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Summary

A historical prospective mortality study of 82 workers exposed to PCB's in their manufacture from 1945-1966 at Monsanto's W. G. Krummrich plant failed to reveal any causes of death, including malignant neoplasms, which were significant. Observed deaths were compared with expected deaths from the U.S. standard population and the St. Clair County population. The observations were based on somewhat small numbers, but the study does not support the carcinogenicity of PCB's in the liver, lung, pancreas, or skin.

ROUGH DRAFT

A HISTORICAL PROSPECTIVE MORTALITY STUDY OF WORKERS EXPOSED TO POLYCHLORINATED BIPHENYLS

Background

The term "polychlorinated biphenyls" (PCB's) describes a group of ~~theoretically two hundred nine different~~ chlorinated biphenyls which, ~~in mixtures,~~ vary in consistency from oils to sticky resins in direct relation to the degree of chlorination of the phenyl rings. 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 PCB's invaluable in scores of industrial uses.

However, these properties also make PCB's more stable as residual pollutants when released into the environment. Current interest in PCB's began in the mid-1960's, when technological developments in gas chromatography and mass spectrometry made environmental detection of low PCB levels possible. The first report 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's and DDT in marine ecosystems of the Pacific Ocean.[2] Detectable levels of PCB's were also found in 8 out of 39 human milk samples in rural Colorado.[3]

The first report of possible PCB effects on humans occurred in 1968, when over 1,200 Japanese were involved in an epidemic of Yusho, an acnelike skin disease which was later traced to the consumption of a rice-oil contaminated with PCB's from a leaking heat-exchange unit. However, it was later shown that the rice oil also contained a high level of polychlorinated dibenzofurans (PCDF's), possibly due to the high temperature of the heat exchange unit.[4] 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.

While acute effects from relatively high PCB exposure levels are known and can be avoided by appropriate control measures, attention has ~~most recently~~ been focused on the chronic effects resulting from long-term low levels of exposure to PCB's. ~~Several tests by Silbergeld~~ 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, 54, and 60% chlorinated ~~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 also noted 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 1260 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.[7] However, their study was not definitive, since they alluded to the non-significant occurrence of gastrointestinal tract carcinomas and hepatocellular proliferative lesions in their test animals as possibly being related to the PCB-containing diet.

There have been very few epidemiological studies of human populations exposed to low levels of PCB's over a long period of time. The Mobil Oil Company released a study in 1976 conducted by Dr. Anita Bahn[8] in which a significant number of melanomas and pancreatic cancers were found in PCB-exposed chemical workers and research personnel. However, the study has been severely critized due to deficiencies in the identification of the study cohort, failure to [illegible] other potentially carcinogenic chemical exposures, and other problems which left the results of the Mobil study highly in doubt.[9]

A preliminary study of PCB-exposed workers was begun at the Monsanto Company shortly after the Mobil study in response to the need for a valid epidemiological study of the chronic effects of PCB exposure on humans. The study focused on workers at the 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 occurrence of lung cancer deaths was found in the study cohort. However, due to the preliminary nature of the study, no follow-up was done on over 30% of the study cohort who had left the company, and further definition of the exposed population was needed.

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. The mortality experience of workers exposed to PCB's in their manufacture has been followed and evaluated.

Study Population

The Monsanto plants involved in 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's were 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 PCB manufacture 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 verify 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. After this, a plant developed computer listing of all department 246 workers was obtained, and the results of the work history search and plant interviews were crosschecked with the computer listing in order to insure completeness of the cohort. It should be noted that some workers, e.g., maintenance and salary, 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 non-white) were identified as meeting the criteria for inclusion in the study 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), and as detailed a work history as was available. The employment and vital status information on the 82 workers is shown in Table 1.

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.

Results

Person-years of observation contributed by each worker was determined over five-year age and time intervals and summed for the total cohort. The mortality experience of the PCB-exposed study group 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 cancer deaths generated by this method were also adjusted to reflect the cancer mortality experience of St. Clair County (in which most of the Krummrich workers reside) by use of data found in U.S. Cancer Mortality by County:1950-69.

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-Haensycl chi-square statistic:

$$\frac{(|\Sigma \text{Observed} - \Sigma \text{Expected}| - 0.5)^2}{\Sigma \text{Expected}}$$

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

The observed deaths by cause and the SMR's associated with each disease category are shown in Table 2. Twenty-eight deaths were observed among the 82 members of the study cohort. The average exposure to PCB's in department 246 for the 28 deceased workers was 33.6 months (vs. 34.8 months for the 54 living). The average age at death was 57.0 years, and the average time between first exposure to PCB's and death was 17.5 years. SMR values for the causes of death listed are not significant at the .05 level. The only category approaching significance was "all malignant neoplasms" in the comparison of observed deaths vs. expected (U.S.) deaths. However, St. Clair County's expected deaths are higher than U.S. experience, so that the county-adjusted SMR is decreased from 206.5 to 190.3.

Tables 3 and 4 summarize the mortality experience of white and nonwhite males, respectively. Seventeen deaths were observed among the 57 white male workers. The average age at death was 59.2 years. These workers were exposed an average of 36.0 months (vs. 37.2 months for the 40 living whites), and lived 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 SMR's 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 a malignant neoplasm of the lung specified as secondary (ICD 165) with no primary site listed. The high SMR's for this category are not significant at the .05 level, and the numbers involved are too few to draw any definitive conclusions.

Table 4 outlines the mortality experience of the nonwhite male subset of the study cohort. There were 11 deaths among the 25 nonwhite study members. The average age at death was 53.5 years, with an average of 12.3 years between first PCB-exposure and death. The 11 deceased workers were exposed an average of 30.0 months (vs. 28.8 months for the 14 living). One category, lymphatic and hematopoietic system cancers, showed significance at the .05 level, and this category only showed 1 observed death. The category of "all malignant neoplasms" had an excess number of deaths which was not significant at the .05 level. As in most of the causes of death in Table 4, the numbers involved are too small to draw conclusions about health effects of PCB's from the SMR values of this table.

Discussion

The workers involved in this study are unique in that they represent the largest cohort available in the United States who were exposed to PCB in its manufacture. However, these workers were also exposed to other chemicals in the process of manufacturing PCB, such as hydrochloric acid fumes, trichlorobenzene, tetrachlorcbenzene, biphenyl, and small amounts of chlorine gas. Furthermore, all of the workers were exposed to other chemicals during their employment at the plant, such as oil additives, dyes, rubber additives, benzene, toluene, aniline, etc. The smoking, drinking, and prior work histories of the study cohort is also unknown. Therefore, in evaluating the effects of PCB's among

workers exposed to these compounds, the investigator must consider not only PCB exposure, but also a host of other potentially harmful agents.

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 have relatively low vapor pressures. However, nost of the chronic animal testing involved low dose ingestion studies, and environmental contaminants which enter the food chain would ultimately be ingested by man. It is unknown whether long-term, low dose PCB ingestion and long-term, low dose PCB skin absorption in humans can be considered as equivalent phenomena in terms of the potential health effects.

With these factors in mind, results from the analysis of the mortality experience of the PCB-exposed workers indicate no statistically significant excess in either total mortality or deaths due to almost all of the other categories - including malignant neoplasms. The results of this study do not support the Mobil study in which melanomas and pancreatic cancers were associated with PCB exposure, nor do the results uphold translating to man the outcome of animal tests, in which hepatomas have been associated with long-term PCB exposure. In the study cohort, the only digestive system cancer which occurred was a cancer of the colon which was diagnosed in a nonwhite study member.

The significant excess of lung cancer observed in the preliminary Monsanto study is not supported by this study. While 3 respiratory cancer deaths were observed and 1.3 to 1.6 were expected, the difference is not statistically significant, and other factors, such as cigarette smoking, would have to be taken into account.

It is important, however, to note that the small size of the study cohort could have prevented the detection of infrequent conditions which had increased in probability of occurrence due to the PCB exposure. A larger sample size would have increased the likelihood of identifying such a condition. However, since this worker population is probably one of the largest occupationally-exposed groups which has been identified and completely followed-up on, the ongoing concern regarding PCB's as possible human carcinogens warrants the continued follow-up of this group's mortality experience. The results of this study, while not conclusive in denying PCB as a health hazard, do fail to support other studies which had internal design problems, and put PCB's in a better perspective in terms of their effects on human health.

TABLE 1

Follow-up Status of Workers Exposed to PCB's

1.	Still Employed	22
2.	No Longer Employed	60
	a. Alive, Employed Elsewhere	10
	b. Alive, Retired	22
	c. Deceased	28

TABLE 2

SMR's Among All Males (n = 82) for Selected Causes of Death

Cause	ICD Code 7th Revision	Observed	SMR	County-Adjusted SMR
All Deaths		28	134.0	
All Malignant Neoplasms	140-205	8	206.5	190.3
Buccal Cavity and Pharynx	140-148	0	-	-
Digestive Organs and Peritoneum	150-159	1	88.8	81.0
Respiratory System	160-164	3	231.5	189.8
Genito-Urinary Tract	177-181	1	236.4	250.0
Lymphatic and Hematopoietic Tissue	200-205	1	326.8	341.3
All Other Cancers		2	346.0	367.0
Vascular Lesions of CNS Circulatory System Diseases	330-334 400-468	14	136.9	
Respiratory System Diseases	470-527	0	-	
Digestive System Diseases	530-587	2	178.9	
All External Causes	800-998	1	233.0	
Other+		3	133.0	

+"Other" ICD codes are all those not listed above.

TABLE 3

SMR's Among White Males (n = 57) for Selected Causes of Death

Cause	ICD Code 7th Revision	Observed	SMR	County-Adjusted SMR
All Deaths		17	134.8	
All Malignant Neoplasms	140-205	4	165.5	146.4
Buccal Cavity and Pharynx	140-148	0	-	-
Digestive Organs and Peritoneum	150-159	0	-	-
Respiratory System	160-164	2	241.1	184.2
Genito-Urinary Tract	177-181	0	-	-
Lymphatic and Hematopoietic Tissue	200-205	0	-	-
All Other Cancers		2	502.8	529.1
Vascular Lesions of CNS Circulatory System Diseases	330-334 400-468	10	158.1	
Respiratory System Diseases	470-527	0	-	
Digestive System Diseases	530-587	1	137.2	
All External Causes	800-998	0	-	
Other+		2	187.7	

+"Other" ICD codes are all those not listed above.

TABLE 4

SMR's Among Non White Males (n = 25) for Selected Causes of Death

Cause	ICD Code 7th Revision	Observed	SMR	County-Adjusted SMR
All Deaths		11	132.9	
All Malignant Neoplasms	140-205	4	274.5	271.7
Buccal Cavity and Pharynx	140-148	0	-	-
Digestive Organs and Peritoneum	150-159	1	209.1	191.9
Respiratory System	160-164	1	214.1	202.0
Genito-Urinary Tract	177-181	1	539.3	619.4
Lymphatic and Hematopoietic Tissue	200-205	1	1098.9	1234.6*
All Other Cancers		0	-	-
Vascular Lesions of CNS Circulatory System Diseases	330-334 400-468	4	102.6	
Respiratory System Diseases	470-527	0	-	
Digestive System Diseases	530-587	1	256.8	
All External Causes	800-998	1	113.7	
Other+		1	84.0	

+"Other" ICD codes are all those not listed above.

* $p < 0.05$

References

1. Jensen, S: Quoted in 'Report of a new chemical hazard.' New Sci. 32:612, 1966.

2. Risebrough, R.W., Reiche, P., Peakall, D.B., Herman, S.G., Kirven, M.N: Chlorinated hydrocarbons in marine ecosystems. Nature 220:1098-1102, 1968.

3. Savage, E.P., Tessari, J.D., Malberg, J.W., Wheeler, H.W., Bagby, J.R.: A search for PCB's in human milk in rural Colorado. Bull. Environ. Contam. Toxicol. 9;222-226, 1973.

4. Nagayama, J., Kuratsune, M., Masuda, Y: Determination of chlorinated dibenzofurans in Kanechlors and "Yusho oil." Bull. Environ. Contam. Toxicol. 15:9-13, 1976.

5. Kimbrough, R.D., Linder, R.E., Gaines, T.B.: Morphological changes in liver of rats fed with polychlorinated biphenyls. Arch. Environ. Health 25:354-364, 1972.

6. Kimbrough, R.D., Squire, R.A., Linder, R.E., Strandberg, J.D., Montali, R.J., Burse, V.W.: Induction of liver tumors in Sherman strain female rats by polychlorinated biphenyl Aroclor 1260, J. Natl. Cancer Inst. 55:1453-1456, 1975. J. Natl. Canc. Inst. 53: 547-55s, 1974.

7. National Cancer Institute: Bioassay of Aroclor 1254 for possible carcinogenicity. Technical Report Series No. 38, DHEW Pub. No. (NIH) 78-838, 1978.

8. Lawrence, CL, PCB? and melanoma. N. Engl. J. Med. 296;108, 1977.

9. Bahn, A.K., Rosenkrantz, H., Hermann, N., et al. Melanoma after exposure to PCB's., N Engl. J. Med 295;450, 1976