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Mortality and Industrial Hygiene Study of Workers Exposed to Polychlorinated Biphenyls

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ABSTRACT. Because of the demonstrated toxic effects on animals resulting from exposure to polychlorinated biphenyls (PCBs), the National Institute for Occupational Safety and Health conducted a retrospective cohort mortality study of 2,567 workers in two plants where PCBs were used in the manufacture of electrical capacitors. All workers included in the study were employed for at least 3 months in areas of the plants where PCBs were used. The vital status of 98% of the two cohorts was determined, and 38,018 person-years were accumulated. All-cause mortality was lower than expected (163 obs. vs 182.4 exp.) as well as all cancer mortality (39 obs. vs 43.8 exp.). Excess mortality was noted for rectal cancer (4 obs. vs 1.19 exp.) and liver cancer (3 obs. vs 1.07 exp.), although neither excess was statistically significant. In one of the plants the observed mortality due to cirrhosis of the liver was also elevated. The results of detailed industrial hygiene surveys conducted in each plant are also presented.

POLYCHLORINATED BIPHENYLS (PCBs) are a class of compounds composed of biphenyl molecules with a varying number of substituted chlorine atoms. In commercially prepared PCB mixtures, the weight-percent of chlorine has varied from 21 to 68%. In some preparations, there has also been some degree of contamination by chlorodibenzofurans.[1]

The primary use of PCBs has been as a liquid insulating material in electrical capacitors and transformers, therefore, the greatest potential for occupational exposure has been in the manufacture and repair of these components. Polychlorinated biphenyls have also been used in heat exchange units, hydraulic systems, vacuum pumps, gas transmission turbines, plasticizers, adhesives, pesticide extenders, paints, and carbonless copying papers.

Since 1971, PCBs were sold in the United States only for use in closed systems. According to the Toxic Substances Control Act of 1976, rules and regulations were promulgated to limit the manufacture and use of PCBs. This Act stipulated that all U.S. production of PCBs end January 1, 1979, and that all U.S. sale and distribution of PCBs end July 1, 1979. However, continual exposure to PCBs will occur among workers who maintain transformers and capacitors, and among the general population via contaminated food.

During the past few years, interest in the health effects among individuals exposed to PCBs has been stimulated by: (a) the tendency for PCBs to accumulate in tissues and certain organs;[2,3] (b) the stability of PCBs and their persistence in the environment;[4,5] and (c) the demonstrated long-term toxic effects, including liver tumors and other liver diseases, in exposed laboratory animals.[6-10] Much of this interest was expressed at the National Conference on Polychlorinated Biphenyls in November, 1975,[10] and the toxicity of PCBs has been extensively reviewed in the NIOSH Criteria Document on PCBs.[11] In comparison to

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the accumulated information on acute toxic effects in humans and adverse effects in animals, little is known about the chronic effects from long-term exposure in man.

To determine whether past occupational exposure to commercially produced PCBs has caused any long-term health effects, NIOSH initiated an epidemiologic study among workers in two capacitor manufacturing plants. In conjunction with this study, detailed industrial hygiene surveys were also conducted by NIOSH to document the levels of exposure to PCBs and other chemicals.

Description of Facilities

Both of the plants chosen for study manufacture electrical capacitors and were selected because: (a) each had a large work force; (b) PCBs had been used for more than 30 yr; (c) there was considerable potential for exposure to PCBs with little potential for exposure to other known toxic contaminants; and (d) the records necessary to identify individuals to be included in the study population were readily available. At the time the study was initiated, both plants were still using PCBs. Plant 1 is located in New York State and is divided into two manufacturing facilities within close proximity. One facility that has used PCBs since 1946 produced small industrial capacitors and the other facility has produced large PCB-filled power capacitors since 1951. The type of PCBs used has varied during the years from "Aroclor" (Monsanto trade name) 1254 (54% chlorine) to 1242 (42% chlorine) to 1016 (41% chlorine). In addition, several other kinds of oils were used, but in a limited number of capacitors.

Plant 2, located in Massachusetts, began to use PCBs to manufacture capacitors in 1938. This plant also changed the type of PCBs used from "Aroclor" 1254 to 1242 to 1016. Until 1972, other types of capacitors which did not contain PCBs were made at this plant. Castor oil was used in lieu of PCBs to produce the large power capacitors at this plant.

Both plants assembled small and large type capacitors using the same general techniques. The following briefly describes the assembly process.

Winding and pre-assembly. The inner components of the capacitor were made of paper, foil, and sometimes plastic film; wound together; and subsequently loaded into metal casings. This job was done in an enclosed dust-free room where there was minimal exposure to PCBs. Therefore, the workers in these jobs were not considered "exposed" when choosing the study cohort.

Impregnation. The pre-assembled capacitors were filled or impregnated with the PCBs. Within this area there was potential for exposure to PCBs, and therefore, those employed in this area were considered "exposed" when choosing the study cohort.

Final assembly. The tops of the capacitors were closed by crimping, rubber stoppers, or soldering, which involved some exposure to PCBs. The capacitors were washed to remove excess PCBs by running them through a detergent wash or a degreaser such as trichloroethylene. Finally, they were sent through the final operations involving drying, testing, and painting. Those employed in several of these jobs were considered "exposed" when choosing the study cohort.

Other areas where there was potential exposure to PCBs in the plants included the laboratory and the area where rejected capacitors were rebuilt. Approximately 10% of the two work forces were employed in areas where there had been potential exposure to PCBs. Those employed in these jobs were considered "PCB exposed" for purposes of choosing the study cohorts.

Historically, the work force at Plant 1 has been composed of approximately 50% white males and 50% white females. Plant 2 has had a less homogeneous work force, with two-thirds being female, and reflects the general ethnic make-up of the area, which is largely Cape Verdean and Portuguese.

METHODS

Mortality study. A retrospective cohort mortality study was conducted to determine whether individuals occupationally exposed to PCBs have experienced any increase in cause-specific mortality. The study cohorts were defined as all workers who accumulated at least 3 months of employment at any time in areas of the plants where there was a potential for exposure to PCBs. These "exposure jobs" were designated by the companies and verified by the labor unions (at Plant 1), and by the NIOSH industrial hygiene surveys to represent the high-exposure jobs. Trichloroethylene (TCE) was used as a degreaser in both plants. Therefore, if the work history records indicated that an employee had potential exposure to TCE, the individual was not included in the cohort. This included very few workers.

An effort was made to determine the vital status (living or deceased) of each individual in the cohorts as of January 1, 1976. Vital status was determined through records maintained by Federal and State agencies, including the Social Security Administration, state motor vehicle registration, and state vital statistics offices. For those individuals who could not be located through these sources, U.S. Postal Mail Correction Services and other follow-up searches were used. For all those known to be deceased, death certificates were requested and causes of death were interpreted by a qualified nosologist according to the International Classification of Diseases (ICDA) in effect at the time of death, and then converted to the 7th Revision of the ICDA. Those who had an unknown vital status were assumed to be alive as of January 1, 1976, therefore the true risk of mortality was not overestimated. Those who died after January 1, 1976, were considered to be alive for purposes of analysis.

Person-years were accumulated for each worker starting after 1940 when 3 months of employment in exposed jobs were completed, and ending at the date of death or the study end date (1/1/76)—whichever occurred first. Using a modified life table computer program similar to that described by Cutler,[16] the person-years for each cohort were combined into 5-yr calendar time periods and 5-yr age groups and multiplied by the corresponding U.S. white male (for male cohort members) and U.S. white female (for female cohort members) cause-specific mortality rates to yield the expected number of deaths. Person-years were additionally distributed by 5-yr exposure and 5-yr latency (number of years from date first employed in exposed

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Table 1.—Vital Status of PCB Workers

	Plant 1			Plant 2			
	Males	Females	Total	Males	Females	Total	Grand Total
Known to be alive	520	360	880	633	836	1,469	2,349
Known to be deceased	55	18	73	28	62	88	163
Unknown vital status	8	7	15	14	26	40	55 (2%)
Total	583	385	968	675	924	1,599	2,567
Person-years	7,825	5,185	13,010	9,229	16,779	26,008	39,018

jobs) categories. Observed and expected cause-specific deaths were compared and differences were tested using the Poisson distribution.

Industrial hygiene survey. The detailed industrial hygiene surveys included personal time-weighted air samples from selected job titles, as well as area air samples. In both plants, samples were taken for PCBs (Aroclor 1016), trichloroethylene, lead, tin, and zinc. In addition, samples for toluene, methyl isobutyl ketone (MIBK), aluminum, and iron were taken at Plant 1. These surveys were designed to characterize the exposures occurring at the time of the survey and may not represent exposures of previous years, especially those of Plant 1 where exposures may have been reduced because of new production techniques recently initiated.

RESULTS

Mortality study. A total of 2,567 workers met the definition of the study cohort. Table 1 gives a breakdown of the vital status ascertainment and the number of person-years within each sub-cohort. The vital status ascertainment is 98% complete.

The possibility that records might be missing from the personnel files used to assemble the Plant 1 cohort was cited at the beginning of the study. In an effort to determine whether eligible workers were missing from the Plant 1 cohort, a validity check was conducted by the New York State Department of Health[16] using methodology similar to that described by Marsh et al.[17] Social Security Administration (SSA) quarterly earning statements (SSA form 941) from 1945-1965 were obtained and compared to the names appearing on the microfilmed personnel records that were used to assemble the cohort. The results of this comparison yielded 35 additional workers (3.5% of cohort) not included in the Plant 1 study cohort. This small portion of the population at risk that is missing from the study cohort should not seriously bias the results. A similar validity check was not done at Plant 2, as it appeared from our inspection that the personnel file system had been maintained intact.

Table 2 shows the distribution of the cohorts by duration of employment in jobs where PCB exposure occurred. The distribution within the two plants is somewhat similar, with the exception of the female workers in Plant 2, where

Table 2.—Duration of Employment among Cohort Members in PCB Exposure Jobs

Plant 1	Males		Females		Total	
	N	(RF)*	N	(RF)	N	(RF)
3-6 mo	137	(23.3)	79	(20.5)	216	(22.3)
6 mo-1 yr	88	(15.1)	59	(15.3)	147	(15.2)
1-2 yr	99	(16.9)	92	(23.9)	185	(19.1)
2-3 yr	53	(9.1)	41	(10.6)	94	(9.7)
3-10 yr	168	(28.3)	82	(21.3)	247	(25.5)
10 yr	47	(8.1)	32	(8.3)	79	(8.2)
Total	583		385		968	
Plant 2	**Males**		**Females**		**Total**	
	N	(RF)	N	(RF)	N	(RF)
3-6 mo	211	(31.3)	207	(22.4)	418	(26.1)
6 mo-1 yr	127	(18.8)	161	(17.4)	288	(18.0)
1-2 yr	118	(17.5)	175	(18.9)	293	(18.3)
2-3 yr	64	(9.5)	82	(8.9)	146	(9.1)
3-10 yr	123	(18.2)	188	(20.3)	311	(19.4)
10 yr	32	(4.7)	111	(12.0)	143	(8.9)
Total	675		924		1599	

*RF = Relative frequency.

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Table 3.—Observed and Expected Deaths (O/E) According to Major Causes among PCB Workers

Cause of Death (7th Revision ICD No.)	Plant 1		Plant 2				
	Males	Females	Males	Females	Total	(SMR)	95% Confidence Interval
All malignant neoplasms (140-205)	9/ 9.70	4/ 7.26	3/ 6.83	23/ 20.00	39/ 43.79	(89)	(63 - 123)
Nervous system (330-334, 340)	3/ 3.14	1/ 1.97	2/ 1.84	5/ 3.00	11/ 12.55	(88)	(44 - 157)
Circulatory system (400-468)	24/ 23.51	7/ 6.83	14/ 14.15	13/ 19.64	68/ 63.93	(99)	(73 - 123)
Accidents (800-962)	7/ 6.66	1/ 1.17	3/ 7.43	3/ 3.67	13/ 18.39	(71)	(38 - 122)
All other causes	10/ 12.80	5/ 5.54	6/ 10.36	19/ 16.19	40/ 44.79	(89)	(64 - 122)
All causes	39/ 53.97	18/ 23.77	28/ 49.51	63/ 69.10	163/ 182.35	(89)	(76 - 104)

more employees had worked for 10 or more yr, and in male workers where there was a high frequency of short-term (3-6 months) employees.

When the two cohorts are examined by year first employed in jobs where PCB exposure occurred, the females in Plant 2 are seen to have had an earlier initial date of exposure. In Plant 1, 49.4% of the males and 45.1% of the females were first employed in PCB exposure jobs before 1955. In Plant 2, 49.3% of the males and 69.6% of the females were first employed in PCB exposure jobs before 1955.

Tables 3 and 4 summarize the number of deaths observed (obs.) from the study cohorts and the number of deaths expected (exp.). The all-cause mortality is lower than expected in each cohort, with an SMR [Standardized Mortality Ratio (SMR = observed deaths/expected deaths X 100)] of 95 (73 obs. vs 76.7 exp.) for Plant 1 and an SMR of 85 (90 obs. vs 105.6 exp.) for Plant 2. These SMRs may be influenced by the "healthy worker effect."[10] There is no increase in observed mortality among the total cohort for any of the major causes of death listed in Table 3.

Table 4 lists the observed and expected number of deaths by specific cancer cause and for cirrhosis of the liver. When both cohorts are combined, the observed number of deaths is more than that expected for cancer of the rectum (4 obs. vs 1.19 exp.) and liver cancer—ICDA = 155, 156A (3 obs. vs 1.97 exp.). The only statistically significant difference ($P < .05$) in observed versus expected deaths occurred in females from Plant 2 for cancer of the rectum (3 obs. vs 0.50 exp., $P < .05$). For both cohorts combined, there are 6 deaths due to cirrhosis of the liver, while 5.66 were expected. Five of these cases are from the Plant 2 cohort, while 3.2 were expected. According to hospital reports, at least 3 of the 6 persons who died of cirrhosis of the liver were known to have consumed alcohol regularly.

The relationship between latency and the mortality from all cancer, cancer of the rectum, liver cancer, and cirrhosis of the liver is shown in Table 5. For "all cancer" there is no apparent pattern in either cohort. For cancer of the rectum, there is a slight increase with an increase in the latency periods. All of the deaths due to liver cancer occur before 20 yr of latency and there is no trend of increasing risk with an increase in the latency period. The risk of mortality due to cirrhosis of the liver does not show a consistent increase with an increase in the latency periods; there is however, a greater risk after a 20-yr period.

The relationship between these same causes of death and length of employment in PCB exposure areas of the plants is given in Table 6. As indicated in the Table, there is no increase in mortality with increasing lengths of exposure, except for cirrhosis of the liver; however, the numbers in this comparison are small.

Industrial hygiene survey. The industrial hygiene survey results of area and personal sampling for PCBs (Aroclor 1016) are summarized in Tables 7 and 8. Because of differences in the production processes, the results by specific jobs or work areas are not comparable between the two plants. However, relative comparisons can be made, and the range of concentrations observed in Plant 1 are lower than those in Plant 2. In Plant 1, the time-weighted average (TWA) personal air samples ranged from 24 $\mu g/m^3$ to 393 $\mu g/m^3$, and the TWA area air samples ranged from 3 $\mu g/m^3$ to 476 $\mu g/m^3$. The TWA personal air samples in Plant 2 ranged from 170 $\mu g/m^3$ to 1260 $\mu g/m^3$, and the TWA area air samples ranged from 50 $\mu g/m^3$ to 810 $\mu g/m^3$.

Trichloroethylene was measured near the degreasers in both plants. Of 11 area air samples from Plant 1, all were less than 35 ppm, except for two which measured 195 ppm and 321 ppm. At Plant 2, three area air samples were taken which ranged from 53.4 ppm to 77.5 ppm.

Area air samples were measured for tin, lead, and zinc near the soldering operations. There were no detectable levels for tin at either plant. Of four samples collected for lead and zinc at Plant 1, lead was detected in one sample at a level of 12 $\mu g/m^3$, and zinc was detected on two samples at levels of 8 and 24 $\mu g/m^3$. At Plant 2, 15 samples were collected for lead and zinc; all but one (41.2 $\mu g/m^3$) of these samples showed no detectable levels for lead. Six of the 15 samples revealed concentrations of zinc ranging from 2.3 to 94.1 $\mu g/m^3$.

Both personal and area samples were taken in the area

Table 4.—Observed and Expected Deaths (O/E) According to Specific Cancer Causes and Cirrhosis of the Liver among PCB Workers

Cause of Death (7th Revision ICD No.)	Plant 1		Plant 2				95% Confidence Interval
	Males	Females	Males	Females	Total	(SMR)	
All malignant neoplasms (140-205)	9/ 9.70	4/ 7.26	3/ 6.83	23/ 20.60	39/ 43.79	(89)	(63 - 122)
Stomach (151)	0/ 0.51	0/ 0.22	1/ 0.31	0/ 0.62	1/ 1.66	(60)	
Intestine exp. rectum (153, 153)	1/ 0.82	0/ 0.70	0/ 0.54	3/ 1.97	4/ 4.03	(99)	(27 - 254)
Rectum (154)	1/ 0.31	0/ 0.16	0/ 0.20	3/ 0.58*	4/ 1.19	(336)	(92 - 860)
Biliary pas liver Liver not specified (155, 156A)	1/ 0.23	0/ 0.18	0/ 0.15	2/ 0.51	3/ 1.07	(280)	(58 - 820)
Pancreas (157)	0/ 0.53	1/ 0.27	0/ 0.35	0/ 0.75	1/ 1.90	(53)	
Respiratory system (160-164)	5/ 3.22	1/ 0.71	0/ 2.22	1/ 1.83	7/ 7.98	(88)	(35 - 181)
Breast (170)	.....	1/ 1.06	.....	6/ 4.56	7/ 6.84	(102)	(41 - 211)
Lymphatic and hematopoietic (200-209)	0/ 1.10	0/ 0.39	0/ 0.94	2/ 1.71	2/ 4.34	(46)	
Other	1/ 2.98	1/ 2.55	2/ 2.12	6/ 7.13	10/ 14.78	(68)	(33 - 124)
Cirrhosis of liver (581)	1/ 1.09	0/ 0.73	2/ 1.26	3/ 1.92	6/ 5.00	(107)	(39 - 233)

*$p < .05$

Table 5.—Observed and Expected Deaths According to Latency* among Male and Female PCB Workers

Latency (yr)	Plant 1 O†	Plant 1 E‡	Plant 1 SMR	Plant 2 O	Plant 2 E	Plant 2 SMR	Plants 1 & 2 O	Plants 1 & 2 E	Plants 1 & 2 SMR
I. All Cancers									
<10 yr	6	5.27	114	6	7.76	77	12	13.03	93
10-<20 yr	3	6.61	45	16	10.91	147	19	17.52	108
>20 yr	4	5.07	79	4	8.17	49	8	13.24	60
II. Cancer of Rectum (ICD = 154)									
<10 yr	0	0.15	...	0	0.21	...	0	0.36	...
10-<20 yr	0	0.19	...	2	0.29	690	2	0.48	417
>20 yr	1	0.15	667	1	0.21	476	2	0.36	556
III. Liver Cancer (ICD = 155, 156A)									
<10 yr	1	0.12	833	1	0.18	556	2	0.30	667
10-<20 yr	0	0.16	...	1	0.27	370	1	0.43	233
>20 yr	0	0.12	...	0	0.21	...	0	0.33	...
IV. Cirrhosis of Liver (ICD = 581)									
<10 yr	1	0.80	125	1	0.95	105	2	1.75	114
10-<20 yr	0	1.01	...	1	1.35	74	1	2.36	42
>20 yr	0	0.61	...	3	0.88	341	3	1.49	201

* Latency = number of years from date first employed in exposed job.
† O = observed deaths.
‡ E = expected deaths.

of welding operations for measuring aluminum and iron at Plant 1. The aluminum samples ranged from nondetectable to 233 μg/m³, and the iron samples ranged from 47 μg/m³ to 123 μg/m³.

Twelve personal samples were collected for toluene and MIBK during painting operations at Plant 1. Toluene concentrations ranged from 0.48 to 22 ppm and MIBK ranged from 2 to 5 ppm.

Although the exposures to PCBs at the dates of survey (Plant 1—April 1977, Plant 2—March 1977), were relatively higher in Plant 2, the historic levels of exposure may have been more equivalent. The exposures that occurred 20 to 30 yr ago are more relevant when considering the occupational cancer risk among the study cohorts. The PCB mixtures used during these time periods were Aroclor 1254 and 1242, whereas Aroclor 1016 was first used in 1971. In addition, several different stabilizers have been added to the PCBs (1% or less by weight) used at Plant 1 since the early 1960s. These include potential carcinogens such as diglyceride ether-diphenol-a and, more recently, vinyl cyclohexene dioxide. It is not known which stabilizers have been used at Plant 2.

DISCUSSION

There are few previous epidemiologic studies that have examined the long-term health effects on humans exposed to PCBs. Individuals poisoned by rice oil heavily contaminated with PCBs (Yusho Disease) have been studied extensively years after the incident took place in Japan in 1968.[19,20] However, the rice oil contaminant also contained polychlorinated dibenzofurans and other contaminants in higher concentrations than those found in commercially prepared PCBs. A high prevalence of skin and eye conditions were noted in the Yusho patients. In addition, there were clinical and laboratory findings that included changes in the microanatomy of liver cells and a decreased concentration of bilirubin in the serum of these individuals.[21,22]

Early reports regarding the health effects from occupational exposure to PCBs include chloracne,[23] digestive disturbances, eye irritation, liver injury, and impotence.[24-26] Most of these findings have been reported as case histories.

In a recent study of volunteers conducted by the Mount Sinai School of Medicine,[27] 326 workers who were em-

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Table 6.--Observed and Expected Deaths According to Length of Exposure among Male and Female PCB Workers

Length of Employment	Plant 1			Plant 2			Plants 1 + 2		
	O*	E†	SMR	O	E	SMR	O	E	SMR
I. All Cancers (ICD = 140-209)									
3 mo -5 yr	11	12.21	90	20	18.78	106	31	30.99	100
5-9 yr	1	2.95	34	2	4.10	49	3	7.05	43
10-14 yr	0	1.00	---	3	2.28	132	3	3.28	91
15-19 yr	1	0.69	145	1	1.04	96	2	1.73	116
≥ 20 yr	0	0.11	---	0	0.63	---	0	0.74	---
II. Cancer of Rectum (ICD = 154)									
3 mo -5 yr	1	0.35	286	1	0.48	208	2	0.83	241
5-9 yr	0	0.00	---	0	0.11	---	0	0.20	---
10-14 yr	0	0.03	---	2	0.06	3333‡	2	0.09	2222‡
15-19 yr	0	0.02	---	0	0.03	---	0	0.05	---
≥ 20 yr	0	0.001	---	0	0.02	---	0	0.02	---
III. Liver Cancer (ICD = 155, 156A)									
3 mo -5 yr	1	0.29	345	2	0.45	444	3	0.74	405
5-9 yr	0	0.06	---	0	0.11	---	0	0.19	---
10-14 yr	0	0.02	---	0	0.06	---	0	0.08	---
15-19 yr	0	0.02	---	0	0.02	---	0	0.04	---
≥ 20 yr	0	0.002	---	0	0.02	---	0	0.02	---
IV. Cirrhosis of the Liver (ICD = 581)									
3 mo -5 yr	1	1.79	56	2	2.26	88	3	4.05	74
5-9 yr	0	0.38	---	1	0.48	208	1	0.87	115
10-14 yr	0	0.13	---	1	0.24	414	1	0.36	278
15-19 yr	0	0.10	---	1	0.13	769	1	0.23	435
≥ 20 yr	0	0.02	---	0	0.08	---	0	0.10	---

*O = observed deaths.
†E = expected deaths.
‡$p < .01$

played at Plant 1 were examined. The most prevalent symptoms noted were dermatological and those of the central nervous system. There was a low prevalence of abnormal liver findings on physical examination. However, a subgroup exposed to PCBs were found to have liver enzyme changes different from those of a normal, non-exposed group. In addition, abnormal serum glutamic oxaloacetic transaminase (SGOT) levels were associated with plasma levels of PCBs. There was a relatively high prevalence of decreased lung capacity among a subgroup of 243 workers tested.[27]

In a preliminary report, Bahn[28] reported an increase in deaths due to malignant melanoma (2 obs. vs 0.04 exp.) and cancer of the pancreas among 31 research and development employees and 41 refinery plant employees at a New Jersey petrochemical facility. These individuals were exposed to Aroclor 1254 during various periods between 1949 and 1957, along with exposure to other toxic and potentially carcinogenic compounds.

In a summary of case histories among approximately 300 workers employed in the manufacturing of PCBs,[29] no malignant melanomas or pancreatic cancers were observed. However, among the death certificates of 50 former workers at this manufacturing facility, 7 cases of lung cancer were observed whereas 2.7 cases were expected. The findings were preliminary and were not adjusted for age or smoking.

These previously reported findings of an increased risk of mortality due to malignant melanoma, cancer of the pancreas, and lung cancer among workers exposed to PCBs are not corroborated in the present study. There are no observed deaths due to malignant melanoma and only 1 observed death from pancreatic cancer while 1.89 are expected. There are 7 observed deaths from respiratory

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system cancer, whereas 7.69 are expected. The only categories of cancer in which the number of observed deaths are greater than expected are for cancer of the rectum and cancer of the liver and only a slight increase for breast cancer. When both cohorts and sex groups are combined, none of the excesses are statistically significant at $P < .05$. However, the excess in liver cancer is noteworthy because it is consistent with the toxicology data observed in laboratory animals exposed to PCBs, where effects have been noted in the liver.[9-13] The slight increase in deaths due to cirrhosis of the liver in the Plant 2 cohort is also consistent with the notion that PCBs have a toxic effect on the liver.

In most occupational health studies where cancer mortality is being assessed, latency is an important variable; the hypothesis being that there is an increased risk of mortality once a certain time period has elapsed after initial exposure. In this study, this hypothesis is difficult to examine because of the small number of deaths. None of the causes of death analyzed according to latency clearly demonstrates this association. Rectal cancer shows a slight increase with an increase in latency, and cirrhosis of the liver shows an increase in risk with an increase in latency after 20 yr.

There is no relationship between increasing durations of employment in jobs involving PCB exposure and the risk of mortality due to cancer or cirrhosis of the liver.

When cancer mortality is examined by Plant, it is evident that most of the excesses occur in Plant 2—especially among the female group. This finding may be related to more exposures to PCBs at Plant 2, as indicated by the industrial hygiene results. In addition, there was an opportunity for earlier exposures at Plant 2, potentially allowing for a longer latency period. However, this difference in mortality may be a function of the size of the cohorts (Plant 1 only has half the number of person-years as Plant 2), and thus, simply be a statistical quirk.

Table 7.—Concentrations of PCBs (Aroclor 1016) at Plant 1 (April 1977)

	A. Power Capacitor Manufacturing Facility						
	Personal Air Samples				Area Air Samples		
Job Titles	No. of Samples	Total Sampling Time (min)	TWA* ($\mu g/m^3$)	Location	No. of Samples	Total Sampling Time (min)	TWA* ($\mu g/m^3$)
Recovery Repair	2	840	298	Test and Paint	2	840	41
Salvage Operator	1	426	155	Assembly	2	851	39
EMF operator	1	431	115	Shipping	1	436	16
Treat helper	2	867	80	Storage	1	427	14
Treat operator	2	731	66	Winding	1	420	3
Repair	1	422	50				
	B. Small Capacitor Manufacturing Facility						
Movoman (Sealing area)	2	680	393	Soldering	2	783	476
Movoman (Testing and soldering area)	3	1306	220	Assembly	2	827	115
Testing	3	1290	218	Shipping	2	838	56
Packer	3	1287	199	Winding	2	828	54
Treat operator	2	845	188	Can Manufacturing	2	836	51
Rework and final assembly	2	824	152	Cover Manufacturing	2	834	45
Maintenance	1	486	150				
Rework tester	1	433	140				
Rework packer	1	436	132				
Rework tester solder	1	271	24				

*TWA is calculated during the total sampling time period.

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Table 6.–Concentrations of PCBs (Aroclor 1016) at Plant 2 (March 1977)

	Personal Air Samples				Area Air Samples		
Job Title	No. of Samples	Total Sampling Time (min)	TWA* ($\mu g/m^3$)	Location	No. of Samples	Total Sampling Time (min)	TWA* ($\mu g/m^3$)
Degreaser	1	361	1,260	Impregnation	2	176	810
Solder	3	884	1,060	Pump room	3	1079	490
Tanker	9	2120	850	Testing	5	1424	320
Movoman (soldering area)	3	752	720	Pre-assembly	4	1213	140
Mist mask operator	3	872	630	Shipping	2	741	90
Tester	3	917	290	Winding	4	637	70
Pump Mechanic	1	377	280	Cover manufacturing	3	1089	60
Fiberman (pre-assembly)	6	1683	170	Office	2	741	50

*The TWA is calculated during the total sampling time period.

A potential confounding variable or interaction variable in this study is the possible effect of alcohol ingestion on the observed increase (at Plant 2) in mortality from cirrhosis of the liver. However, this cannot be properly assessed in the present study, since not enough is known about the ingestion of alcohol among the entire study cohort.

CONCLUSIONS

Because a relatively small number of deaths were observed, conclusions drawn from the results of this study are tentative.

All-cause mortality is lower than expected, and there was no increase in mortality for the major causes of death that were examined. Among the cancer causes, there was increased cancer of the liver and rectum. Cirrhosis of the liver was also elevated in one of the plants. The slight excesses for liver cancer and cirrhosis of the liver are consistent with previously reported findings on experimental animals exposed to PCBs, and suggest that there may be an association between these causes of death and occupational exposure to PCBs (i.e., Aroclor 1254 and 1242). However, the findings for liver cancer do not reflect a relationship with leukemy that has been observed for other carcinogens found in the workplace. The observed excess in cancer of the rectum related to PCB workers was unexpected and requires further investigation.

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Does business stress cause high blood pressure?



Stress on the job is a real problem for most of us. Many people think high-pressure jobs cause high blood pressure.

Scientists and doctors aren't sure if stress causes high blood pressure. But one thing is for sure: *anybody*, no matter how they react to stress, can have high blood pressure.

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use in their microprocessor products. The UNIX system is known for its "portability" which permits it to be used in the full range of computers from personal computers to mainframes. The agreement was interpreted in the trade press as a move by AT&T to have the system become standard in the industry.

Companies that adopt the UNIX system for their products pay licensing fees to AT&T. Perhaps more significant, Bell Labs and Western Electric have developed a broad range of software products based on the UNIX system that the company will be free to sell after divestiture.

AT&T has already made an aggressive move to capitalize on lightwave technology developed at Bell Labs and Western. The company, for example, is optimistic about its bid in the competition for the contract to lay the first Atlantic cable using fiber optics technology. Bell Labs also is regarded as having put the company in a strong position to exploit new developments in laser transmission of voice, data, and visual information via lightwave technology and is rumored to be nearing the commercial application of the technology to computers and memories.

AT&T is also regarded as capable of emerging full armed into the savagely competitive semiconductor industry. Western Electric is already among the dozen largest manufacturers of integrated circuits, although its products have been made only for internal consumption.

ITT's Cermak appears to express a view widely held in the industry with his appraisal that Western will be "a major force in semiconductors in a couple of areas. Their design capability is very good and they've invested a lot of money in tools," particularly for semiconductor applications in semicustom products. Such products are based on standard chips whose design can be varied to suit customer specifications.

Western will plunge into the vortex of semiconductor competition by vying for a share of the market for the 256K random access memory chip, the prospective big seller among integrated circuits. This will pit Western against the toughest Japanese and American competition. Western is already shipping 256K chips for its own products, but observers say that it will have to succeed in increasing production and lowering costs in its unionized factories in order to establish itself as a front runner.

Western is the developer of admired microprocessors used in its switching equipment and in fact is the source of many advances in computer science and design. Much speculation has centered on the question of what strategy AT&T will be following in venturing into the computer business. Company sources are noncommittal about the rumor that Western will produce a personal computer and make a bold challenge to IBM on its own ground.

For Bell Labs and its AT&T parent, divestiture obviously brings risks and opportunities. Bell Labs officers jest wryly that since they managed the chaos of reorganization they should be able to survive mere competition. The restructuring, in fact, is not yet complete. Appeals about some details are still pending. Furthermore, Bell Labs and AT&T will have to live with vestiges of regulation. To satisfy the antitrust lawyers' aversion of cross subsidies, for example, Bell Labs is required to deal at arms length in various ways with AT&T's marketing subsidiary. AT&T Information Services (ATTIS), so that competitors are not put at unfair advantage. And other difficulties could arise. The move to cost-based pricing has upset the system of subsidies designed to promote universal telephone service by keeping local telephone service inexpensive. The cost of local service will rise with divestiture and a backlash is already building in Congress. An attempt by Congress to revise the overall settlement is seen as highly possible. And despite divestiture, the shock of political intervention could still be transmitted along the network to Bell Labs.—JOHN WALSH

EPA, Utilities Grapple with PCB Problems

PCB's in transformers may be a thing of the past sooner than expected

The Environmental Protection Agency (EPA) and a few utility companies seem ready to accede to demands that steps be taken quickly to replace electrical equipment containing polychlorinated biphenyls or PCB's. This appears to be a reversal, at least on the part of EPA, of a long-standing view that PCB's in electrical equipment pose no significant health hazard. The utility companies, however, have responded as a result of recent PCB accidents and the lawsuits that followed.

In 1976, when Congress banned the manufacturing of PCB's, it presumably thought that problems with this pervasive and toxic chemical were for the most part solved. But a loophole in the law allowed the continued use of PCB's in electrical transformers and capacitors as insulation. A year ago, the utility industry successfully argued before EPA that transformers filled with PCB's should only be replaced as the equipment wore out. At this rate, transformers would be replaced in 20 years. The cost to proceed any faster would be prohibitive, the industry contended.

Now EPA is moving to close the loophole. Because accidents involving the release of PCB's are occurring much more frequently than previously believed, EPA is considering a costly proposal that would ban PCB transformers in public buildings. But in the past 6 months, two utility companies say they have decided to speed up the replacement program not because they believe there are serious health hazards linked with PCB's but because they say they are weary of trying to counter the public perception that PCB's are extremely toxic. Public concerns were heightened after transformer accidents in Binghamton, New York, and San Francisco resulted in the contamination of commercial buildings, costing millions of dollars to clean up.

Other companies are campaigning to calm public fears about PCB's. General Electric and Monsanto, for example, have been active in disseminating information claiming that the health effects of PCB's have been overblown. Although there is good evidence that PCB's are toxic at high dose levels, the companies maintain that the data on low-dose effects are far less clear cut.

Last May, the Pacific Gas and Electric Company decided to replace its large transformers shortly after one of them

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exploded and contaminated a high-rise office building in San Francisco. The episode, and the subsequent lawsuits, prompted the company to allocate $60 million over the next 5 years to replace about 1600 PCB transformers. "We got tired of hunting public perception," said company spokesman Tony Ladwell. Recently, the Florida Power and Light Company, which services half of Florida, took the same step and will spend $15 million over the next 5 years. Although it has not had a major PCB accident with its transformers, "we're getting ahead of the game before a problem occurs," said company spokeswoman Stacey Shaw, citing the accident in San Francisco and a similar one in Binghamton that occurred in 1982. "The public's concerns about PCB's have been severely exaggerated," she said.

The cause for concern can be largely attributed to the fact that PCB's are pervasive in the environment. According to EPA, there are 750 million pounds of PCB's either in storage or in use in the United States. In a national health study, EPA found that almost everyone has a detectable amount of PCB's in adipose tissue, although the number affected has dropped since Congress banned the production of PCB's in 1976. About 1 percent of the U.S. population in 1981 had more than 3 parts per million in their fatty tissue, a drop from 8 percent in 1977. The meaning of these low levels is not clear.

But many studies show that heavy PCB exposure is toxic, according to data presented at a recent meeting on PCB's held at the National Institute for Environmental Health Sciences at Research Triangle Park, North Carolina. PCB's are in a class of compounds related to dibenzodioxins and dibenzofurans. According to Ernest McConnell, chief of the chemical pathology branch at the National Institute of Environmental Health Sciences, PCB's rank third behind dioxins and furans when the most toxic isomer of each group is considered.

Although General Electric has stated that "the question of whether PCB's cause cancer in animals is unresolved," there is little, if any, doubt in the academic scientific community that PCB's are animal carcinogens at high dose levels. According to separate studies by Diane Norback, a pathologist at the University of Wisconsin Medical School, and Renate Kimbrough, a medical officer at the Centers for Disease Control, PCB's cause liver tumors in rats when the animals are fed a heavy dose of 100 parts per million over a period of 2 years.

In animal studies, large doses of PCB's are also known to cause a drop in body weight, enlarge the liver, damage kidneys, and change skin pigmentation. They cause reproductive disorders in minks and monkeys. According to one study, minks fed a diet of fish contaminated with PCB's showed a severe decrease in their reproductive rate. Monkeys exposed to PCB's became infertile. If, however, the monkeys were taken off the diet with PCB's, their fertility returned. It is not clear whether PCB's are mutagenic.

Several accidents with PCB's have provided some clinical data, but Kimbrough of CDC said at the institute meeting that "it is difficult to sort out the toxicity" because some of the accidents occurring in other countries may involve different mixtures of PCB isomers. Another problem is how to test for the presence of PCB's and how to best determine adverse health effects. The consensus seemed to be that fatty tissue provides the most sensitive sample for PCB's. Some scientists advocated serum samples, however, as a speedier and less invasive test. The drawback is that serum does not bind PCB's as much as adipose tissue.

Several studies do reveal some toxicity of PCB's. In 1968, about 1300 Japanese became ill after eating rice oil contaminated with PCB's that had leaked from a heat exchanger. With PCB concentrations exceeding 100 ppm, many developed chloracne, a disfiguring acnelike disorder. According to a literature search by Robert Miller, chief of the epidemiology branch of the National Cancer Institute, nine pregnant Japanese women who had eaten the rice oil gave birth to children with various abnormalities. Some of the babies showed dark pigmentation, which disappeared several months later. At least two children developed overgrown gums. The babies were also underweight. Kimbrough suggested that more extensive study of reproductive effects in humans is needed.

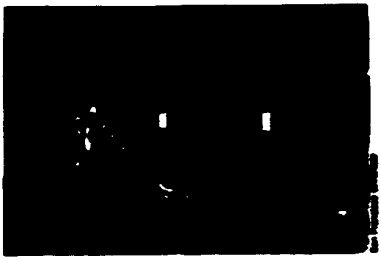
A number of Taiwanese were also poisoned in 1979 by rice oil that had been contaminated with PCB's. Shu-yung Tang, a physician and biochemist at National Taiwan University, reported that researchers in her group have correlated neurological damage with PCB exposure among the Taiwanese who consumed the oil. Other scientists also noted molecular changes in liver cells from patients who have been exposed to PCB's. It is unclear, they say, what these changes mean because the patients have not as yet shown any clinical symptoms of disease.

Arnold Schecter, professor of preventive medicine at the State University of New York at Binghamton who has been studying the firefighters and others involved in the accident there, suggests that PCB's in transformers may even be more hazardous than currently believed because furans are formed when PCB's are subjected to the intense heat of a fire. Soot taken from the contaminated state building contained from 270 to 1200 parts per million of dibenzofurans.

According to Martin Halper, chief of the exposure evaluation division at EPA, fires involving transformers and capacitors containing PCB's are much more common than once thought. "It's no longer a one in a million chance. It's much more prevalent." By contacting fire departments, for example, EPA has discovered that "there have been a couple hundred fires involving transformers. Now the whole picture has changed."

Halper estimates that there are 28,000 to 30,000 transformers with PCB's. Whether other utility companies will follow the lead of those in California and Florida is unclear, but Halper speculates that the majority "will have to be forced to replace the old equipment."

—Thaddeus Trzyna



Workers clean up after a PCB transformer fire in San Francisco last May. The accident prompted Pacific Gas and Electric to spend $60 million to replace all the companies large transformers with PCB's.

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CHAPTER 8

Immune alterations

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8.1. Introduction

Interest in the influence of chemicals on the immune system has increased markedly in recent years, as a growing number of compounds have been shown to alter immunocompetence. Most attention has been given to chemicals of environmental concern that decrease the immunological responsiveness or increase the susceptibility to infection or tumor cell challenge. This is particularly true for polychlorinated biphenyls (PCBs), polybrominated biphenyls (PBBs) and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). Much less information is present on the immunotoxicity of 2,3,7,8-tetrachlorodibenzofuran (TCDF), while no data are reported for halogenated terphenyls and naphthalenes.

After a short overview of the immune system, the immune effects as produced in different species and with different exposure regimens will be discussed, and an attempt will be made to provide some insight into the complex action of the various chemicals on immunocompetence.

Effects on weight and histology of lymphoid organs are discussed in Chapter 5.

8.2. The immune system

The immune response comprises all the phenomena that result from the interaction of cells of the immune system with antigen. A fundamental characteristic of specific immunity is the establishment of immunological memory: the first contact with the antigen (*e.g.* an infectious organism) imprints specific information. Upon a second contact with the same organism, a so-called secondary immune response will occur.

Kimbrough (ed.) Halogenated biphenyls, terphenyls, naphthalenes, dibenzodioxins and related products
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and macrophage activating factor (MAF), have profound effects on the macrophage functions. Killer cells are cytotoxic and have a key role in the rejection of tumor cells and transplants. As will be discussed later, T helper cells collaborate with B cells in antibody production against most antigens. Suppressor T cells function to suppress the activity of B cells (Taylor and Basten, 1976) or effector T cells (Atherton and Zembala, 1976). In addition, there are indications for the presence of B cells that suppress T cells (Turk et al., 1976). Suppressor and helper cells play a major role in the regulation of an immune response.

The bursa of Fabricius in birds or the bursa-equivalent in mammals (possibly gut associated lymphoid tissue or bone marrow) acts as a central lymphoid organ in which stem cells are induced to become (bursa-derived) B cells (Fig. 8.1). B cells circulate and temporarily reside in the thymus-independent areas of the spleen (follicles and peripheral regions of the white pulp) and lymph nodes (follicles and medulla). Upon antigenic stimulation, B cells specific for that particular antigen proliferate and develop into plasma cells that secrete antibody or serve as memory cells. The main immunoglobulin (Ig) classes are IgG, IgA and IgM. IgG is the most abundant antibody and is primarily synthesized during the secondary response. It diffuses readily into the extravascular tissue where it combines microorganisms and their toxins. IgA is the major Ig in the seromucous secretion, and as such is to defend the external surfaces of the body. IgM is a high-molecular weight antibody that is a very efficient agglutinator. IgM is produced early in the response to infection and is, therefore, the most effective first-line defense.

This division in the organization of the immune system does not imply that T and B cells are totally independent. For most antigens, cooperation between them is necessary for the generation of an antibody response (the so-called T cell-dependent humoral response), although the mechanism of this cooperation is not known. Cooperation by these T helper cells is not necessary for all antigens: type III pneumococcal polysaccharide and *E. coli* lipopolysaccharide are so-called thymus-independent antigens and can generate substantial antibody responses in nude, athymic mice. Dependency of T cell cooperation also varies with the class of immunoglobulins: the IgM response is less dependent on T helper cells than is the IgG response.

Fixed and free macrophages and their precursors (promonocytes in the bone marrow and monocytes in the blood) belong to the mononuclear phagocyte system (MPS) (Langevoort et al., 1970). Macrophages are intimately involved in the initiation phase and the effector phase of humoral and cell-mediated immune reactions. In contrast to lymphocytes they do not clonally divide and are not antigen specific (Pierce and Kapp, 1976). Processing of antigen by macrophages seems to be necessary: removal of macrophages from lymphocyte suspensions abrogates the induction of an immune response. Most antigens are rapidly broken down inside the macrophage, but some material is probably retained on the surface. This surface-bound antigen and perhaps a soluble factor from the macrophage interact with lymphocytes to induce an immune response.

Interactions of macrophages and sensitized lymphocytes in the effector phase of the cell-mediated immune response are probably mediated by the earlier mentioned lymphokines.

Different environmental, physiological and pathological conditions can either directly – or indirectly – effect the structural and functional capacity of the immune system. Therefore, in evaluating chemical effects on the immune system, these factors should be considered (see Vos, 1977). For example, when atrophy of thymus and peripheral lymphoid organs is found in a toxicity study at a toxic level where there is also a reduction in body weight, special attention should be given to the possibility that the atrophy is produced by undernourition (Seriabnaw et al., 1968; Gonzalez, 1974). An interaction of the chemical with the endocrine system should also be considered, since various hormones (in particular glucocorticosteroids) modify the immunological responsiveness (White and Goldstein, 1972).

8.3. Polychlorinated biphenyls (PCBs)

The first suggestion that PCBs might affect the immune system stemmed from general toxicity studies. In 1965 Flick et al. reported that ingestion of PCBs resulted in small spleens in chickens. Following this initial report, Vos and Koeman (1970) reported that ingestion of PCBs induced atrophy of lymphoid tissue in chicken. Similar effects on lymphoid tissue were also observed in the rabbit and guinea pig. Vos and Beems (1971) applied 110 mg of the three PCB preparations, Phenoclor DP6, Clophen A60 and Aroclor 1260, to the dorsal skin of rabbits 5 times a week for 38 days. Exposure to these PCB preparations resulted in lymphopenia, atrophy of the cortex of the thymus and a reduction in the number of germinal centers in the spleen and lymph nodes. Vos and van Driel-Gesteranus (1972) fed guinea pigs varying levels (ranging from 0 to 250 mg/kg diet) of Clophen A60 and Aroclor 1260 for 4 or 6 weeks. At levels as low as 10 mg/kg in the feed both PCB preparations significantly reduced the numbers of circulating leukocytes and lymphocytes (see Table 8.1). In addition, there was a significant reduction in the relative thymus weight at the 50 mg/kg dosage level (see Table 8.2). A further indication that PCBs may affect immunocompetence was furnished by Friend and Trainer (1970) who showed that ducklings fed low levels of Aroclor 1254, while showing no overt signs of toxicity, were more susceptible to challenge with duck hepatitis virus. The significance of this last report needs to be considered carefully as the interactions between hepatotoxins and liver pathogens may result in increased susceptibility following viral challenge without any dysfunction in immunity.

Studies have clearly shown that PCB exposure suppresses humoral immunity. Vos and de Roij (1972) and Vos and van Driel-Gesteranus (1972) reported that chronic exposure of guinea pigs to Clophen A60 and Aroclor 1260 at levels as low as 10 mg/kg diet caused a significant reduction in antibody titers to common toxoid (Table 8.1). Keller and Thigpen (1973) reported that chronic exposure of rabbits to 300 mg of Aroclor 1221, 1242 or 1254 resulted in a reduction of both primary and secondary

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B.4. 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)

From an immunological standpoint, TCDD has been the most extensively studied halogenated aromatic hydrocarbon. Severe thymus atrophy has been reported to occur in almost all laboratory animals exposed to lethal or sublethal doses of TCDD. Of course, thymic atrophy is only an indication of immunosuppression since many toxic compounds or stressful events may induce thymic lesions although not necessarily to the same degree as TCDD. Histologically, the thymus in TCDD-exposed animals is characterized by depletion of lymphocytes throughout the cortex and lymphocytic necrosis has been observed early after exposure (Vos et al., 1973; Gupta et al., 1973; McConnell et al., 1978). The thymic medulla is not affected as severely as the cortex and in many respects appears similar to cortisone induced atrophy of the thymus (reviewed by Bach, 1975). Interestingly, the thymic medulla is populated with mature T cells while the cortex contains pre thymic or immature T cells (reviewed by Spreafico and Anacterio, 1977). Peripheral lymphopenia has been observed in laboratory animals following TCDD exposure, although fairly high dosages may be required (Zinkl et al., 1973; Vos et al., 1973). Elevated numbers of circulating lymphocytes have also been reported to occur following TCDD exposure (Weissberg and Zinkl, 1973). Alterations in the number of circulating lymphocytes should not be considered a criterion for immune dysfunction since suppressed cell mediated immunity has been reported at exposure levels that do not induce lymphopenia (Vos and Moore, 1974).

The immunologic effects following in vivo TCDD exposure in both the adult and neonatal animal have been well characterized. Guinea pigs exposed to as little as 40 ng TCDD per kg body weight weekly for 8 weeks had depressed delayed hypersensitivity reactions to tuberculin (Vos et al., 1973). In addition, the secondary, although not primary, antibody response to tetanus toxoid was depressed at higher dosages. In mice, graft vs. host reactivity was suppressed following dosages of 0.5 μg/kg body weight weekly for 4 weeks (Vos et al., 1973), while lymphoproliferative responses following stimulation with PHA were decreased only at the 25 μg/kg level (Vos and Moore, 1974). Sharma et al. (1978) reported that a number of immunological parameters were effected in mice and rabbits following exposure to low levels of TCDD (less than 1.0 μg/kg/week for 8 weeks). These included decreases in lymphoproliferative response to lymphocyte mitogens (at levels as low as 0.1 μg/kg) and decreases in antibody response (tetanus toxoid), skin reactivity (tuberculin) and serum immunoglobulin levels at dosages of 1.0 μg/kg body weight. Dietary feeding of mice with levels as low as 10 ng TCDD/kg reduced serum γ-globulin, primary and secondary antibody titers to SRBC, delayed-type hypersensitivity reactions and enhanced the susceptibility to *Salmonella* infection (Hinsdill et al., 1980).

A recent report has described the immune status of 44 children (20 had chloracne) who resided in the immediate area of the TCDD contamination in Seveso, Italy (Reggiani, 1978). These studies found no abnormalities in serum immunoglobulin concentrations, circulating levels of complement and lymphoproliferative responses of T and B cells following mitogen stimulation (see also Chapter 9B2).

TCDD administered during the pre/postnatal or postnatal period via maternal dosing has been reported to cause severe effects on the immune system in both mice and rats and may be a prerequisite for TCDD-induced suppression at least in the rat. Dosage of 5.0 μg/kg in mice and rats on various days of gestation and weaning suppresses a variety of cell-mediated immune correlates including proliferative responses of phytohemagglutinin (PHA)- and concanavalin A (Con A)-stimulated splenic and thymic lymphocytes (Vos and Moore, 1974; Faith and Moore, 1977; Luster et al., 1979c), delayed hypersensitivity reactions (Moore and Faith, 1976; Faith and Moore, 1977; Luster et al., 1979c; Thomas and Hinsdill, 1979), graft vs. host reactivity of spleen cells (Vos and Moore, 1974) and the ability to reject skin allografts (Vos and Moore, 1974). As would be expected, the effects are more severe when the chemical is administered during the pre- and postnatal periods than if administered solely in postnatal life (Vos and Moore, 1974; Faith et al., 1978; Luster et al., 1979c). Furthermore, the effects are relatively long lasting, persisting up to 4 months of age (Faith et al., 1978; Luster et al., 1979c).

TCDD affects humoral immune responses but apparently requires higher doses than that which induces defects in cell-mediated immunity. As previously mentioned, TCDD exposure causes reduction of serum γ-globulin levels and antibody responses to tetanus toxoid in adult guinea pigs (secondary only) (Vos et al., 1973), rabbits, mice (Sharma et al., 1978) and plaque-forming cell (PFC) responses to SRBCs in perinatally exposed mice (Thomas and Hinsdill, 1979). Fetal and/or neonatally exposed rats respond normally to bovine γ-globulin as measured by passive hemagglutination although lymphoproliferative responses following stimulation with T cell mitogens and delayed hypersensitivity reactions are severely depressed (Faith and Moore, 1977; Luster et al., 1979c). These studies suggested that TCDD induced suppression of T cell functions was selective in that T helper cell function was not affected (Faith and Moore, 1977). Further studies in which neonatal antibody responses in neonatally thymectomized rats occurred following adoptive transfer of bovine γ-globulin-primed T cells from perinatally TCDD-treated rats further confirmed these observations (Faith et al., 1978). The lymphoproliferative response to the B cell mitogen, lipopolysaccharide (LPS), were depressed in mice exposed pre/postnatally to TCDD, but required exposure levels higher than that which caused suppression of T cell mitogenic responses (Luster et al., 1979c). Lymphoproliferative responses following stimulation with LPS and antibody responses to LPS reside in distinct B cell populations and thus should not be considered synonymous (Poo and Michael, 1976).

Thigpen et al. (1975) reported that subclinical doses of TCDD in mice (1.0 μg/kg/week for 6 weeks) followed by infection with *Salmonella typhi* resulted in increased mortality and decreased time from infection to death. Infection by *Herpes zoster* (Pseudorabies) did not effect mortality. It was subsequently observed that mice treated with single or repeated doses of TCDD revealed a marked increase in suscep-

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sitivity of Environmental Health Sciences, Research Triangle Park, NC 27709, U.S.A.), a reduced number of peritoneal leukocytes (both lymphocytes and monocytes) was noted 3 days following induction with thioglycollate in mice exposed to low levels of TCDD as adults. While the significance of this finding is presently unknown, it is interesting to note that similar observations have been reported following treatment with cyclophosphamide (Gaidberg et al., 1975). Although macrophage functions do not appear severely altered by TCDD, it is still conceivable that the increased susceptibility to endotoxin may be due to a yet undetermined TCDD-induced macrophage defect involved directly in detoxification.

Attempts have been made to elucidate the mechanism(s) responsible for TCDD-induced immunosuppression. While, in general, these studies have not culminated in definitive findings, they have provided valuable information into the relationship between TCDD and the immune system. Early studies indicated that the atrophy of the thymus by TCDD is not indirectly mediated by altered pituitary or adrenal functions since thymic atrophy occurs in adrenalectomized or hypophysectomized rats treated with TCDD (van Logten et al., 1980). Furthermore, normal levels of circulating corticosteroids can be found in immunosuppressed TCDD-treated guinea pigs (Vos et al., 1973). TCDD treated mice have also been found to contain normal serum levels of zinc (Vos et al., 1978). TCDD-induced thymic atrophy is not caused by reduced food intake (van Logten et al., in preparation) or alterations of serum α-fetoprotein (Vos and Bartkestens, unpublished data). Treatments of exposed mice with thymosin, a thymic hormone which plays a vital role in T cell maturation, does not restore normal thymic architecture nor lymphoproliferative response of thymocytes to T cell mitogens (Vos et al., 1978). This may be indicative that immunosuppression is not due to a defect in T cell maturation. It was reported in an earlier review that serum from pre/postnatally exposed rats suppressed the in vitro lymphoproliferative responses of normal rat spleen cells, which would indicate a cytotoxic factor was present in serum from exposed animals (Faith et al., 1980). However, we have been unable to confirm these findings using serum from pre/postnatally exposed immunosuppressed mice (Luster et al., unpublished data).

One of our laboratories have screened for suppressor cell activity in pre/postnatally exposed mice (Luster et al., 1980). These studies were prompted by recent findings that a high incidence of immunosuppressed cancer patients and tumor bearing animals possess a sub-population of cells residing in either the B, T or macrophage cell populations capable of producing soluble factors which suppress the immune system. Cocultivation experiments in which spleen cells from normal mice were cultured with spleen cells from TCDD-treated mice which had previously been treated with either anti-T cell antisera plus complement (to destroy T cells) or mitomycin C (to block DNA synthesis but not production of suppressor factors) failed to suppress lymphoproliferative responses of normal spleen cells when compared to spleen cells from similarly treated normal mice (Luster et al., 1980). These studies indicated that while the defective cell type resided in the T cell population,

no suppressor cell activity was produced. Lymphocyte homing studies have been conducted in rats exposed pre/postnatally to TCDD (Faith and Luster, 1979). While the alterations were primarily focused on thymocytes, the studies indicated that TCDD altered normal homing patterns of lymphocytes from treated rats when adoptively transferred to untreated rats as well as lymphocytes from normal rats when transferred into treated recipients.

A number of studies have attempted to study the direct effects of TCDD on lymphocytes by in vitro exposure. In vitro studies have often been hampered by the insolubility of TCDD in physiological buffers (Matsumura and Benezet, 1973). It was found that 100 ng of TCDD was only 5% soluble in 1 ml solution containing equal volumes of dimethylsulfoxide (DMSO) and phosphate-buffered saline, although addition of normal serum enhances the solubility (Luster, unpublished observations). Nonetheless, Kouri et al. (1975) showed that 0.1 ng of TCDD/ml of culture media was sufficient to induce aryl hydrocarbon hydroxylase activity in human lymphocyte cultures while Niwa et al. (1975) reported that 320 ng/ml of TCDD in media is toxic to human lymphocytes. Vos and Moore (1974) were unable to affect the lymphoproliferative response of spleen cells to T cell mitogens at concentrations up to 20 ng/ml in culture media. Luster et al. (1979b) reported that brief treatments of whole spleens with TCDD dissolved in DMSO (50 ng TCDD/ml) prior to culture severely suppressed the mitogenic response to PHA, Con A and LPS. However, these studies were hampered by the solubilizing agent (DMSO) which itself was somewhat lymphotoxic. These studies further noted that the ability of lymphocyte mitogens to bind to cell surface receptors was not affected by TCDD treatment suggesting that an active event is being effected by TCDD. In the light of these results, it is interesting to discuss the existence of a TCDD receptor in lymphocytes. In this respect, tissue distribution studies with [^{3H}]TCDD given orally in rats (Van Miller et al., 1976) and dibenzofurans in mice (Morita and Oishi, 1977) indicated that splenic retention was relatively high. Furthermore, Poland and Glover (1976) have provided evidence for a TCDD receptor present in hepatic cytosol, whose binding affinity corresponds with the inductions of hepatic aryl hydrocarbon hydroxylase (AHH) activity. As mentioned previously, human lymphocyte cultures treated with TCDD induce AHH activity (Kouri et al., 1975). The recent finding of Cockrell-Duke (1979) that a number of organs studied (including the liver) rat thymus had the highest concentrations of the TCDD receptor, is a strong argument in favour of the suggestion of Poland et al. (1979) that the initial event in the toxic action of TCDD (including thymus atrophy) is mediated through the cytosolic TCDD receptor.

Recently, the effects of TCDD-treatment on bone marrow stem cells have been examined in pre/postnatally exposed mice (Table II.3; Luster et al., in preparation). Bone marrow cellularity and colony-forming units in culture (CFU-C) designed to measure macrophage-granulocyte progenitor cells were depressed only at lethal doses. Of particular interest, however, colony forming units in spleen (CFU-S) which measures pluripotent stem cells were suppressed at sublethal as well as lethal levels. This may indirectly suggest that lymphocyte progenitors are defective

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TABLE 9.5

Mixed leukocyte culture (MLC) reactions and membrane markers from peripheral blood lymphocytes of PBB-exposed Michigan dairy farm residents[a]
(Adapted from Bekesy et al., 1978)

Subjects	N	Total Ig (mg/dl)	Total lymphocytes ($\times 10^3$/mm^3)	E rosettes		E-AC rosettes		Lymphocytes with an identifiable monocyte marker	
				%	$\times 10^3$/mm^3	%	$\times 10^3$/mm^3	%	Absolute No.
Normal subjects (New York)	79	2.6 ± 0.4	0.8	71 ± 2	1900 ± 250	23 ± 1	521 ± 32	35 ± 0.1	82 ± 15
Positive dairy farm residents	48	2.5 ± 0.1	1.2 ± 0.2	71 ± 3	1474 ± 93	22 ± 1	481 ± 29	34 ± 0.5	143 ± 11
PBB-exposed Michigan dairy farm residents (with normal lymphocyte blastogenesis)	27	2.2 ± 0.2	2.0 ± 2.1[b]	60 ± 3[b]	1241 ± 79	21 ± 1	467 ± 30	19.9 ± 1.2[c]	406 ± 33[c]
(with depressed lymphocyte blastogenesis)	10	2.1 ± 0.2	1.0 ± 0.3[b]	44 ± 4[b]	917 ± 110[b]	16 ± 1[b]	331 ± 33[b]	40.5 ± 3.9[b]	850 ± 90[b]

[a] Mean values ± S.E.

[b] $P \leq 0.05$ between Michigan farm residents and Normal farm residents.

[c] $P \leq 0.05$ between Michigan farm residents and Positive farm residents.

[d] $P \leq 0.0001$ between Michigan farm residents and Normal farm residents.

should be noted, however, that more than a year had elapsed between testing in these two experiments (see also Chapter 9A).

A number of studies have examined PBB-associated effects in laboratory animals. Farber et al. (1978) fed PBB to dogs for 64 days at dosages ranging from 0.05 to 4.0 mg/kg per day. The reported immunopathological alterations were primarily associated with the 4.0 mg/kg dosage group and to a much lesser extent in the 1.0 mg/kg group (dosages that induced overt signs of toxicity). Primary findings in the higher dosage group included reduced hematocrits in the bone marrow, a variable degree of lymphocyte depletion in the T cell area of lymph nodes as well as the white pulp of the spleen, and a reduction in IgG-containing lymphocytes in popliteal lymph nodes. Although thymic atrophy was present in all groups to a variable extent, there was no effect on the sheep red blood cell hemagglutination titer or sensitivity to tuberculin. A preliminary report in abstract form, has indicated that alterations may occur in both B and T cell functions in rhesus monkeys after feeding PBB at levels of 1.5 mg/kg for 5 months and 25 mg/kg for 10 weeks (Allen and Landrecht, 1978). It has been reported that White Leghorn cockerel chicks chronically fed PBB had depressed splenic bursa and thymic weights (Ringer, 1978).

A number of investigators have studied immunological alteration following PBB exposure in rodents. PBB administered orally in mice and rats for 30 days (total of 22 doses) at levels ranging (from 0.03 to 30 mg/kg per day caused a reduction in thymic weights of rats and splenic weights of mice (Luster et al., 1978). Furthermore, lymphoproliferative responses following stimulation with T cell mitogens were depressed in the highest dosage group in both species and to a lesser extent in the next highest dosage group (3.0 mg/kg), indicating a dose response. Alterations in humoral-mediated immunity occurred only in mice at the 30 mg/kg dosage level as evidenced by decrease in LPS mitogenic response of splenic lymphocytes, serum immunoglobulin concentrations and antibody responses to SRBCs (PFC/10^6 spleen cells). Wilson et al. (1979) reported depressed antibody responses following acute exposure (167 mg/kg diet for 3 weeks) with respect to both PFCs/10^6 cells as well as total spleen cell yields. After 6 weeks of feeding, however, the PFC/10^6 cells returned to normal values, possibly indicating immunological recovery. Further studies showed the mean survival time of mice fed a diet containing 167 mg PBB/kg for 3 weeks was not affected by *Plasmodium berghei* infection (Hinsdahl et al., 1979). Fraker and Aust (1979) reported that PFC responses to SRBCs in mice fed diets containing 1, 10 and 100 mg/kg for 30 days were 89%, 39% and 12%, resp. of control values, although it was not reported whether this was due to PFCs/10^6 cells or total cell yields. Delayed hypersensitivity responses were not affected by this exposure regimen. Recently, Luster et al. (1979a) evaluated immune function following low level chronic exposure (6 months) in mice and rats at dosages ranging from 0.1 to 10.0 mg/kg body weight per day as well as pre/postnatal exposure in mice via maternal dosing. In chronically exposed rats, depressed immune functions were evident in the highest dosage group and included decreased antibody responses to bovine γ-globulin, delayed hypersensitivity responses, and lymphoproliferative

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immunological studies be performed in non-human primates exposed under laboratory conditions to determine if there is a potential for immunosuppression at dosage levels approximating those theoretically determined to have occurred in the Michigan population. The primate studies by Allen and Lambrecht (1978) appear to have been designed to answer these questions.

Evidence also suggests that acute vs. chronic exposure may induce differential effects on the immune system. Splenic weights have been reported decreased following acute exposure (Luster et al., 1978; Wilson et al., 1979) and increased after chronic exposure (Gupta and Moore, 1979), and may indicate recovery. While acute PBB exposure may primarily effect humoral mediated immunity, chronic exposure appears to focus on cell-mediated immunity and in this sense, is not unlike acute vs. low level chronic cyclophosphamide exposure (reviewed by Bach, 1975). This may be interpreted as indicating that PBBs preferentially affect those cells undergoing increased proliferation since B cells are normally more proliferative than T cells. On the other hand, low-level chronic exposure would affect T cells as much if not more than B cells because of their slower renewal.

The severe PBB-induced liver lesions that precede observations of immune dysfunction in rodents may be more than coincidental. Since the primary metabolism of PBB probably occurs at the level of liver microsomal enzymes (Bubsch et al., 1975), quantitative and/or qualitative changes in PBB metabolism, may be required for immune suppression to occur. This may result directly through PBB or a metabolite acting on immunocompetent and/or precursor cells following liver saturation or indirectly through alteration of steroid metabolism, indicating a PBB- steroid interaction or antagonism. In this respect phenobarbital, a typical microsomal inducer, is an immunosuppressive antagonist when given in conjunction with some weak immunosuppressive drugs (Spreafico et al., 1974).

The various immune studies with PCBs and PBBs were all carried out with mixtures of which the individual compounds will differ in their immunotoxicity potency. In this respect the study of McKinney et al. (1976) is interesting. These authors compared the toxicity of five hexachlorobiphenyl congeners in 'ochms: 2,3,6,2',3',6'-, 2,4,6,2',4',6'-, 2,4,5,2',4',5'-, 2,3,4,2',3',4'- and 2,4,5,3',4',5'-. The latter chemical was the most toxic and was the only one to produce thymus atrophy and edema in the chicken; toxic responses similar to those found with TCDD. As reported by Poland et al. (1979), of a series of 16 halogenated biphenyl congeners, only three (3,4,3',4'-tetrachloro-, 3,4,5,3',4',5'-hexachloro- and 3,4,5,3',4',5'-hexabromo-; which are stereoisomers of TCDD), induced hepatic aryl hydrocarbon hydroxylase activity. One of these compounds (3,4,5,3',4',5'-hexachlorobiphenyl) has been shown to depress parameters of the cell-mediated immunity in young rats after perinatal maternal exposure (Vos et al., unpublished data) and in adult guinea pigs (Luster et al., unpublished data), mimicking the immune effects of TCDD. As PCBs can be contaminated with chlorinated dibenzofurans (Vos et al., 1970), it can be concluded that the immune effects of halogenated biphenyls will largely depend on the presence in the mixture of those compounds that are stereoisomers of TCDD.

The mechanisms by which halogenated biphenyls alter immune function are presently not known. There are at least three basic mechanisms by which these chemicals may alter immune function. These include chemical induced alterations in normal hormone levels which indirectly can alter immune functions, chemically induced functional defects of cells involved in the immune response and chemically induced alterations in numbers of responding cell types. Indirect effects of chemicals on the immune system mediated through hormones is certainly possible as various hormones are known to affect immune functions. Chemically induced functional defects in lymphoid tissues could result in a defect in recognition phenomena by lymphoid cells, defects in cellular activation processes or induction of suppressor cells. Depletion of responding cell types as a result of chemical exposure could be due to direct lymphocytotoxicity resulting in death of lymphocytes, blockage of the maturational sequence of specific lymphocyte population development at some point in this sequence, and direct chemical interference with lymphocyte function. The likelihood is that most chemically induced modulation of immune responses is a complex process and involves more than one of the above potential mechanisms of immune suppression.

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