. Although some members of the group exposed to PBBs have relatively high body burdens, these burdens are still appreciably lower than those of rats in which liver cancer developed.

In the study by Kimbrough et al (11), liver cancer developed in the rats that received a dose of 1,000 mg/kg body weight. This dose for humans would roughly translate into a dose of 70 grams per person. These amounts are much greater than the estimated mean total exposure per person. The highest exposure was about 11.7 grams, and the mean was 170 mg per person. In rats given 200 mg/kg, a dose that for humans would be between 12 and 14 grams, only neoplastic nodules developed in their livers; there was no evidence of hepatocellular carcinomas. Of course, whether humans would be more or less susceptible to the toxic effects of PBBs and whether their response would be similar to that of rats is not known.

In conclusion, various toxic effects of PBBs and PCBs have been described in laboratory animals. In humans, acute poisoning outbreaks have only occurred following exposure to a combination of PCBs and PCDFs. When humans were exposed only to PCBs or PBBs, the only observed acute effects have been generally minor. So far, no significant chronic health effects have been causally associated with exposure to PCBs or PBBs.

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