1st Draft

A Historical Prospective Mortality Study of Workers Exposed to Polychlorinated Biphenyls.

BACKGROUND

The term "polychlorinated biphenyls" describes a group of two hundred nine different chlorinated biphenyls which, in mixtures, ~~range from~~ vary in consistency from oils to sticky resins. ~~Mixtures~~ PCB's are manufactured by the chlorination of biphenyl with anhydrous chlorine in the presence of a ferric chloride or iron filing catalyst.

Mixtures of PCB's have been in use since 1929 in transformers, capacitors, lubricants, "carbonless" duplicating paper, fireproof sealants, plastics, adhesives, and many other products. Their resistance to biodegradation, photodegradation, oxidation, acids, bases, and other chemical agents made ~~them~~ PCB's invaluable in scores of ~~uses~~ industrial uses. ~~PCB's these properties [illegible] more stable as residual pollutants when released into the environment. [illegible] mixtures are [illegible] Clophen, [illegible], Pyranol, and others.~~

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However, these same properties make PCB's more stable as residual pollutants ~~[illegible]~~ when released into the environment. Current interest in ~~p~~ PCB's began in the mid-1960's, when technological developments in gas chromatography and mass spectrometry made environmental detection of low ~~levels~~ PCB levels possible. The first reports of PCB's in the environment came from Sweden, where Jensen identified residues of PCB's in fish from various Swedish waters.[1] Risebrough et al found PCB and DDT in marine ecosystems of the Pacific Ocean.[2] Savage et al found detectable levels PCB's in 8 out of 39 human milk samples in rural Colo

The first report of possible PCB effects on humans occurred in 1968, when over 1200 Japanese were involved in an epidemic of Yusho, an acnelike skin disease which was later traced to consumption of a rice-oil contaminated with PCB's from a leaking heat-exchanger. However, it was later shown that the rice oil also contained a high level of polychlorinated dibenzofurans (P possibly due to the high temperature of the heat-exchange unit.

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7 Kimbrough, R.A. et al, "Induction of Liver Tumors in Rats by Polychlorinated Biphenyl Aroclor 1260", Journal of the NCI, December, 1975

PCDF's were shown to be relatively more concentrated in the liver than PCB's, and these findings clearly indicated the necessity to pay greater attention to PCDF's for clarification of the nature of Yusho.[4]

While acute effects from relatively high PCB exposure levels are known and can be avoided by appropriate ~~housekeeping~~ control measures, attention has more recently been focused on the chronic effects ~~of~~ resulting from long-term low levels of exposure to PCB's. ~~Animal tests have proved to be equivocable.~~ The Environmental Protection Agency considers PCB's to be suspect carcinogens, but animal tests have not given any definitive answer to their suspicions. In extensive two-year chronic oral toxicity tests of Aroclor 1242, 1254, and 1260 (42-60% chlorine Monsanto PCB products) conducted by Industrial Biotests for the Monsanto Company, no carcinogenic effects were observed in the rats and beagles tested. Hyperplasia, hypertrophy, and several benign tumors were observed in the livers of the rats, but there was no evidence of malignancy in any of the test animals.

Other investigators have shown liver tissue effects ranging from hyperplasia to well-differentiated hepatocellular carcinomas in rats or mice fed with various PCB-containing diets. For example, Kimbrough et al fed rats with Aroclor 1254 and 1260, and observed hypertrophy, lipid accumulation, and adenofibrosis, but no malignancies, in the livers of the test animals.[5] In a later experiment, the same investigator fed Sherman rats 100 ppm of Aroclor 126 for 21 months and reported the induction of hepatocellular carcinomas and neoplastic nodules in the test animals' livers, whereas control animals showed little or no effects.[6]

The recent National Cancer Institute report of its carcinogenicity tests on Aroclor 1254 concluded that the substance was not carcinogenic in Fischer 344 rats under the conditions of the bioassay. However, their study was not definitive, since they alluded

to the non-significant occurrence of gastrointestinal tract [redacted] carcinomas and hepatocellular proliferative lesions in their test animals as possibly being related to the PCB diet.[7]

There have been very few epidemiological studies of [redacted] human populations exposed to low levels of PCB's over a long period of the [redacted]. The Mobil Oil Company released a study in 1976 conducted by Dr. Anita Bahn in which a significant number of melanomas and pancreatic cancers were found in PCB exposed chemical [redacted] workers and research personnel. However, the study has been severely criticized due to deficiencies in the identification of the study cohort, failure to identify other potentially carcinogenic chemical exposures, and other problems which left the results of the Mobil study highly in doubt.[8]

A preliminary study of PCB-exposed workers was begun at ~~Monsa~~ the Monsanto Company shortly after the Mobil study in response to the need for a valid epidemiological study of the ~~Sp~~ chronic effects of PCB exposure on ~~humans~~ humans. The study focused on workers at the ~~P~~ W.G. Krummrich plant in Sauget, Illinois, where PCB's were manufactured from 1936 until production ceased in 1977. This preliminary study failed to support the Mobil Study results. No melanomas or pancreatic cancers were found, but an excess ~~incidence~~ incidence of lung cancer deaths occurred in the study cohort. However, due to the preliminary nature of the study, [redacted] no follow-up was done on over 30% of the study cohort who had left the company, and further definition of the ~~exposure~~ exposed population was needed, ~~since no distinction was made between workers exposed for 1 month and 10 years in the analysis.~~

The study being reported here is an attempt to complete the epidemiological evaluation of the worker population at Monsanto's W.G. Krummrich plant and evaluate the chronic effects of PCB-exposure ~~on humans~~ on humans, ~~and attempts have been successfully made at obtaining complete vital with complete vital status information on a verified, exposed worker cohort status information on a verified, exposed worker cohort.~~ The mortality experience of two ~~exposed~~ workers exposed to PCB's in their manufacture ~~The mortality experience of workers exposed to polychlorinated biphenyls in their manufacture has been evaluated followed and evaluated~~ has been followed and evaluated.

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Study Population

The Monsanto plants involved in the United States manufacture of PCB's were the W. G. Krummrich plant in Sauget, Illinois, and the Anniston, Alabama plant. Since the preliminary study, upon which this study is based, involved the Krummrich plant alone, the present study deals solely with the Krummrich worker population.

The study population from the Krummrich plant consists of all male, waged employees who worked at least six months in department 246 – where PCB was manufactured – between January 1, 1945 and December 31, 1965. This population includes active, retired, and terminated employees. Through interviewing plant personnel, it was determined that exposure levels of workers involved in the manufacture of PCB's did not vary considerably; therefore, all male, waged workers in department 246 are considered to have a common exposure level.

Methodology

Work histories for all past and present Krummrich employees were obtained from the plant and screened for department 246 work. In order to check the completeness of this search, two other sources were researched. Interviews were conducted with supervisory personnel from department 246 and any names which they recalled were recorded and checked. After this, a plant-developed computer listing of all department 246 workers was obtained, and the results of the work history search and the interviews were cross-checked with the computer listing in order to insure completeness of the cohort. It should be noted that some workers, e.g., maintenance, may have had significant exposures to PCB's, but were not included in this study due to exposure verification difficulties.

By using these methods of identification, 82 male, waged workers (57 white, 25 black) were identified as meeting the criteria for inclusion in the PCB manufacturing cohort. For each worker, the following information has been obtained from company records: employee name, clock number, social security number, race, sex, date of birth, date of hire, date of termination (if applicable

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and as detailed a work history as possible was available. The employment and vital status information on the 82 workers is illustrated in Table 1. Information was obtained. Vital status information was obtained by use of standard follow-up techniques such as worker interviews, Veteran's Administration files, Polk City Directories, and local telephone directories. All active employees and retirees currently receiving pension checks as of December 31, 1977 were assumed to be alive, and all persons known to have died on or after January 1, 1978 were assumed to be alive for the purposes of this study. For the 28 workers known to have died, a state death certificate has been obtained and coded by an experienced, trained nosologist for the underlying cause of death according to the International Classification of Diseases, Seventh Revision.

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Results Person-years of observation contributed by the workers were determined over the mortality experience of the PCB-exposed study cohort was compared to the age, sex, race, and time-specific death rates of the standard United States population using the method of indirect standardization. The expected deaths generated by this method were also adjusted to reflect the cancer mortality experience of St. Clair County, in which most of the plant's workers reside, by use of U.S. Cancer Mortality by County: 1950-69. This allowed comparison of observed cancer deaths with the overall United States population and

5-year age groups summed for the total cohort.

For selected causes of death,

A standard mortality ratio (SMR) was calculated by the following formula: $SMR = \frac{\text{OBSERVED DEATHS (BY CAUSE)}}{\text{EXPECTED DEATHS (BY CAUSE)}} \times 100$.

Statistical significance of the SMR's was measured by the Mantel-Haenszel chi-square statistic:

$$\frac{(|\Sigma \text{OBSERVED} - \Sigma \text{EXPECTED}| - 0.5)^2}{\Sigma \text{EXPECTED}}$$

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The Poisson assumption is made in computing this statistic - the variance ~~of the expected is assumed to be the mean~~ and mean of the expected are assumed to be equal.

Table 2 shows the observed deaths by cause and the SMR's associated with each disease category. 28 deaths were observed among the 82 members of the study cohort. The average exposure ~~to~~ to PCB's in department 246 for these 28 ~~former~~ deceased workers is ~~[illegible] years~~ was 33.6 ~~y~~ months. ~~[illegible]~~ The average age ~~at~~ of death was 57.0 years, and the average time between first exposure to PCB's and death was 17.5 years. The SMR values for the causes of death listed are not significant at the .05 level. The only category approaching significance was the category of "all malignant neoplasms"; ~~when the 8 observed deaths~~ in the comparison of observed vs. ~~U.S. [illegible] males~~ expected (U.S.). However, St. Clair County's expected deaths are higher than the U.S. experience, so ~~that~~ ~~County~~-adjusted SMR is decreased from 206.5 to 190.3.

Tables 3 and 4 summarize the mortality experience for white and nonwhite males, respectively. 17 deaths were observed among the 57 white male ~~study~~ workers. The average age at death was 59.2 years. These workers were exposed an average of 36.0 months (vs. 37.2 for living white), and lived for an average of 20.8 years after their first exposure to PCB's in department 246. As in the case of all males (Table 2), no cause of death category showed significance at the .05 level. The high ~~[illegible]~~ SMR's ~~[illegible]~~ in the "all other cancers" category resulted from an observed - expected distribution of 2 - 0.398 (U.S. and 2 - 0.378 (St. Clair). The two observed cancers in this category were a generalized carcinomatosis (ICD 199) and ~~one unspecified~~ a malignant neoplasm of the lung specified as secondary (ICD 165) with no primary site known. However, ~~these two~~ the resulting SMR's for this category were insignificant at the .05 level, and the numbers involved are too few to ~~[illegible]~~ draw any conclusion of concern.

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Table 4 outlines the mortality experience of the nonwhite male subset of the study cohort. There were 11 deaths among the 25 nonwhite male study members. The average age at death was 53.5, with an average of 12.3 years between first PCB exposure and death. The eleven deceased workers were exposed an average of 340 months, while the 14 living workers were exposed 28.8 months on the average. Only one category, lymphatic and hematopoietic system cancers, showed significance at the .05 level, and this category only showed 1 observed death. As in most of the causes of death in Table 4, the numbers involved are too small to attach any statistical significance on the SMR's generated. The category of all malignant neoplasms had an excess amount of deaths which was not significant at the .05 level.

Discussion

The workers involved in this study are unique in that they represent a clearly defined group of industrial workers exposed to PCB. They represent the largest cohort available in the U.S. who were exposed to PCB in its manufacture. However, these same workers were also exposed to hydrochloric acid fumes, trichlorobenzene tetrachlorobenzene, biphenyl, and small amounts of chlorine gas in the manufacture of PCB's. Furthermore, all of the workers were involved with other chemicals during their employment at the plant - and these included oil additives, dyes, rubber additives, benzene, toluene, aniline, and etc. The smoking, drinking, and prior work histories of the study cohort is also unknown. Therefore, in evaluating the effects of PCB among workers exposed to this compound, the investigator is faced with not only PCB-exposure, but also a host of other potentially harmful agents.

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Another factor to consider is the route of entry into the body. The workers' main exposure to PCB's was through skin absorption, since PCB's ~~in general~~ have relatively low vapor pressures. However, most of the long-term animal testing ~~which has been done~~ involves low dose ~~feeding~~ ingestion studies, and environmental contaminants which enter the food chain and ultimately would be ingested by man create the most concern ~~am~~ today. It is unknown whether chronic PCB ingestion and chronic PCB skin absorption can be considered as equivalent phenomena in terms of the effect, if any, on human health.

~~While there are many~~ ~~Wide~~ With these factors in mind, ~~the~~ results from the analysis of the mortality experience of these PCB-exposed workers indicate no statistically significant excess in total mortality or deaths due to almost all of the other categories - including malignant ~~neoplasms~~. neoplasms. ~~Excluding the~~ ~~It is important, however, to note that the small size of the study cohort~~ ~~[illegible]~~

The results of this study do not support the Mobil Oil study in which melanomas and pancreatic cancers were ~~[illegible]~~ associated with PCB exposure, nor do the the results uphold animal testing in which hepatomas have been diagnosed. The only digestive system cancer which occurred was a cancer of the colon which was diagnosed ~~occurred~~ in a nonwhite male study member ~~Monsanto~~ The significant excess of lung cancer observed in the preliminary Monsanto study is not supported by this study. While 3 ~~lung~~ ~~ca~~ respiratory cancers were observed and 1.3–1.6 expected ~~[illegible]~~ among ~~all~~ the study cohort, the difference is not ~~[illegible]~~ statistically significant, and other factors, such as cigarette smoking, surely play the major role in these cancers.

~~It is important, however, to note that the study cohort was small size of the study cohort could prevent us from identifying adverse health effects.~~

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The concept of a latency period in cancer mortality was considered in this study, but no proper analysis could be done, since it would not be a comparison of whites vs. nonwhites if an arbitrary period of latency of time of 10, 15, or 20 years was used. Table 5 shows the nonwhite members entered employment 24 at an older average age (42 vs. 39) than the whites, and the nonwhites average age at death was much younger than the whites (53 vs. 59).

It is important, however, to note that the small size of the study cohort could have prevented us from detecting a very rare condition which has increased in probability of occurrence due to the PCB exposure. From a statistical standpoint, a larger sample size would have been desirable. However, since this worker population is probably one of the largest occupationally-exposed groups which can has been identified and completely followed-up on, the ongoing concern regarding PCBs as possible human carcinogens warrants the continued follow-up of this group's mortality experience.

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