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Polychlorinated Biphenyls (PCBs) and Human Health: An Update*

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ABSTRACT: Polychlorinated biphenyls (PCBs) are a mixture of 209 different chlorinated biphenyl congeners (forms) of which 36 are environmentally relevant. PCBs are lipid (fat)-soluble, stable compounds. PCBs may be contaminated with more highly toxic polychlorinated dibenzofurans (PCDFs). Some PCDFs were primarily responsible for the two poisoning outbreaks — Yusho and Yu-Cheng.

Based on the reports on workers and the general population, no clear and convincing evidence that PCB exposures were casually associated with adverse health effects was advanced; this included cancer for a wide range of body burdens and exposures for serum PCB concentrations >1000 ppb (μg/l) and adipose PCB levels >400 ppm (mg/kg). No meaningful reproductive problems have been identified in female capacitor workers. In the opinion of the review author, the available evidence for cancer and for reproductive effects is inconclusive.

Adverse neurobehavioral effects in infants and young children have been reported in a study of women in the general population and a study of fish eaters and their offspring. The adverse effects observed in the two studies were not the same; the exposure assessments in both studies are not well defined and have many uncertainties.

Subhuman primates appear to be more sensitive to reproductive and other adverse effects of PCBs than humans. Obvious external clinical signs are observed in the offspring of subhuman primates at dosage levels below those experienced by female capacitor workers and members of the general population prior to the control of PCBs.

KEY WORDS: polychlorinated biphenyls, carcinogenicity, humans, toxic equivalency factors.

I. INTRODUCTION

Polychlorinated biphenyls (PCBs) are a mixture of 209 different chlorinated biphenyl congeners (forms). According to McFarland and Clarke,[1] only 36 of these congeners are environmentally relevant (Table 1). PCBs are lipid (fat)-soluble, stable compounds. Their stability depends on the number of chlorine atoms and the position of the chlorine atoms on the biphenyl molecule. If few chlorine atoms are attached to the biphenyl molecule or if at least one paraposition on the molecule is not occupied by a chlorine, then they can be more easily metabolized and eliminated. The lower chlorinated PCBs are more easily broken down in the environment. Thus, the composition of a given commercial mixture of PCBs changes in the environment through selective degradations of congeners.

PCBs were first produced commercially in the 1920s, although it was not until the 1950s that the industrial application of PCBs increased significantly. They were used as capacitor, hydraulic, and transformer fluids in carbonless copying paper and as plasticizers in paint. Through industrial applications, PCBs entered the environment and contaminated the food chain, most notably fish.

In response to public concern over the environmental build-up of PCBs and results from animal feeding studies, Monsanto Chemical Company, the sole U.S. producer of PCBs, voluntarily stopped open-ended uses of PCBs in 1971. Subsequently, the lower chlorinated biphenyls, Aroclor 1016, 1242, and some 1254 were produced.[2] Prior

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TABLE 1
IUPAC Numbers for 36 PCB Congeners Considered Environmentally Relevant and Congeners Included in the Canadian Marine Analytical Standards Program (CLB-1)

McFarland and Clark	CLB-1 standard contains all congeners listed by McFarland and Clarke except	Additional congeners that are included but according to McFarland and Clarke are irrelevant
18	37	15
37	70	31
44	74	40
49	81	54
52	119	60
70	123	86
74	126	103
77	157	121
81	158	129
87	167	137
99	168	141
101	169	143
105	177	154
114		159
118		171
119		173
123		182
126		185
128		191
138		195
151		196
153		200
156		202
157		203
158		205
167		206
168		207
169		208
170		209
177		
180		
183		
187		
189		
194		
201		

to 1971, other more highly chlorinated biphenyl mixtures such as Aroclor 1248, 1254, and 1260 were also marketed. In 1977 Monsanto Chemical Company ceased production of PCBs entirely.

Since the 1970s, levels of PCBs in the environment have decreased overall;[3] however, capacitors and transformers with PCBs as dielectric fluid are still in operation and their containment is still of some concern. In addition to the presence of PCBs in capacitors and transformers, PCBs are also formed through incineration, most likely by the dimerization of chlorobenzenes. The major PCBs formed through incineration are the coplanar congeners characterized by 3,3′,4,4′ substitution. The formation of 2,6 substituted PCB congeners is less favored.[4] It is unclear at this time whether formation

through combustion makes a major contribution to the input of PCBs into the environment.

Since PCB production ceased in 1977, body burdens in the general population of the U.S. have decreased.[3,5,6] The extent of this decrease is uncertain. Significant changes introduced over the years in PCB analysis and quantitation directly impact the validity of trend analyses and make time trend analysis difficult to interpret.

PCBs may be contaminated with polychlorinated dibenzofurans (PCDFs), which are also a mixture of many homologues. If PCBs are heated to temperatures between 300°C, PCDFs may be formed[7] and may, in specific situations, be responsible for the toxic effects. Some PCDFs are much more toxic than PCBs in comparatively smaller amounts. In incomplete combustion situations, they may also be formed at temperatures between 600 and 800°C.[7a] In the commercial mixtures of PCBs produced by Monsanto Chemical Company, PCDFs only occurred in trace amounts or were not detected at all. In Japan, in 1968, and in Taiwan, in 1978–1979, poisoning outbreaks of Yusho and Yu-Cheng occurred. The affected population had ingested rice-oil contaminated with PCDFs, PCBs, polychlorinated naphthalenes, dibenzodioxins, and quarterphenyls. In the poisoning outbreaks, the PCDFs, not the PCBs, caused the adverse human health effects.[8] At similar PCB tissue levels in the general population without corresponding levels of PCDFs, no adverse human health effects have been noted. Observations made in the Yusho and Yu-Cheng outbreaks should, therefore, not be construed as adverse effects of PCBs.

In this review, the more recent PCB literature is summarized, data related to human health are examined in detail, and the relevance of recent animal data to predict human health effects is discussed. The review begins with human exposure pathways and a discussion of available data from air, water, and food monitoring. The literature on PCB metabolism in humans is reviewed as well as the literature regarding the human health effects of PCBs and the scientific evidence for reproductive, developmental, immunologic, and carcinogenic effects of PCBs. More recent animal data and the toxicity equivalency factors and dose response relationship are discussed.

II. HUMAN EXPOSURE

A. Monitoring Data

Monitoring data of PCB levels in humans provide some information about the extent of human exposure to PCBs. However, results from different laboratories are difficult to compare because chemical analytical methods and PCB quantitation have changed over the years and differ between laboratories.[4] The analytical method of choice for many years was gas chromatography using packed columns. With this method about 12 PCB peaks each containing many congeners can be separated in human milk,[9] while with a more sophisticated method that uses glass capillary columns, about 70 PCB congeners can be separated. The average levels in human milk in the U.S. are around 1 ppm (mg/kg) if more than six peaks of the gas chromatogram are used for quantitation and about 1.5 ppm (mg/kg) if 1 to 4 peaks are used.[9] When similar quantitation methods are used, the average PCB levels in human milk do not differ much between industrialized countries. Differences in clean up and in the use of solvents for extraction also affect quantitation.

PCBs are persistent and lipid soluble and accumulate in fluids and tissues. On a wet weight basis, PCB concentration in fatty tissue is much greater than in vital organs. On a lipid basis, the differences between blood, fatty tissue, and vital organs disappear. Overall, PCB levels in humans, in food, and in the environment seem to be declining in the U.S.[6] Median PCB levels in whole serum in the general U.S. population now range between 2 and 7 ppb (µg/l). Levels in workers and in some subpopulations of the general population may still be higher because of past exposures. Levels in adipose tissue and in human milk fat in industrialized countries average around 1 ppm (mg/kg)[9] and fewer people overall have detectable levels of PCBs.[3]

1. PCBs in Air

In air, PCB levels of 0.1 to 10 ng/m^3 have been reported.[4] Between 1 and 3 µg/m^2 are deposited by air per year.[4] Similar or higher aerial depositions have been reported for Lake Michigan

and remote lakes surrounding the Great Lakes[10] and in Sweden.[11] For southern Lake Michigan, the atmospheric flux to the lake is around 7.5 μg/m²/year and the flux back to the atmosphere is about 5.6 μg/m²/year, resulting in a net deposition of approximately 2 μg/m²/year. Based on mass balance analyses made prior to 1985,[10] net atmospheric deposition and nonatmospheric sources each account for about half the total PCB input into Lake Michigan.

2. PCBs in Food

Several years ago, the mean daily intake from food was calculated by Bennett to range from <0.1 to 1.9 μg per person per day.[12] The Food and Drug Administration (FDA) estimated that for the years 1982 to 1984, the average human PCB intake was 0.042 μg/d. For a 70-kg person, the average PCB intake was 0.0006 μg/kg/d and for infants and toddlers it was 0.001 μg/kg/d.[13] According to Fensterheim,[3] PCB intake from food was 0.05 μg/d (0.0007 μg/kg bodyweight/d) for the years 1987 to 1989.

B. Fish Consumption and PCB Serum Levels

In the 1970s, consumption of Lake Michigan sport-caught fish produced higher PCB body burdens in humans with a reported maximum of 360 ppb (μg/l) in whole serum of an angler who ate an average of 40 kg of fish per year. No adverse health effects associated with the PCB body burdens were identified.[14] Many of these same anglers were studied again recently.[16] The fish eaters now have a mean serum PCB level of 19 μg/l with a range of 4.9 to 173.8 μg/l. However, the higher PCB levels had resulted from exposures prior to 1982. The mean PCB serum level in a group of non-fish-eating controls was 6.8 μg/l. Neither the controls nor the fish eaters showed a decline of PCB serum levels between 1982 and 1989,[16] whereas DDT levels declined significantly.

In a recent study of 801 Wisconsin anglers (Lake Michigan), PCB congener specific analyses were performed on 192 serum samples.[17] In 31% of the samples, the PCB concentrations were below the limit of detection of 0.6 ppb (μg/l). The annual mean number of sport-caught fish meals ranged from 19.5 per year for individuals with no detectable PCB in serum to 32.3 per year for individuals with PCB levels >5 μg/l. A total of 13 congeners were identified in the 192 serum samples. The most frequently identified congeners were 2,2′,4,4′,5,5′ hexachlorobiphenyl (153), 2,2′,3,4,4′,5 hexachlorobiphenyl (138) and 2,2′,3,4,4′,5,5′ hepatochlorobiphenyl (180). The numbers in parentheses are IUPAC (International Union for Pure and Applied Chemistry) numbers.[4] The mean sum of these congeners was 2.2 ppb (μg/l).

In another study during 1987 to 1989, reproductive outcomes were examined in 1112 women from the Green Bay area of Wisconsin.[18] Among the women, 100 participants were randomly selected for serum PCB analysis. Detectable PCB levels were only found in 24 sera. The limit of detection for the PCB isomers was 0.6 μg/l. There were 13 PCB specific congeners determined. Only five of the congeners were present above the limit of detection, namely, 2,2′,3,4,4′,5′ hexachlorobiphenyl (138), 2,2′,4,4′,5,5′ hexachlorobiphenyl (153), 2,2′,3,4,4′,5,5′ (180) heptachlorobiphenyl (180), 2,2′,3,4,5,5′,6 heptachlorobiphenyl (187) and 2,3,4,4′,5 pentachlorobiphenyl (118). Only isomer 153 was found in all samples. Isomer 187 was only identified in one sample. The arithmetic sum of these congeners ranged from 0.6 to 5.0 ppb (μg/l). No association between PCB exposure and adverse reproductive outcomes was found. Birth weight was found to be positively associated with fish consumption and PCB serum levels. It is known that greater fish consumption is associated with larger babies.[19] Olsen et al.[19] suggested that the association between fish consumption and birth size was related to marine n-3 fatty acids. These fatty acids improve placental blood flow by increasing the ratio of prostacyclins to thromoxane.

C. PCBs in Human Milk

PCBs are present in human milk fat. A number of studies have examined the risk associated with ingesting such milk.[20,21] Certain subpopulations such as the Inuit women from Arctic Quebec have reportedly higher PCB milk levels than other popu-

lations. It has been suggested that their high consumption of fish and marine mammals[22] has resulted in the higher PCB milk levels. In the Inuits, the mean concentration of PCBs in human milk fat was 3.6 ppm (mg/kg), while the comparison group of Caucasians from Quebec City and from Baie Comeau had mean PCB levels of 0.77 ppm (mg/kg) in milk fat. However, high PCB milk levels were not present in the American Indians living on Cornwall Island in Upstate New York.[23] They were exposed to contaminated fish because of the presence of a hazardous-waste site in their neighborhood. Their arithmetic mean PCB concentration in milk fat of 0.554 ppm (mg/kg) was similar to a control group of 0.516 ppm (mg/kg). No association between PCB milk levels and fish consumption could be demonstrated in the American Indians living on Cornwall Island. Concern has been raised that PCB levels in human milk are at times above the FDA guidelines of acceptable levels of PCBs in food.[20] When such concerns are raised, the physiology of the growing infant and the variations of the composition of human milk are not considered. Furthermore, the benefits of breast feeding are also not included in the evaluation.[21] Several nutritional committees have recommended a 6-month period of exclusive breast feeding. Beyond that point exclusive breast feeding is nutritionally no longer desirable. The fat concentration in human milk averages 3.5 g/100 ml and the infant consumes 4.2 g/kg body wt/d of fat if it consumes 120 ml/kg body wt d of milk. Accepting 1 mg/kg of PCBs in human milk fat, the infant consumes 4.2 µg/kg/d or a total of 750 µg/kg of PCBs over a 6-month period. In 1987, a WHO work group estimated that the daily intake of PCBs for a 70-kg person was 0.2 µg/kg/d, or over a life time, a total of about 5.1 mg/kg PCBs. Thus, during an exclusive nursing period of 6 months, the infant accumulates 6.8% of its lifetime PCB body burden in some industrialized countries. PCB levels in human milk fat in the U.S. have averaged about 0.5 ppm (mg/kg), resulting in a 3.4% uptake of the lifetime accumulation based on the estimates of WHO.

D. Miscellaneous PCB Exposures of Specific Subpopulations

In the past, segments of the general population received additional exposures.[14] Dairy cattle became contaminated in Ohio from PCB containing paint used to paint the inside of silos between 1941 and 1970. The PCBs leached into the silage fed to dairy cattle and entered the human food chain through milk and cheese. PCBs were also present in breakfast cereals because PCBs leached out of the recycled paper used to make cereal boxes.

Humans living in contaminated environments where food contamination is not an issue usually do not accumulate additional body burdens of PCBs. In 10 of 12 site-specific investigations, Stehr-Green et al.[24] found that PCB serum levels of people considered to be exposed to PCB waste sites did not exceed those of a local or national reference population. In these waste sites, PCB concentrations reached 13% in soil and 0.002% in surface water leaching from the site. In two instances an increased proportion of persons with higher PCB levels was found because occupational exposure and consumption of PCB contaminated fish occurred.

In an earlier study of a community, PCB contaminated sludge was used as fertilizer in gardens.[25] The mean PCB levels for the controls were 24.4 and 17.4 ppb (µg/l) for the sludge users. This suggested that the PCB uptake from sludge through gardening was negligible. The mean levels in the sludge-treated soil was approximately 17 ppm (mg/kg) and ranged from 0.1 to 1700 ppm (mg/kg).

Similar findings at low PCB concentrations in soil were made by Yafe and Reeder.[26] In Greater New Bedford, MA, high concentrations of PCBs had been identified in sediment, wildlife, and fish. Serum specimens were obtained from 391 male and 449 female volunteers. These volunteers had resided in the area for at least 5 years. The prevalence of elevated PCB serum levels in this group was typical of an urban unexposed population. Only 1.3% of the study participants had PCB serum levels above 30 ppb (µg/l).[27]

Poor skin absorption of PCBs from soil and no direct contact may explain the lack of PCB uptake from PCB contaminated waste sites. Schmid et al.[28] demonstrated that the maximum dermal uptake of PCBs was 6% of the absorption after oral intake of the same amount of PCBs. Absorption of PCBs in solution following ingestion is usually at least 90%.[28]

III. METABOLISM OF PCBs IN HUMANS

Steele et al.[29] estimated the half-life in humans for lower chlorinated biphenyls (Aroclor 1242) as 6 to 7 months and the corresponding half-life for the more highly chlorinated biphenyls as 33 to 34 months. The reported half-lives of mixtures reflect the percent reduction of the individual congeners, resulting ultimately in a reduced number of more gradually excreted congeners in tissues.

Buehler et al.[30] studied the elimination of a ^{13}C-labeled PCB mixture similar to Aroclor 1254. A single dose of 329 µg/kg body weight was administered orally to a human volunteer and blood samples were taken over a period of 260 d. The half-lives for the isomers 2,2′,3,4,4′,5′ hexachlorobiphenyl (138), 2,2′,4,4′,5,5′ hexachlorobiphenyl (153), and 2,2′,3,4,4′,5,5′ heptachlorobiphenyl (180) were 321, 338, and 124 d, respectively. The study illustrates that different persistent isomers[30] are excreted at different rates. Borlakoglu and Walker[31] identified 12 PCB congeners that account for 80% of the total PCB adipose tissue burden in humans. Eight of these congeners appear to be persistent (IUPAC numbers 28, 118, 138, 153, 170, 180, 183, and 202). These compounds do not have meta-para-vicinal protons and are mostly highly chlorinated. The two congeners, 2,4,4′ trichlorobiphenyl and 2,3′,4,4′,5 pentachlorobiphenyl, represente the lowest chlorinated compounds in this group. The congeners used by Buehler et al.[30] in their volunteer study were part of these 12 congeners.

Wolff et al.[32] determined PCB body burdens in male and female current and past capacitor workers in two factories with several years of exposure. Aroclor 1242, 1016, 1221, and some Aroclor 1254 were used. The lower chlorinated biphenyls in 61 fatty tissue samples ranged from 0.6 to 414 ppm (mg/kg), with a geometric mean of 28 ppm (mg/kg), and in 290 plasma samples from 6 to 2530 ppb (µg/l). The more highly chlorinated biphenyls ranged in fatty tissue from 1 to 165 ppm (mg/kg), with a geometric mean of 14 ppm (mg/kg) and in plasma from nondetectable levels to 546 ppb (µg/l) with a geometric mean of 21 ppb (µg/l). It was reported, 25 workers in high exposure jobs had PCB plasma levels of 300 ppb (µg/l) or above. In workers with less than 5 years employment, the higher chlorinated biphenyl levels were similar to the general population with a partition value between plasma and fatty tissue of about 160. In a follow-up study of 165 of these workers after cessation of exposure, the lower chlorinated biphenyl congeners similar in appearance to Aroclor 1242 had decreased by 25 to 90%.[33] The more highly chlorinated biphenyl congeners, similar in appearance to Aroclor 1254, did not decrease significantly as a whole, although six congener peaks declined by 15 to 25%.[33] For workers with an initial geometric mean PCB serum level of 100 ppb (µg/l), a half-life of 4.8 years was estimated. For workers with a mean PCB serum concentration of 39 ppb (µg/l), a half-life of 17 years was calculated. These half-lives were longer than half-lives published by other authors. This may, in part, be explained by different methods of quantitation and differences in the amount and congener distribution of the initial body burden.

Phillips et al.[34] studied the metabolism of PCBs in 58 male workers with predominant exposure to Aroclor 1242 and 1016 until 1977. In 1977, the range of the lower chlorinated biphenyls in serum was 2 to 3300 ppb (µg/l) with a median of 155 ppb (µg/l). The range of the more highly chlorinated biphenyls was 5 to 250 ppb (µg/l) with a median of 39 ppb (µg/l). In a follow-up study in 1985, the half-life was longer when the initial PCB level was lower.

For the entire group of workers, the half-life for the lower chlorinated biphenyls (Aroclor 1242) was 2.6 and 4.6 years for the higher chlorinated biphenyls (Aroclor 1254). This illustrates that PCBs were eliminated. Elimination was faster for lower chlorinated mixtures and the half-life varied for different congeners.

Congener specific PCB determinations have been made in present and former capacitor workers, transformer workers, workers without specific exposure to PCBs, and in human milk and serum of the general population.[9,33,35,36] The capacitor workers were exposed to Aroclor 1254, 1242, and 1016. The transformer workers were primarily exposed to Aroclor 1260. Based on the results by Fait et al.,[36] the congener specific analyses suggested that in serum, the total PCB con-

centrations were underestimated while the sum of the congener specific PCB quantitation and the total PCB quantitation on packed columns were quite similar for adipose tissue. These differences between serum and adipose tissue may be a reflection of the limit of detection for PCB congeners present in lower concentrations in serum. In currently exposed workers with higher levels, more congeners could be identified and quantitated.

IV. CROSS-SECTIONAL AND CLINICAL STUDIES

In this and in the section on mortality the published human studies are reviewed. These studies were performed because increased exposure to PCBs had occurred and because of adverse effects observed in animals studies. None of them were disease investigations or triggered by the occurrence of a specific disease. These studies should therefore be considered as hypothesis generating rather than hypothesis testing studies. In the laboratory animal studies the liver in some but not all species was a target organ for PCBs. Furthermore, reproductive effects in female animals, immunotoxicity, hyperplasia of the mucosa of the stomach, chloracne-like lesions and hyperpigmentation of the skin were reported in some studies in rodents or subhuman primates following exposure to different PCB mixtures. In female rats an increase of hepatocellular carcinomas and a concomitant decrease in mammary gland tumors, tumors of the thyroid, and of the pituitary were noted following long-term exposure to Aroclor 1260 and Chlophen A-60.

In reviewing the accumulated reports on studies in humans, it appears that investigators in the design of clinical and cross-sectional studies focused on the adverse effects observed in laboratory animals and also took other measures commonly performed in routine medical examinations such as cholesterol measurements, blood cell counts, and measurement of blood pressure. Comparison groups matched on age, smoking, and socioeconomic status were usually not included in these studies. It is therefore unclear whether the observed findings made in these assorted groups were related to their PCB exposures. In examining whether the findings made in humans are related to PCBs consistency across studies at similar exposures should be determined. A dose-response relationship should exist. Workers with higher and longer exposures as a group should be affected more, even though some people may be more sensitive to the toxic effects of a chemical than others. It must also be evaluated whether confounders and biases were examined and discussed and whether the measured perturbation represented a true adverse health effect. Finally, for biochemical measurements such as liver function tests slight increases or decreases outside the established normal range for a test should be confirmed by repeating the test before it is assumed that the result was abnormal. Such results may represent outliers of the normal range of the tests rather than abnormal clinical findings or may represent laboratory aberrations on a given day or artifacts because of high serum lipid concentrations. Furthermore, some of these tests such as liver function tests are not very specific. To properly interpret such results, other tests would have to be conducted, particularly if only one or two tests of a battery of tests were abnormal. Without follow up and additional information gathering the observed findings should not simply be attributed to PCB exposure or to ill health. Follow up and an adequate diagnosis is even more important if these abnormalities occur relatively frequently in the general population. Specifically, they may be unrelated to the PCB exposure if only a few workers of a similarly exposed group show such manifestations.

For instance, in Triana, AL, 458 persons were examined in a community-wide study.[37] The study was initiated because this population ate fish with high levels of DDT (1,1'-(2,2,2-trichloroethylidene)*bis*[4-chlorobenzene] and its metabolites. In addition to DDT, PCBs were also present in serum. The geometric mean PCB serum level in this population was 17.2 ppb (µg/l), 80 to 90% of the study population had levels similar to those found in other communities at the time of the study. Older people had higher PCB serum levels and levels were higher in males than in females. PCB serum levels were also higher in members of the study population who reported higher alcohol consumption and in people with higher serum

cholesterol levels. A liver function test, the gamma-glutamyl transpeptidase (GGT), was elevated in participants with higher PCB serum levels as an independent variable but when included into multiple regression analyses, this positive association disappeared. In this particular population, high blood pressure occurred much more frequently than has been reported as national rates for a population of the same sex, age, and ethnic composition. Analysis of the data suggested that a statistically significant positive correlation existed between diastolic blood pressure and PCB serum levels. In this study, blood pressure was only measured at one point in time. The authors stated that "in the absence of a control group the explanation for the excess prevalence of hypertension among Triana residents is debatable. However, the absence of a control group with blood pressure measurement does not weaken our observation that persons in the Triana study population with higher PCB serum levels tended to have higher blood pressure." For a diagnosis of hypertension several blood pressure measurements have to be taken over time. Although a statistical association was noted with diastolic blood pressure, such an association could have occurred by chance. To adequately control for confounding by age, sex, obesity, and ethnicity might be impossible in a population with a high prevalence of high blood pressure particularly as PCB levels also increased with age.

Lawton et al.[38] studied capacitor workers that were exposed to the commercial mixtures of Aroclor 1016, 1242, and/or 1254. Air levels in 1975 around the capacitor filling and sealing area ranged from 200 to 2000 $\mu g/m^3$ with a geometric mean of 690 $\mu g/m^3$. Earlier air level measurements were not available and later measurements made by the National Institute of Occupational Safety and Health (NIOSH) showed TWA values for personal air samples that averaged 168 $\mu g/m^3$. Initially, the serum PCB levels ranged from 57 to 2207 ppb ($\mu g/l$). Lawton et al.[38] found positive correlations with serum cholesterol, the liver function tests, GGT, and alanine aminotransferase. A positive association with high blood pressure was noted. However, when PCB serum levels were expressed on a lipid basis, the associations disappeared, suggesting that they were spurious and related to the concentration of the lipids in serum and indirectly to age. In this study PCBs also increased in serum with age and were higher in males than in females.[37] The authors concluded that "these findings differ from those of most other recent studies of environmentally or occupationally exposed populations in offering evidence of microsomal enzyme induction which is consistent with the extensive LPCB (low polychlorinated biphenyls) clearance also observed in these highly exposed workers. The evidence is statistical in nature and the associated parameters remained within their normal clinical ranges. The effects were therefore physiological rather than pathological and appeared to subside following the cessation of PCB use."

Maroni et al.[39] studied 40 male and 40 female workers from two plants with 6 or more years of exposure. A total of 67 workers were exposed to pyralene 3010 (PCB with 42% chlorination) in a plant manufacturing capacitors, and 13 additional workers were exposed to Apirolio, also a 42% chlorinated mixture of PCBs. The 13 workers tested electrical capacitors by short-circuiting them. Occasionally, during testing, the capacitors exploded and the PCBs dispersed. Air concentrations in the factory ranged from 48 to 275 $\mu g/m^3$, surface contamination from 0.2 to 159 $\mu g/cm^2$, and 2 to 27 $\mu g/cm^2$ were measured on the palms of the workers' hands. The PCB blood levels ranged from 41 to 1319 ppb ($\mu g/l$) with mean total PCB levels of 337 and 292 ppb ($\mu g/l$) for current and former workers, respectively. Four workers had definite chloracne. The mean PCB level of the chloracne patients was 450 ppb ($\mu g/l$) with a range of 310 to 547 ppb ($\mu g/l$). The frequency of abnormal liver function tests increased with increasing PCB serum concentrations. Most workers had an enlarged liver on physical examination and the GGT was elevated. A case of chronic myelocytic leukemia and two cases of cavernous hemangioma were noted among the workers but were thought by the authors to be unrelated to the PCB exposure.[39] According to the authors three of the workers with abnormal liver function tests had underlying disease that could have been the cause of the enlarged livers and only in a few additional cases was a well-defined mild liver failure present. When the authors tested the frequency of hepatic involve-

ment against blood PCB concentrations a significant trend was observed for trichlorobiphenyls but not for pentachlorobiphenyls. It was unclear from the report whether findings in females and males were the same. A closer examination of the results of the liver function tests listed in the paper showed most of them to be in the normal range of most laboratories to 10 to 45 U/l for AST (aspartate aminotransferase), and 10 to 35 U/l for ALT (alanine aminotransferase). The normal ranges given in the paper were unusually low unless they did not represent international units. Only one worker had a definite elevated GGT; however, his exposure was less than the exposures of other workers with normal liver function tests. PCBs, other chlorinated compounds, medicinal drugs, alcohol, and drugs of abuse are known to induce GGT.

Chloracne observed in four workers may have resulted from exposure to chlorinated dibenzofurans or other chemicals because electrical grade PCBs per se have not been reported to produce chloracne in most other plants where PCBs were used and exposure was similar or higher.[38,40,41]

In earlier years, some workers in the U.S. exposed to PCBs also developed chloracne in unusual situations.[41–43] However, exposure to chlorinated dibenzofurans and perhaps chlorinated naphthalenes could not be ruled out in these earlier chloracne reports.

Colombi et al.[44] studied 40 male and 27 female workers who made transformers and electrical condensers with a mean age of 37 years and a mean exposure of 12 years. The PCBs used were Aroclor 1254 during 1949 and 1965, and Pyralene 3010 from Prodelec, France, with 42% chlorination since then. These workers smoked no more than one pack of cigarettes a day and drank no more than 80 g of alcohol/d. The controls consisted of 30 male and 37 female volunteers with a mean age of 35 years. The mean PCB blood level of the exposed workers was 386 ppb (µg/l) with a range of 162 to 1319 ppb (µg/l). Increased urinary uroporphyrin excretion in the PCB workers was reported by the investigators with a normal uroporphyrin/coproporphyrin ratio. Careful examination of the data provided in the paper suggests that porphyrin levels were not reported for all participants, but no information is given on the number of workers with nondetectable levels. The ranges of the different porphyrins given for the exposed and the control group in the paper are not elevated above the normal ranges established by Hill et al.[45] and personal communication except for four coproporphyrin values. These four elevated coproporphyrin levels appear to be unrelated to the PCB exposure because no changes in the porphyrin pattern were observed. According to the authors the uroporphyrin:coproporphyrin ratio was normal. The authors concluded that "at the present time it is not known whether PCBs can also be considered porphyrogenic to man; in other words, whether the observed alteration can progress to the subsequent stage of chemical porphyria. Although clinically evident porphyrias have never been reported in subjects with occupational exposure to PCBs or in subjects with acute or subacute PCB intoxication (Yusho patients), this possibility cannot be excluded."

Smith et al.[41] conducted a survey of three groups of workers occupationally exposed to PCBs in the U.S. One group made capacitors and was exposed to Aroclor 1242 and 1016. The other two groups were transformer maintenance workers for a public and a private utility company and were exposed to Aroclor 1254 or 1260. For capacitor workers, the air levels ranged from nondetectable levels to 264 µg/m^3, and the skin wipes ranged from 10 to 668 µg/cm^2. The lower chlorinated PCB serum levels ranged from 2 to 3330 ppb (µg/l) and the higher chlorinated PCBs from 1 to 250 ppb (µg/l). The hematology tests did not reveal any abnormalities related to PCB exposure. No consistent pattern of abnormalities was noted on physical examination. None of the participants had acneform lesions suggestive of chloracne. Although a correlation was noted by the authors between serum log HPCB (highly chlorinated PCBs) and diastolic blood pressure multiple linear regression analysis showed the apparent association to be attributable to an association primarily with age and gender. Urinary creatinine, porphyrins, glucose, and steroids were normal. The log transformations of two liver function tests, AST and ALT, were positively and significantly correlated with log PCB serum levels. A positive correlation with triglycerides and an inverse correlation with high-density lipoprotein cholesterol in fasting serum specimens was noted. Although

statistically significantly different, it cannot be determined from the information given in the paper whether these findings have any clinical significance because the ranges and means of the liver function tests were not provided. No clinical abnormalities related to PCB exposure were noted. According to the authors, "alterations in liver enzyme tests in association with increasing serum PCB concentration may not themselves be predictive of future chronic liver disease but may reflect liver microsomal enzyme induction." Chloracne or other occupationally related skin lesions were not observed.

Air levels in the public utility company ranged from 37 to 215 $\mu g/m^3$. In the public utility transformer workers, the lower chlorinated biphenyls in serum ranged from 1 to 59 ppb ($\mu g/l$) and the higher chlorinated biphenyls from 1 to 24 ppb ($\mu g/l$). No hematologic changes that correlated with PCB exposure were noted after adjusting for confounders. Two liver function tests, AST and ALT, were positively and significantly correlated with PCB levels. An inverse correlation with high-density lipoprotein cholesterol and a positive correlation with triglycerides in fasting serum specimens were observed. Urinary porphyrins, steroids, and glucose were normal. Results for the private utility company were similar. Air levels ranged from 0.4 to 82.3 $\mu g/m^3$, PCB concentrations on skin wipes ranged from 5 to 487 $\mu g/100\ cm^2$. The serum PCB levels for the lower chlorinated biphenyls ranged from 9 to 52 ppb ($\mu g/l$) and for the higher chlorinated biphenyls from 3 to 250 ppb ($\mu g/l$). The results of hematological studies were within the normal range after adjusting for confounders.

The age-related effects mentioned by the authors have been well established. Patients with higher low-density lipoproteins and higher cholesterol are more likely to be older, overweight, have arteriosclerosis, hypertension, and higher liver function tests.[46,47] Such individuals also have higher PCB serum levels, as a proportionally larger amount of PCBs will remain in serum with higher lipid levels.

Fischbein et al.[40] conducted a clinical field survey of capacitor manufacturing workers, 168 males and 158 females. The workers had been exposed to some Aroclor 1254 and 1221, but mainly to Aroclors 1242 and 1016. They were between 30 and 70 years old and 69% had been exposed to PCBs for more than 10 years. Their general health was not affected and clinical laboratory test results were within the normal range, except that there was a positive statistical correlation between the AST liver function test and serum levels of the more highly chlorinated biphenyl congeners. It is difficult to interpret the abnormal liver function tests because the authors of the studies provided little detail and did not control for confounders. The authors noted that "the paucity of the physical findings in the PCB workers was striking and that this included a very low prevalence of abnormal liver findings although in a subgroup of the workers it was demonstrated that the cytochrome P-450 was induced in the liver." Additional studies of this type have been reviewed previously.[48]

Meigs et al.,[43] Ouw et al.,[49] and Elo et al.[50] also noted slightly elevated liver function tests in one or more workers exposed to PCBs. To appropriately interpret these results the tests would have to be repeated in conjunction with other clinical laboratory work[51] to ascertain the reason for the abnormal liver function tests. Furthermore, the serum PCB levels would have to be quantitated on a lipid basis. In the study by Elo et al.,[50] worker exposure to polychlorinated dibenzofurans and perhaps other chemicals may have occurred. In the study by Meigs et al.,[43] the PCBs were used as heat exchangers that may have resulted in the formation of chlorinated dibenzofurans.

In conjunction with the Fischbein et al.[40] study, Warshaw et al.[52] surveyed the respiratory function of 309 male and female capacitor workers. An additional 66 workers were excluded because of exposure to asbestos, talc, or textile dust. The mean age of the males was 41.1 ± 12.6 years and of the females it was 47.3 ± 12.5 years. The average length of exposure for the male workers was 14.9 years (S.D. = 8.11) and 16.1 years (S.D. = 8.3) for the females. Results in a group of nonsmokers reported by Morris et al.[53] were used for comparison. A total of 48% of the capacitor workers reported eye and upper respiratory irritation; 10% had experienced tightness of the chest; 35% of the males and 30% of the females were smokers or ex-smokers; 13% reportedly had

chronic bronchitis; an abnormal forced vital capacity was found in 14% of the males and 13% of the females; 13% of the males and 9% of the females had restrictive impairment; and interstitial changes were seen on X-ray in 6 workers.

The normal population of Morris et al.[53] of 957 subjects had a 5.6% prevalence of abnormal vital capacity. Vital capacity measurement is affected by age, height, and by the individual's effort to maximally inhale and exhale. In normal individuals the test is affected by smoking within the last hour before the test, use of bronchodilators, a heavy meal within the past 2 h, or an upper respiratory infection within the past 3 weeks before the test. NIOSH recommends that the test be performed in a sitting position unless the patient is obese. However, in the present study the test was performed in the standing position. Apparently, 13% of the workers had "chronic bronchitis". In chronic obstructive bronchitis prevalent in smokers forced vital capacity and forced expiratory volume are reduced. This observation raises questions about the appropriateness of the control group. Because only summary results were reported, it is unclear whether the authors compared the results of the individual workers based on age and height to the results of Morris et al.[53] or whether they compared means. In the original PCB study[40] from which these workers were drawn 40% of the male and 53% of the female workers were older than 50 years. Furthermore, it was not clarified in the paper whether the observed chronic bronchitis was present in smokers or ex-smokers and whether they accounted for most of the workers with abnormal pulmonary function tests.

Kalina et al.[54] studied chromosome aberrations and sister chromatid exchanges (SCEs) in 32 PCB exposed workers in Czechoslovakia and two sets of 20 controls matched on smoking behavior. The authors noted a higher frequency of chromosome aberrations in the PCB workers exposed for more than 10 years. SCE values were significantly increased in workers exposed for 15 years. According to the authors, the workers may also have been exposed to benzene and formaldehyde. The authors collected information on exposure to medications, radiation, and other factors but did not report on these results. Increases in SCEs have been found in smokers, but more importantly the workers were exposed to chemicals known to produce these types of aberrations. Because PCBs are relatively inert chemicals, they would not be expected to produce chromosome aberrations. Similar observations have not been reported in other worker populations.

Kilburn et al.[55] examined 14 firemen who had been exposed to byproducts generated in a transformer fire and found memory impairment, and impairment of cognitive function. No correlation was found with the firemen's serum or adipose tissue PCB levels, which were within the range of the general population. Following 2 to 3 weeks of supervised diet, daily exercise, sauna, and the administration of unsaturated fat and niacin, a significant improvement in behavioral performance was noted. It is the opinion of this reviewer that the observations made in the firemen seem to be unrelated to their potential exposure to PCBs from the transformer fire.

In another electric transformer fire in a State office building in Binghamton, NY, reported exposure in fire fighters was positively related to PCB serum levels. However, the means and individual values were within the range reported in other studies unrelated to any unusual PCB exposure. Although significant correlations were observed between serum PCB levels and levels of liver enzymes and serum lipids, mean levels of these biochemical parameters were not associated with reported exposure after an adjustment for relevant covariables, such as age and alcohol consumption.[56] These two studies of fire fighters exposed to transformer fires suggest that very little PCBs, if any, were taken up by these fire fighters.

Alvares et al.[57] measured the half-life of antipyrine in five workers occupationally exposed to Aroclor 1016 in a capacitor manufacturing plant. In the exposed workers, the antipyrine half-life was significantly lower (10.8 h) than in matched controls (15.6 h) of the general population. The authors found that Aroclor 1016 elicits the barbiturate type of inducing effects on drug metabolism in humans. The authors also demonstrated this effect in rats.[58]

Recently, the suggestion has been made that PCBs may play a role in the development of breast cancer.[59] Falck et al.[59] found elevated lev-

els of PCBs and DDT and its derivatives in mammary tissue of women with breast cancer when compared with women with benign breast cancer when compared with women with benign breast disease. The median age of women with benign breast disease was 58 and 64 years for women with malignant disease. Because chemicals such as PCB and DDT (1,1'-(2,2,2-trichloroethylidene)*bis*[4-chlorobenzene]) increase in humans with age, part of the observed increase may be explained by the differences in age distribution.[37] A review of the data given in the paper indicates that several cancer patients did not have higher PCB levels than patients with benign breast disease. Slight but statistically significant differences in body burdens of persistent lipophilic compounds have also been reported for other cancers by other authors.[60-65] On the other hand, Teufel et al.[66] did not find elevated levels of PCBs in children with tumors or congenital malformations if PCB concentrations in adipose tissue were compared with those of children without such lesions. No inferences can be drawn from these findings. The underlying disease may affect body functions. Metabolism, excretion, and distribution of these chemicals may be altered in some situations affecting PCB levels. Furthermore, slightly higher concentrations of chlorinated aromatic compounds in different groups of people may be a reflection of differences in lifestyle. Industrial chemicals are usually slightly higher in urban populations, while the concentrations of pesticides are higher in people living in rural areas and in the South. It may also be fallacious to correlate tissue levels with the clinical expression of a disease that may have existed in a dormant stage for some time in the past. The principal risk factors for cancer of the breast are marital status, parity, urban residence, older age at marriage and first pregnancy, lack of exercise, heredity and hormonal factors, early menarche, late menopause, and perhaps regular alcohol consumption.[67,68] Low-level exposure to environmental chemicals such as PCBs and DDT and their derivatives would be inconsequential compared with these major risk factors. Based on these and other more recent studies, Key and Reeves concluded "that for PCBs there is no evidence for an association with breast cancer risk."[68a]

In conclusion, based on the findings reported in the various studies reviewed in this section, no abnormal clinical findings that could be related to PCB exposure were made in the workers. The positive association with diastolic blood pressure when investigated further was found to be related to aging and to serum lipid concentrations that increase with aging in populations on a Western diet. It was also found that as lipids increase in serum so do PCBs. To eliminate this confounder PCBs should be expressed on a lipid basis in serum. By most authors, the slightly elevated liver function tests were thought to be an expression of the induction of mixed function oxidases (microsomal enzymes) rather than an expression of liver disease. Some study subjects had high-serum lipids. High-serum lipids (turbidity) could have interfered in occasional study subjects with the liver function test measurements resulting in higher liver function tests as a laboratory error. This possibility would have to be considered only when occasional members of a group were affected. The abnormal pulmonary function tests reported in one study may have been related to smoking rather than PCB exposure. The differences in body burdens between assorted groups with and without breast cancer or with benign or malignant disease were small, as were the number of study subjects. Although statistically significantly different, they were within the range of levels found in the general population. It is unclear whether the observed differences in tissue levels could be the result of a selection bias unrelated to the disease or whether the differences in levels represent a proxy for other factors. Biologically, the small differences in amount of chemicals that these different groups were conceivably exposed to make a causal association with the underlying disease implausible.

V. REPRODUCTIVE AND DEVELOPMENTAL EFFECTS

Taylor et al.[69] studied the reproductive effects of PCB exposure in female capacitor workers by reviewing birth weight on birth certificates. The exposed group consisted of 51 infants of female capacitor workers. The mothers of these infants had been exposed to Aroclors 1254, 1242, and

1016 for 1 year or more prior to the birth of the infant. Their mean age was 32.4 ± 6.3 years. Controls were 337 infants of other female (mean age of 26.5 ± 4.9 years) workers in the same plant with indirect low exposure to PCBs. The gestational age at birth for the infants born to mothers who had high exposure to PCBs was 6.6 d shorter than in the controls. After adjustment for gestational age, the exposed infants weighed an average 58 g less than the controls. According to the authors of this study, it was not possible to control for tobacco use, underlying medical conditions, maternal height, or a previous history of low birth weight. The small number of observations, lack of information on important influencing factors, and questionable biological significance of birth weight and gestational age differences of this small size made any conclusions about the effect of PCBs on birth weights tentative.

In 1989, Taylor et al.[70] reported an additional expanded reproductive study in the same capacitor work force. The exposed group of this second study consisted of offspring of 200 female capacitor workers that had been exposed to Aroclors 1254, 1242, or 1016 for 1 year or more prior to the birth of the infant. The controls consisted of infants of 205 other female workers in the same plant with indirect low exposure. Again, a significant negative correlation among birth weight, gestational age, and estimated serum PCB levels was noted. An average decrease of 33 g in the birth weight of infants born to mothers with direct exposure to PCBs was observed. According to the authors, the biological importance of such a small difference in birth weight has no clinical significance for term infants.

In North Carolina and Michigan, studies have been performed to elucidate the effect of PCBs on infants of the general population. In both studies, the authors concluded that postnatal exposure through human milk was not associated with any ill effects. They indicated, however, that a transplacental neurobehavioral effect could be demonstrated. This effect was transient in one study (North Carolina) and persistent in the other.

In the North Carolina cohort, a total of 856 infants of the general population were enrolled in the study as neonates and followed for several years.[71] Selection of the study participants was not based on presumed higher exposures than the general population. PCBs and DDT and derivatives were measured in human milk, serum, placenta, and cord blood. Results of these measurements were used to calculate prenatal exposure of the infants. In the final exposure assessment, PCB levels from cord blood and placenta were excluded because they were mostly below the limit of detection of the analytical method.[72] In the assessment it was assumed that the mother weighed 60 kg, 25% of her weight was fat, the only means of excretion of PCBs for the mother was deposition of PCBs into the fetus and through lactation, the daily dose was constant over a lifetime, and the mother was primiparous. However, these assumptions are erroneous as it was not considered that PCBs are metabolized and excreted in humans with congener specific half-lives of days, months, or years. In addition, Tilson et al.[73] in a review article using the same data estimated the dose response relationship differently. These authors[73] arrayed the crude neurobehavioral data (percent abnormal on the Brazelton neonatal behavioral assessment scale or means on the Bayley scales of infant development) of the North Carolina cohort by the PCB level in milk fat and estimated a no observed adverse effect level (NOAEL) by inspection. It was not stated in the paper how missing PCB values were treated. The NOAEL appeared to be about 3.4 ppm (mg/kg) PCBs in human milk fat for the percent abnormal on the Brazelton assessment or means on the Bayley scales. For visual recognition memory the level was 1.0 ppm (mg/kg) in human milk fat.

In the Michigan study, a population eating fish from Lake Michigan was compared with a control group that did not consume such fish. In several papers describing these studies,[74–78] neurobehavioral changes lower birth weight and a reduced gestation period were reported in association with higher fish intake presumed to also represent higher PCB intake. According to Paneth,[79] who reviewed these reports, exposure in this population was poorly defined, dose response relationships were not well established, and other potential confounders such as exposure to heavy metals, the mothers lifestyle and well being, and genetic make-up were not considered. The Michigan studies are based on a group of infants of which 242 were considered exposed because their mothers stated that they

ate Lake Michigan fish and 71 were considered not be exposed because their mothers denied eating Lake Michigan fish. The PCBs were measured in samples of cord serum, serum from the mothers, and in the mothers milk. Results of PCB measurements were published in two papers.[74,80] In the Schwartz et al.[74] paper, it is unclear in how many of the 71 "controls" (non-fish eaters) and of the 242 "exposed" (fish eaters), PCBs were detected or quantified because the controls and the exposed groups were combined in the report. Two standards were used for the quantitation of the PCBs: Aroclor 1016 and 1260. In a number of sera and milk specimens, PCBs could not be quantitated or were not detected.[74] The mean maternal serum PCB concentrations were 5.5 ppb (μg/l) for Aroclor 1260 and 1.6 ppb (μg/l) for Aroclor 1016. As expected, the cord serum levels were lower because lipid levels are lower in cord blood than in maternal blood. The non-fish-eating group had mean PCB serum levels of about 4 ppb (μg/l) and those eating 52 to 183 meals of fish per year had mean PCB serum levels around 9 ppb (μg/l). It is not clarified in the papers how the many nondetectable levels and the nonquantifiable levels were accounted for in the correlation analyses.

In contrast with the Michigan studies, no effect on birth weight was observed in the North Carolina studies,[72] even though the cohort was much larger and the serum PCB levels of the mothers were about the same. The neurobehavioral effects in the Michigan and the North Carolina studies differed (Table 2), suggesting that in the two study groups the same region of the brain was not affected and that the two studies were inconsistent with each other.[71] The children in both studies were followed for several years and a variety of tests were performed (Table 2). At the time of delivery the infants in the North Carolina study received a physical examination and the Brazelton neonatal behavioral assessment scales (BNBAS) were administered. The BNBAS yields results of 27 behavioral scales and 20 reflexes. To simplify analysis, the results were summarized into clusters[81] using the clusters developed by Jacobson et al.[76] For the BNBAS, the only cluster scores significantly affected by PCBs or DDE were the tonicity and reflex scores. Higher PCB levels were associated with less muscle tone and activity. The authors also noted that infants who were delivered by emergency Cesarean section or with low forceps or suction had a greater number of abnormal reflexes, but this did not change the significantly positive correlation with PCBs or DDE. Mothers with higher PCB serum levels were older and were more likely to consume one or more alcoholic beverages per week. It is not stated in the paper what the association was between alcohol consumption and abnormal reflexes.[71,72] The BNBAS were performed during the first week in 51% of the infants, in 20% during the second week, and in 16% during the third week of life. According to some investigators, the BNBAS should only be administered during the first 3 d of life.[71] Jacobson et al.[76] also administered the BNBAS and reported a decrease in reflexes, but an increase in startle reflexes. The increase in startle reflexes was not noted by Rogan et al.[71] and is usually not observed with hyporeflexia (decrease in reflexes as reported by Jacobson et al.)[76] and hypotonia. In a subset of these children at the age of 4 years, Jacobson et al.[83] noted a decrease in verbal and memory scales, while no such association was found among exposure and verbal and memory scales in the North Carolina cohort. In the North Carolina cohort, at 12 months of age, the psychomotor development was decreased as the calculated *in utero* PCB exposures increased. The observed neurobehavioral effects were no longer detectable at the ages of 3, 4, and 5 years in the North Carolina cohort,[82] while this was not the case in Michigan.[83,84]

In addition to these epidemiology studies, Leoni et al.[85] collected blood samples from 120 women who miscarried and 120 women who carried their infant to term. PCBs reported as Fenclor 54 were significantly higher in women who miscarried. However, if PCBs were quantitated as decachlorobiphenyl following perchlorination, this statistically significant difference disappeared. Thus, the initial quantitation may have introduced an error that was removed when PCBs were quantitated as decachlorobiphenyl. These authors reported that PCB levels correlated negatively with milk and fish consumption and positively with age and alcohol consumption. It is well known that age and alcohol consumption affect the prevalence of miscarriages. Because PCBs increase with age and have been shown to increase with alcohol

TABLE 2
Neurobehavioral Tests and Outcomes from Two Prospective Studies of Children

Authors	Tests	Age	Outcome
Jacobson et. al.[75,76,78,80,83,84] Schwartz et al.[74] Fein et al.[77]	Ballard maturity Brazelton neonatal behavioral assessment	3 d	Motoric immaturity; lability poor; startle ↑; reflexes ↓
	Infant fixation to novelty (illuminated pictures)	7 months	Less fixation with higher transplacental placental PCB exposure
	McCarthy scales Mother: Peabody picture vocabulary test	4 years	Verbal scales ↓; memory scales ↓; reduced activity based on composite rating between mother and examiner; test retest reliability moderate; r = 0.44
	Child behavioral record (adapted from Bayley infant behavior record)		Outcomes unrelated to 4 year body burden; therefore effect transplacental?
Gladen[72] Gladen and Rogan[82] Rogan et al.[71,81]	Brazelton test	3 d-weeks	Hydroreflexia
	Bayley scales of infant development	6 months	Verbal and memory scales normal
		12 months	Psychomotor development ↓ with increased transplacental PCB exposure; unrelated to hyporeflexia noted at birth
	McCarthy scales	3, 4, and 5 years	No association between mental and psychomotor scales and PCB exposure
	Report cards	8 years	No relationship between poorer grades and PCB exposure

consumption, they may in this case have served as a proxy for other parameters.

In conclusion, the studies on reproductive effects show a slight but clinically insignificant effect on birth weight in highly exposed workers. Because the information in the worker studies was obtained from birth certificates, other factors that would affect birth weight could not be effectively controlled and not all confounders may have been considered. In reproductive animal studies, effects on birth weight represent a sensitive indicator of fetal toxicity. It is remarkable that even with the very high exposures of female capacitor workers no clinically significant effect on birth weight of their offspring was noted.

In the study of capacitor workers and in the North Carolina and Michigan studies, *in utero* exposures of the infants were estimated indirectly, which may have introduced a misclassification bias. In the Michigan studies exposure assessment was partly based on fish consumption; however, the levels of PCBs and other chemicals in the consumed fish were unknown. In the North Carolina studies in indirectly assessing *in utero* exposure the erroneous assumption was made that humans do not excrete PCBs. In addition, analy-

sis of a few milk samples does not capture the fluctuations of PCB levels in human milk over the months of nursing and during a given feeding period and are not a good estimate of maternal body burdens during pregnancy and transplacental exposure of the fetus. Thus, the estimated NOAELs calculated by Tilson et al.[73] based on this information are also tenuous.

In addition to the uncertainties in exposure assessment, the neurobehavioral tests used have not been standardized for large population studies. Because of their subjectivity, differences between examiners exist and customarily the interpretation of these tests is combined with other clinical information. Merely by chance some statistically significant differences would be expected as these tests generate information on many endpoints. The fact that the two studies did not show the same results supports the possibility of a chance finding or may have been unrelated to PCBs because the exposures were not well defined. Some of the infants in the Michigan studies may have been premature (the lowest birth weight was 909.1 g), and the authors reported that the infants born to mothers who consumed Lake Michigan fish were lighter[75,77] than the controls. For premature infants the neurobehavioral test results would be different than for term infants. It is not stated in the published papers how immaturity might have affected the results.

VI. IMMUNOLOGICAL EFFECTS

Immunological responses to PCB exposure have been evaluated in a limited number of epidemiology studies. None of these studies established a causal link between PCB exposure and immunotoxicity.[2,86,87] Emmett[86] evaluated delayed hypersensitivity of the dermal reaction to 0.1 cc intradermally injected mumps and trichophyton antigen in transformer maintenance and repair workers and a matched control group not exposed to PCBs. The delayed hypersensitivity reaction is a measure of a type IV delayed hypersensitivity reaction mediated by sensitized T-cells and macrophages. The proportions of positive responses to mumps (92% for the exposed transformer maintenance workers, 89% control) and trichophyton (17% exposed, 8% control) did not differ significantly.[86,87] The mean diameters of the skin reactions to mumps antigen in the two groups were identical. The serum PCB concentrations in the 54 past and presently exposed workers tested with the antigens ranged from nondetectable levels to 300 ppb (μg/l) and in the nonexposed comparison group they ranged from nondetectable levels to 15 ppb (μg/l). Emmett[86,87] also performed a battery of clinical laboratory tests in these PCB-exposed transformer maintenance workers. According to the authors, except for a possible positive association between PCB serum levels and increases in mixed function oxidases, no other changes were positively associated with PCB serum levels after the results were controlled for confounders.

In conclusion, it is uncertain whether and at what serum PCB concentrations adverse effects would occur in humans, including immunotoxicity. Illnesses such as increased numbers of acute or chronic infections have not been observed, even in highly exposed individuals. However, such effects were reported in the Yusho and Yu-Cheng outbreaks. In these two poisoning episodes, exposure to high concentrations of PCDFs also occurred. The "PCB exposed" cohort of Emmett et al.[86,87] had similar geometric mean serum PCB concentrations of 9.7 ppb (μg/l) (highest level 300 μg/l) as the steady-state serum level of 10 ppb (μg/l) in a study of rhesus monkeys given 5 μg/kg/d PCBs for 23 to 55 months.[88] The rhesus monkeys were reported to have abnormal immune function tests,[88] suggesting that rhesus monkeys may not represent a good animal model for humans.

VII. MORTALITY IN CAPACITOR AND TRANSFORMER WORKERS

Several mortality studies of workers with very high and long-term exposure to PCBs have been conducted to determine cancer mortality. These studies (in the reviewer's opinion) have not provided any convincing evidence that PCBs are human carcinogens. To evaluate mortality studies in the aggregate and conclude whether a causal association exists is determined by several con-

siderations. Results from similar studies should provide similar results. The same type and site-specific cancers should be increased at similar exposures in comparable studies. Workers with higher and longer exposures and longer latency periods should be more highly affected. Exposures should be well characterized. When comparing observed and expected cancers, the confidence intervals should generally not include one. If the confidence intervals are wide (e.g., risk ratio = 3 and C.I. = 2–20) the precision of the risk ratio is low. For cancers known to have specific etiologies such as lung cancer and smoking, control for confounders is important. How data are evaluated is also governed by the types of cancers observed. Some cancers such as the mesotheliomas are usually associated with exposure to asbestos, while the prevalence of other cancers such as the carcinomas of the gastrointestinal intestinal tract are thought to be affected by lifestyle and diet.

A slight increase in liver (3 observed, 1.07 expected) and rectal (4 observed, 1.19 expected) cancers among 2567 male and female capacitor manufacturing workers in two facilities located in upstate New York and western Massachusetts were noted by Brown and Jones.[89] One hepatocellular carcinoma occurred in a male worker at one plant. The other two carcinomas occurred in two females in the other plant. Similarly, one rectal cancer occurred in a male worker at one plant, while the other three rectal cancers occurred in females in another plant. In a follow-up study of the same cohort several years later, a continued excess of cancer of the liver was found (5 observed, 1.9 expected), but no additional rectal cancers were observed and the previous excess in rectal cancer was no longer statistically significant (4 observed, 1.9 expected).[90] No additional tumors of the liver occurred in one of the plants. In the other plant one additional cancer of the liver was found in a female worker. Review of hospital records by Brown[90] showed that not all of the liver cancers were primary liver cancers. Once Brown reclassified the tumors, the differences for liver tumors between the workers and the general population were no longer statistically significant. In the statistical analysis the male and female workers were combined.

Taylor[91] followed the mortality of 6292 male and female capacitor workers in upstate New York. The overall cohort mortality was significantly less than the general population (510 observed vs. 614 expected; SMR 83, 95% C.I. 0.76–0.90) and no increase was noted for total or specific cancers.

In Sweden, Gustavsson et al.[92] performed an SMR analysis on 142 male capacitor workers. A total of 21 deaths was reported and 22.1 were expected. Neither total cancer deaths (7 observed, 5.39 expected) nor incident cases (7 observed, 7.58 expected) were elevated. The small sample size of this cohort precludes meaningful interpretation.

Bertazzi et al.[93] studied total and cancer mortality in 2100 Italian workers employed in a capacitor manufacturing plant. Deaths for all causes were not affected in males (30 observed, 27.8 expected; SMR 108). The SMR analysis resulted in an excess of total cancers among males (14 observed, 5.5 expected; SMR 253, C.I. 1.44–4.15), mainly in the digestive tract, the lung, and hematologic sites. Overall mortality in females exceeded expectation (34 observed, 25.8 expected, SMR 132 for the national comparison, 16.5 expected for the local comparison; SMR 206, 95% C.I. 1.45–2.85), as did total cancer mortality observed, 7.7 expected. The increase in all cause mortality in females was primarily the result of 9 accidental deaths of which 7 were non-work-related traffic accidents. In this cohort, work histories for employees were not available prior to 1954 and exposure was not well documented. Additionally, these workers were exposed to other chemicals in the plant. According to the authors "the cancer excess mortality was statistically significant only when compared with the local population. The local population was known to have a lower cancer mortality than the national population. Analysis by duration of exposure, latency, and year of first exposure did not reveal any definitive pattern or trend of mortality for any of the relevant causes." The authors in their report of the results also pointed out that for some tumors the latency period was very short, 3 months in one example, or workers had been hired at an advanced age. They state: "given this information no clearcut and definite conclusion regarding the association between cancer of the GI tract and exposure to PCBs can

be drawn from the results of the study." The authors also pointed out in their discussion that "the limitations discussed did not permit a causal association to be either proved or dismissed."

More recently, Sinks et al.[94] conducted an SMR study of 3588 male and female workers at a capacitor plant and found a significant increase in melanocarcinomas (8 observed cancers vs. 2 expected). A nonsignificant increase in cancer of the brain was also noted. A dose-response relationship or increase with latency could not be established, nor were medical records available for all cases to confirm that all tumors were primary tumors. Furthermore, one of the melanocarcinomas originated in the gallbladder and should not have been coded as a tumor originating in skin. Another melanocarcinoma was diagnosed before the individual began employment at the plant. The observed number of deaths from all causes was 192 and the expected number was 283.3, with an SMR of 70 (95% C.I. 0.60–0.80). Similarly, the observed number of all cancers was lower than expected (54 observed vs. 63.7 expected; SMR 80, 95% C.I. 0.60–1.10).

Bahn et al.[95] in a letter to the editor reported two melanocarcinomas from a group of 72 petrochemical workers exposed to PCBs in New Jersey when only 0.04 were expected. These workers were exposed to other chemicals and the potential confounding of these other exposures was not analyzed.

In conclusion, the epidemiological studies in the aggregate have failed to provide consistent data regarding an increase in overall mortality or in specific cancer mortality of workers exposed to PCBs. The lack of a consistent increase in total or specific cancer mortality across studies does not suggest any particular trend between PCB exposure and cancer mortality. The workers were primarily exposed to the lower chlorinated mixtures such as Aroclor 1242 and 1016 with some exposure to Aroclor 1254, while the rat studies showing a carcinogenic effect of PCBs were conducted with a more highly chlorinated PCB mixture, Aroclor 1260 or Chlophen A-60.

The majority of mortality studies were conducted on relatively small study populations. Differences in sample size, in the quality of PCB exposure assessment, in the length of exposure, time of exposure required to be eligible for inclusion in the study, and differences in the cancer incidence of the control populations from different countries preclude any comparisons across studies or combining the study populations for a "meta-analysis" as reported by the Industrial Disease Standards Panel, Report no. 2, Toronto, Ontario, December 1987 and published in the Ontario Gazette. The Panel stated that while only seven deaths from liver and biliary cancer occurred, the association was strong and achieved statistical significance when these studies were combined in a meta analysis. However, the Panel did not consider that four cancers occurred in males, two in the Bertazzi[93] study and one each in the Gustavsson[92] and Brown[90] studies. Among females, all three liver cancers and cancers of the biliary tracts occurred in one plant. Furthermore, a higher than expected number of liver cancers was not found in all mortality studies now available. The number of tumors in the different plants was very small and on follow-up in the Brown study,[90] for instance, no further liver cancers or cancers of the biliary tract were found. It is also debatable whether tumors of the biliary tract and gallbladder should be combined with hepatocellular carcinomas as their etiologies differ. The various statistically significantly increased site-specific tumors may have occurred by chance. The findings are not consistent across studies, the actual number of specific tumors was small, the number of tumors did not increase with latency or were they primarily found in workers with the highest exposures. In the aggregate the results of these studies are inconclusive. Further follow-up of these and other workers may ultimately clarify the reported findings as the different cohorts age and more data and longer follow-up periods become available.

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VIII. RECENT STUDIES IN LABORATORY ANIMALS

A wide range of adverse effects of PCBs have been investigated in numerous animal studies over the past 20 years. At lower doses, reproductive and developmental as well as immuno-

toxic effects have been reported primarily in subhuman primates and mink. It is beyond the scope of this manuscript to review these data in detail. They have been summarized recently.[96-100] Only a few recent studies are mentioned here. The primary focus is on studies where effects were noted at comparatively low doses. Furthermore, the recent reevaluation of the liver tumors in rodents is summarized and the toxicity equivalency approach is discussed.

A. Reproductive Effects in Animals

In a study of rhesus monkeys exposed to Aroclor 1248, Barsotti et al.[101] reported decreased birth weights. However, toxicity was observed in the adult females at all dose levels and the decreased birth weights could have resulted from maternal toxicity. It has been suggested that a chemical should only be classified as a developmental toxicant, if it produces an effect on the conceptus at levels not or only slightly toxic to the mother.[102]

Barsotti and Van Miller[103] also reported decreased birth weights in the offspring of rhesus monkeys receiving approximately 0.04 mg Aroclor 1016/kg body weight/d. The EPA[104] has used the NOAEL of 0.01 mg/kg/d from this study to derive a guideline level for noncarcinogenic effects of PCBs. The EPA-IRIS,[104,105] derived a guideline intake level of 1×10^{-4} mg/kg/d by dividing the NOAEL of 0.01 mg/kg/d from the Barsotti and Van Miller[101] study by an uncertainty factor of 100.

However, questions have been raised about the use of this study for regulatory purposes. Although birth weights of animals in the high-dose group and the control group differed statistically, birth weights in both groups were within the range of historical measurements for rhesus monkeys reported by Van Wagenen and Catchpole.[106] All adult subhuman primates were feral; however, the control animals were purchased 4 years before the experimental animals. Because the control animals were likely to be older than the experimental animals and had been in captivity longer, the prepregnancy maternal weights may have been greater and may have influenced infant birth weights. Significant differences in genetic makeup may have existed between the two groups of monkeys. Furthermore, the monkey chow used in the study was found to be contaminated with polybrominated biphenyl (PBB) and other halogenated chemicals. This additional exposure may have affected the results. The results of the Barsotti and Van Miller[103] study, therefore, are inconclusive. Additional reproductive studies have been conducted in Macaca mulatta monkeys but have not been reported in detail.[107]

B. Immunotoxicity

Immune function has been tested by several investigators in laboratory animal species exposed to PCBs.[108-112] These data have been reviewed by Vos and Luster.[100] PCBs have also been suspected of being a cofactor in phocine distemper virus (PDV) infections in harbor seals. When seals were infected with PDV under experimental conditions and some of them were also exposed to PCBs, no difference in mortality was noted between the two groups.[113] It is unclear whether the dose given was sufficient. Additional on-going experiments in another laboratory may resolve this issue.

In a series of three recent papers, Tryphonas et al.[88,114,115] reported results of immune function studies in subhuman primates. Five groups of rhesus monkeys (16 animals each) received dietary doses of Aroclor 1254 of 0, 0.005, 0.02, 0.04, or 0.08 mg/kg/d. After 23 months a statistically significant ($p < 0.05$) dose-related decrease of less than half of the original values in antibody titers of the immunoglobulin IgM and IgG isotopes to SRBCs (sheep red blood cells) was noted. This difference has no clinical relevance. At least a fourfold change in titer count is necessary to be considered clinically meaningful.[116] Lymphocyte levels were measured in the control and 80 µg/kg/d exposed group. A significant increase in T-suppressor (Ts cells [CD4 cells]) and a significant reduction in relative number of T-helper (TH) cells (CD8 cells) and in the TH/Ts ratio when compared with controls was reported. The number of B-lymphocytes (CD20 cells) and total lymphocytes or lymphocyte proliferation induced by pokeweed were not affected. Stimulation by standard mitogens produced no significant differences in lymphocyte transformation rates. Serum im-

munoglobulin, serum protein, and hydrocortisone levels did not differ from controls. After 55 months of exposure, a statistically significant dose-related decrease in IgM antibodies but not in the IgG levels was observed in the immunized SRBCs monkeys. Antibody response to pneumococcal antigen and lymphocyte proliferation following stimulation by mitogens were similar in treated and control groups. A significant change in the relative number of CD2 cells when compared with controls was observed in all treated groups. Results for all other lymphocyte subpopulation analyses, including absolute number of total CD2 cells, were not affected. Results of a mixed lymphocyte culture assay and a monocyte activation assay were similar in control and treated groups.[88] Hydrocortisone and interleukin-1 concentrations were not affected.[88]

In an additional publication, Tryphonas et al.[115] reported that the serum complement (CH50) activity was significantly higher in all treated groups. However, a dose response relationship was not noted. A significant trend toward increased natural killer cell activity was observed at the adjusted effector (E) to tumor (T) target cell ratio (E:T) at the 75:1 but not at the 50:1 or 25:1 ratios. No difference in activity was found when a pairwise comparison was made between the treatment and control group. Interferon levels were significantly higher than those of the controls in the 20 and 80 µg/kg/d PCB exposed groups but lower than controls in the 40 µg/kg/d group, and the same as the controls in the group given 5 µg/kg/d. Because a dose-response relationship was not found, these changes seem to be unrelated to PCB exposure.

In conclusion, the immunological responses reported by Tryphonas et al.[88,114,115] in the aggregate do not suggest immunotoxicity. The TH/Ts ratio reported to be lower in treated animals may be in error because cytotoxic T lymphocytes were excluded. CD8 cells and the CD4/CD8 ratio were not affected by PCB treatment.[114] Furthermore, a positive control group as recommended by Luster et al.[117] was not included in the studies.[88,114,115]

C. Carcinogenesis in Animals

In several 2-year rat-feeding studies an increase in tumors of the liver has been observed in Aroclor 1260 or Clophen 60 exposed animals. No such increase in liver tumors or any other tumors has been noted following the exposure to lower chlorinated mixtures. Recently, four 2-year rat-feeding studies reporting hepatocellular carcinomas were reviewed.[118] Since the results of the original rat bioassays were first reported, the criteria for classification of hepatic proliferative lesions in the rat have been revised. In the original studies, liver lesions were diagnosed using the classification scheme of Squire and Levitt.[119] Rat liver lesions were diagnosed as neoplastic nodules (sometimes referred to as hyperplastic nodules) or carcinomas. A revised classification for proliferative rat liver lesions was subsequently developed by the National Toxicology Program (NTP)[120,121] and endorsed by the EPA.[122] The current NTP guidelines distinguish between hyperplasia, a nonneoplastic response and adenomas, a benign tumor.[120,122] The neoplastic nodule (hyperplastic nodule) category in the Squire and Levitt[119] system included both adenomas and hyperplasia.

Based on the Institute for Evaluating Health Risks[118] review, it was reaffirmed that chronic dietary exposure of rats, in three different studies, to 60% chlorinated PCB formulations (Aroclor 1260 or Clophen A 60) resulted in the development of benign and malignant liver tumors. Chronic exposure of rats to a 54% chlorinated PCB formulation (Aroclor 1254) did not yield a statistically significant increase of benign or malignant tumors.[123] Rats chronically exposed to a PCB formulation that was 42% chlorinated (Clophen A 30) did not develop a statistically significant increase in benign or malignant liver tumors.

It was established by this review that not all PCB formulations are probable human carcinogens and that different PCB mixtures do not have the same quantitative potency to cause cancer.

In its previous derivation of a cancer potency factor (CPF) for PCBs, the EPA[104] considered the results of the three positive rat studies of PCB mixtures with 60% chlorination[124–126] but used only the female rat data from Norback and Weltman[126] to calculate the CPF of 7.7 (mg/kg/d). The CPF is also influenced by the way the dose given to the laboratory animals is extrapolated to humans. To extrapolate from rats to humans, body weight scaling to the two thirds power was used by the EPA

but not by other federal agencies with a scaling factor of 5.85. The EPA based their scaling factor on the assumption that body surface is a better predictor for interspecies variations than body weight. Recently, the EPA, the FDA, and the Consumer Products Safety Commission (CPSC) reached a consensus on a method for cross-species scaling and proposed it as a uniform compromise policy position. Using the approach proposed by these agencies, scaling would be performed on the basis of body weight raised to the three fourths power. This correlates to a scaling factor of 3.76 when using the rat and human body weights of 450 g and 70 kg, respectively. Use of the new scaling factor would reduce prior EPA estimates of CPFs by approximately 35%.

Furthermore, the reassessed data underscore major differences in carcinogenic potential based on the degree of chlorination of the PCB mixture. Studies of PCB mixtures with 60% chlorination consistently result in a high incidence of rat liver tumors. Rats fed mixtures with 54 or 42% chlorination did not develop a statistically significant increase in liver tumors.

Comparison of the results of studies with Aroclor 1260[124-126] showed a striking similarity in the nature of the tumor response even though three different strains of rats were used. The carcinogenic potential of 54% chlorinated PCB mixtures has also been tested in rats by Ito et al.[127] and in two mouse studies.[128,129] These studies were deemed inadequate to assess the carcinogenic potency of PCBs due to their short duration, limited number of animals, and the absence of information on the animals' health.[104]

Other studies of 48 or 42% chlorinated PCB mixtures have not demonstrated a carcinogenic effect.[127,130] Kimura and Baba[130] conducted a study of the carcinogenicity of Kanechlor 400, a commercial PCB mixture containing 48% chlorine. The authors observed changes in the liver, including benign neoplasms, but they were not statistically significantly elevated. This study did not show that Kanechlor 400 was carcinogenic in the rat.

In conclusion, based on the available data, 60% chlorinated PCB mixtures are carcinogenic in rats producing hepatocellular tumors. At similar dosage levels lower chlorinated PCBs do not appear to be carcinogenic in presently available studies. However, more comprehensive studies with lower chlorinated mixtures are needed to confirm these observations because the general population as well as the workers proportionally received more exposure to the lower chlorinated mixtures.

IX. TOXICITY EQUIVALENCY FACTORS (TEFs)

The concept of toxicity equivalency factors (TEFs) to estimate the relative toxicity of structurally similar compounds evolved during the 1980s.[131,132] The TEF approach provided a relatively straightforward and simplistic method of evaluating complex mixtures. The TEF approach was first developed to assess the risks associated with air emissions of polychlorinated dibenzodioxins (PCDDs) and PCDFs formed during high-temperature incineration of industrial and municipal waste.[131,133] Subsequently, the EPA[132] proposed interim guidelines for estimating risks associated with mixtures of PCDDs and PCDFs for other media as well.

The TEF values are based on an estimate of relative toxicity of PCDDs and PCDFs using 2,3,7,8-TCDD as a reference. With the exception of 2,3,7,8-TCDD and hexachlorinated dibenzodioxins all TEFs for chronic toxicity and carcinogenic potential of PCDDs and PCDFs are estimated from results of short-term *in vivo* and *in vitro* tests. For most PCDDs and PCDFs, chronic toxicity studies have not been conducted. For each congener, one or more of the following endpoints were used to derive TEFs: enzyme induction, thymic atrophy, body weight gain, potential bioaccumulation, teratogenicity, immunotoxicity, and lethality.[132]

The TEF approach as implemented now has many uncertainties and has been questioned on scientific grounds. Neubert et al.[134] outlined a number of prerequisites that would have to be fulfilled in order to improve the TEF approach:

1. The actions of the congeners must be strictly additive in the dose range to be evaluated.
2. The dose response curves for the various congeners must run parallel.
3. The organotropic manifestations of all congeners must be identical, also over the relevant dose ranges.

4. Dose response curves for various toxicological endpoints for a given congener must run parallel.
5. For extrapolations between species, the kinetics must be identical, or differences have to be taken into consideration.
6. With respect to risk assessment in humans, toxic or biological manifestations in the lower dose ranges are of special interest, and LD_{50} values and effects induced in laboratory animals by highly toxic doses are of minor importance.

These prerequisites have either not been met for the PCDDs and PCDFs or the information is not available. Nonetheless, in the U.S. and in other countries some risk assessors have now proposed to assess the combined potential toxicity using the TEF approach of 2,3,7,8-TCDD, PCDDs, PCDFs, and co-planar PCB congeners. In 1990, at an EPA Workshop on PCBs, it was decided not to adopt such a scheme for PCBs because of large data gaps.[135,136] Research data collected since the 1990 Workshop indicate that calculated equivalency values for some PCB congeners are inaccurate by better than two orders of magnitude or incorrectly predict toxic endpoints.[137,138]

X. CONCLUSIONS: THE HUMAN RISK

In a pilot study of four female cynomolgus monkeys (*Macaca fascicularis*) and four female rhesus monkeys (*M. mulatta*) receiving daily oral doses of 0.280 mg/kg Aroclor 1254, the monkeys developed chloracne-like lesions, edema of the eyelids, eye exudate, conjunctivitis, dry and necrotic nail beds, and loss of nails.[139] In addition, the rhesus monkeys had gingival hyperplasia and the cynomolgus monkeys had mammary gland exudate. Adult female rhesus monkeys on oral doses of 0.080 mg/kg body weight for 37 months developed chloracne-like lesions or a reduction of sebaceous glands[107] (Dr. Douglas L. Arnold, personal communication). In the monkeys given oral doses of 0.080 mg/kg body weight and in monkeys on even lower doses, weight reduction was noted. These clinical signs would be easily recognizable had they occurred in the hundreds of workers that have been studied and in the thousands of workers that made capacitors. However, they have not been reported.

In the offspring of monkeys receiving oral doses of 0.005 mg/kg body weight and at adipose tissue levels around 5 ppm (mg/kg) and serum levels around 10 ppb (μg/l) (Tables 3a and 3b), facial pigmentation, enlargement of Meibomian glands, discolored and hyperkeratotic finger nails have been observed in offspring[107] (Dr. D. L. Arnold, personal communication). These tissue levels are within the range of levels found in the general population, particularly before PCBs were phased out. Such changes would be easily recognizable in human infants, but they have not been described in infants in the U.S. Many of the women working in capacitor plants with much higher tissue levels had children, but none of these clinical signs were reported in the offspring by local hospitals or factory physicians. The studies of children exposed to low levels of environmental PCBs and other persistent chemicals also did not reveal such clinical signs. However, humans are capable of producing such lesions. They were described by Japanese and Taiwanese physicians initially unfamiliar with this syndrome in conjunction with the Yusho and Yu-Cheng poisoning outbreaks caused mainly by PCDFs.

In humans, for the most part, the doses received can only be estimated, while more precise information is available for PCB-fed laboratory animals. However, PCB serum and adipose tissue levels have been determined in the general population, in groups of workers, and some experimental animals. Comparing tissue levels across species (Tables 3a and 3b) and correlating them to adverse effects and the cumulative dose may be helpful when extrapolating across species. Tissue levels could also be used to estimate daily PCB intake if the length of exposure and the amount excreted were known. For example, in rats dietary levels of 100 ppm (approximately 5 mg/kg body weight/d) of Aroclor 1242 or 1016 for 6 months resulted in PCB adipose tissue levels of about 200 ppm (mg/kg).[140] Subhuman primates developed similar body burdens at five daily doses per week for 37 months of 0.08 mg/kg Aroclor 1254, a more persistent PCB mixture. Adipose tissue levels of about 1200 mg/kg fat were present in rats receiving

TABLE 3a
Examples of Recent PCB Levels in Tissues (mg/kg) and in Blood (μg/l) in Humans and Adverse Effects

Humans (N)	Aroclor	Air levels range mean (μg/m³)	Time exposed	Serum	Adipose tissue	Adverse effect	Ref.
Workers (221)	1242 1016	ND–264	Years	HPCB 1–250; LPCB 2–3330		No convincing effects reported (see text)	34, 41
Workers (39)	1254	0.4–82	Years	LPCB 1–59; HPCB 1–24		No convincing effects (see text)	34, 41
Workers (196)[38,140] (51)[69] (200)[70]	1016 1242 1254	200–2000 690	17 Years	57–2207 393[a]	101[b]	No convincing effects (see text); clinically insignificant decrease in birth weight	38, 142, 69, 70
Workers (80)	Pyralene 3010; Apirolio	48–275 (2–27 μg/cm² Skin)	Years	41–1319; 337 current; 292 former		Chloracne in 4 workers, most likely exposure to chlorinated dibenzofuran as well	39
Humans general pop		0.0006 μg/kg diet		ND–8	≈1.0	No convincing effects reported (see text)	9

Note: Analytical methods and quantitation differ. PCB levels may be higher or lower than reported.[142] Partition value between serum and adipose tissue is about 160.[33] The concentration in adipose tissue in workers would be between 6 and 235 ppm.

[a] Composed of 363 ppb lower PCBs (eluting before DDE) and 30 ppb higher PCBs.
[b] Serum lipid PCB, presumably equal to adipose tissue PCB on a fat basis.

a total dose of 4500 mg/kg over a 6-month period, while monkeys receiving a total dose of 65 mg/kg body weight over a 37-month period (5 d/week) had tissue levels of about 109 mg/kg fat. The total dose given to the monkeys was 69 times less than the dose given to the rat, while the adipose tissue levels in the rat were only 10 times higher. Dosing in the rats occurred over a longer period of the rat's lifespan than in monkeys and they had also been held for an additional 4 months without being given PCB before the concentrations in adipose tissue were determined. During that time some depletion of PCB tissue levels occurred. Better data are needed to determine whether retention of PCBs, particularly the more biologically active congeners in subhuman primates, is more pronounced than in other species. Hayes,[141] for instance, showed that for DDT, another lipophilic compound at dosage levels in the microgram range, rhesus monkeys stored proportionally more DDT in their adipose tissue than humans.

At low doses of PCBs, the onset of toxicity occurs slowly in experimental animals, suggesting that the total cumulative dose may be impor-

TABLE 3b
Mean or Average PCB Levels in Tissues (mg/kg) and in Blood (ng/ml) in Different Species and Adverse Effects

Species	Aroclor	Daily dose (mg/kg)	Months dosed	Serum	Adipose tissue	Adverse effect	Ref.
Rats	1016	5	10	334	188	Enlarged liver cells	140
	1242	5	10	172	133	Enlarged liver cells	140
	1254	25	6 (+4 recovery)		1192	Liver pathology	146
Rats	Clophen A-50	2	1.5		46	Liver necrosis cholesterol ↑ at 2 mg/kg. Serum bilirubin ↑, serum protein ↑, ALT ↑, and AST ↑ at 50 mg/kg	147
		10			277		
		50			≈2000		
		250			5114		
Rhesus monkeys infants	1248	Transplacental and milk	Mothers dosed		Skin 86–136	Facial edema, acne, hyperpigmentation	148
Rhesus monkeys	1254	0.005	37	10	5	Reduced number term infants, still-births, discoloration of nail beds, facial pigmentation	149, 107
		0.020		30	24		
		0.040		80	52		
		0.80		130	109		
Mink	Clophen A-50; 1254	≈2.0	3		180	Reproductive failure	149
		≈1.5	3		70		

Note: Analytical methods and quantitation differ. Actual PCB levels may be higher or lower than reported.[142]

tant. However, at very low doses, such as 0.006 µg/kg/d, that the general population received during the 1980s, a toxic dose would never be reached in a lifetime. In this case the total lifetime cumulative dose would be 0.153 mg/kg body weight, while capacitor workers received a cumulative dose during a 200-d work period of 14.4 mg/kg body weight without showing ill effects.

The relationship between the acute and the chronic toxic dose of a given chemical has been termed the chronicity factor or chronicity index. For some chemicals, the degree of accumulation, metabolism, and excretion determines these doses. For other chemicals, the type of toxicity the chemicals produce and the ease or inability of the exposed to compensate or repair these perturbations affects this relationship. This concept is discussed in detail by Hayes.[141] It appears that for PCBs the cumulative dose is more important than the daily dose unless very large doses (e.g., g/kg doses for rats) are given. The cumulative dose is associated with the accumulation of the PCBs in tissues.

In subhuman primates adverse effects are still reported at adipose tissue concentrations of about 5 ppm (5 mg/kg), which were achieved at daily doses of 0.005 µg/kg body weight. Human workers, at levels up to about 400 ppb (µg/l) serum and up to about 100 ppm (mg/kg) adipose tissue on a wet-weight basis, have not suffered from impaired health as a result of their exposure. Based on air levels and assumptions about dermal absorption, workers with these tissue levels could have received daily doses between 70 and 140 µg/kg/d for months to years.

The PCB tissue levels in these various studies were determined in different laboratories and, therefore, only rough comparisons can be made. To improve these data, all specimens would have to be analyzed in the same laboratory under strict quality control.[142] Despite the shortcomings of the avail-

able data, humans appear to be less sensitive to PCBs than subhuman primates and no more sensitive to the toxic effects of PCBs than other less-sensitive laboratory animals. However, the data are insufficient to make detailed comparisons.

Workers with high PCB exposures have shown some elevation of liver function tests, particularly the GGT. The finding of an induction of hepatic microsomal monooxygenases in some workers from a capacitor plant suggested that drug metabolism and metabolism of xenobiotics was induced in humans at high PCB exposure. This induction would explain at least in part the shorter half-life of PCBs in highly exposed worker populations. However, GGT may also be elevated in alcoholic liver disease, following exposure to a number of therapeutic drugs and drugs of abuse, and may represent an incidental finding in some workers and in the general population.

In the U.S., in PCB exposed workers or in the adult general population, the combination of hyperpigmentation, chloracne, and discolored nails has never been observed. However, they were reported by the Japanese and the Taiwanese that developed Yusho or Yu-Cheng following exposure to PCDFs.[8] Similarly, they have been identified in adult subhuman primates following the administration of PCBs. These alterations of the skin and nails were very obvious even to the uninitiated and would not have been missed by health professionals or the workers themselves. Thus, there appeared to be a difference in response to PCBs between subhuman primates and humans. On a quantitative basis, adult subhuman primates were either more sensitive to the toxic effects of PCBs or they preferentially retained the more toxic PCB congeners, while humans were able to excrete them more efficiently. Such differences in metabolism and excretion of specific congeners and differences in enzyme induction have been demonstrated with PCBs for several species.[58,143,144]

Toxicity in different species may be modulated by species-specific differences in lipid metabolism, quantitative differences in binding of PCBs to receptors in target organs, enzyme induction, or other differences in the toxicokinetics of PCBs. Proportionally, humans may also be able to sequester more PCBs into adipose tissue away from vital organs and from skin. Instead of only extrapolating from laboratory animals the evaluation of the toxicity of PCBs should rely more on the available human data.

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