PROPOSAL FOR A HISTORICAL PROSPECTIVE MORTALITY STUDY OF POLYCHLORINATED BIPHENYL EXPOSED WORKERS

BACKGROUND

The polychlorinated biphenyls (PCB's) have attracted much attention since the late 1960's when technological developments in gas chromatography and mass spectrometry made the detection of PCB's at low levels in the environment possible. PCB's have been in use since 1929 in transformers, lubricants, "carbonless" duplicating paper, fireproof sealants, plastics, adhesives, and many other products. Their resistance to biodegradation, photodegradation, and oxidation made them invaluable in scores of uses but also made them more stable as residual pollutants when released into the environment.

PCB's are highly lipid soluble compounds. Lipid solubility enables a proportion of food chain PCB residues to be stored in the fat depots of the body. The first reports of PCB's in the environment came from Sweden, where Jensen (1966)[1] identified residues of PCB's in fish from various Swedish waters. Risebrough et al (1968)[2] found PCB and DDT in marine ecosystems of the Pacific Ocean. Early reports of wildlife effects included egg shell thinning and baby seal effects, but subsequent studies have failed to conclusively show PCB's as the causative agent.

The first report of possible PCB effects on humans occurred in 1968, when over 1,000 Japanese were involved in an epidemic of Yusho, an acnelike skin disease which was traced to rice oil contaminated with PCB's. However, it was later shown that the rice oil also contained a high level of polychlorinated dibensofurans (PCDF's), possibly due to use of the contaminating PCB as a high temperature heat transfer medium. It was shown that PCDF's are relatively more concentrated in the liver.

and the investigators' findings clearly indicated the necessity to pay greater attention to PCDF's for clarification of the nature of Yusho.[3] While acute effects from relatively high PCB exposure levels are known and can be avoided by appropriate control measures, attention has more recently been focused on the chronic effects 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 based on its own animal tests. Monsanto's extensive two-year chronic oral toxicity tests of Arochlor 1242, 1254, and 1260 in both rats and beagles at dose levels of 1, 10, and 100 ppm concluded that PCB's were non-carcinogenic. 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.[4]

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 at al (1972)[5] fed rats with Arochlor 1254 and 1260, and found hypertrophy, lipid accumulation, and adenofibrosis in liver tissue, but found no malignancy. The same investigator fed Arochlor 1254 to mice for 11 months and reported the induction of malignant hepatomas in the test animals.[6]

The recent National Cancer Institute report [7] of its carcinogenicity tests on Arochlor 1254 concluded that the substance was <u>not</u> carcinogenic in Fischer 344 rats under the conditions of the bioassay. However, they allude to the non-significant occurrence of gastrointestinal tract carcinomas and hepatocellular proliferative lesions in their test animals as possibly being related to the Arochlor diet.

There have been very few epidemiological studies of human populations

exposed to low levels of PCB's over a long period. 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 exposed chemical workers. While these results received publication, the study was severely criticized[9] due to deficiencies in the identification of the study cohort, failure to identify other potentially carcinogenic chemicals to which the workers and research personnel were exposed, and other problems which left the results of the Mobil study highly in doubt.

A preliminary study of PCB-exposed workers was begun at Monsanto shortly after the Mobil study in response to the need for a valid epidemiological study of the effect of PCB's on humans. The study focused on workers at the Krummrich Plant, where PCB's were manufactured from 1936 until production ceased in 1977. No melanomas or pancreatic cancers were found, but an excess incidence of lung cancer deaths was seen. However, due to the preliminary nature of the study, several necessary steps to complete the epidemiology study remained unfinished, such as following up on the mortality experience of over 30% of the study cohort who were lost-to-follow-up. In addition, no minimum limits on exposure time were used in the preliminary study. Thus, no attempt was made to distinguish between the workers exposed for years and the worker exposed for a few days.

The investigators involved in the preliminary Monsanto PCB study realized these deficiencies and advised that the study population should be further defined and evaluated so that a valid, comprehensive report could result. Therefore, due to the preliminary nature of the epidemiological data available and the inconclusive toxicological data, it is necessary to pursue further epidemiologic study in order to evaluate the chronic effects of PCB-exposure to man with more complete vital information on a verified, exposed worker cohort.

PURPOSE OF THE STUDY

This epidemiological study will investigate the mortality experience of workers exposed to polychlorinated biphenyls in their manufacture. Through studying this cohort we intend to (1) identify groups of workers that have PCB exposure of a sufficient latency to demonstrate any chronic health effects, and (2) analyze the mortality experience of these workers with attention given to malignant neoplasms especially of the lung, liver, skin, and pancreas.

STUDY POPULATION

The Monsanto plants involved in the U.S. manufacture of PCB's are the W.G. Krummrich plant in Sauget, Illinois, and the Anniston, Alabama plant. Since the preliminary study, upon which the proposed study is based, involved the Krummrich plant alone, the proposed study will deal solely with the Krummrich workman population.

The study population from the Krummrich plant consists of all male waged employees who have worked at least six months in a job involving exposure to PCB after December 31, 1944, and prior to 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 waged workers involved in the manufacture of PCB's will be considered to have a common exposure level.

Work histories for all past and present Krummrich employees have been obtained and screened for PCB-department work by the Department of Medicine and Environmental Health (DMEH). A plant-developed computer listing of all PCB department workers has also been supplied to the DMEH, and the computer listing has been cross-checked with the hand work history search in order to insure completeness. It should be noted that some workers, e.g., maintenance, may have had significant exposures to PCB's, but are not included in the study due to exposure verification difficulties.

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For each worker the following information has been obtained: name, social security number, employee number, race, sex, date of birth, date of hire, date of termination (if applicable), and as detailed a work history as is available. For those known to have died, the date and place of death, and a copy of the death certificate are being obtained.

MORTALITY FOLLOW-UP

1. All active employees, and retirees who are currently receiving pension checks will be assumed to be alive as of December 31, 1977.

2. All persons known to have died on or after January 1, 1978, will be assumed to be alive for the purposes of this study.

3. Personnel folders and pension files will be searched for death certificates or for pertinent information about the decedent if no death certificate is present.

4. The names of persons for which there is no information on vital status will be reviewed with plant personnel for any information which they can provide.

5. Other follow-up procedures, such as Veteran's Administration files, Polk Directories searches, telephone directories searches, and state driver's license files will be used, if necessary, to determine the vital status of lost-to-follow-ups.
6. A state death certificate will be obtained for every person known to have died.
7. An experienced, trained nosologist will review and code all death certificates for the underlying cause of death to the International Classification of Diseases, Seventh Revision.

ANALYSIS

The data will be analyzed using the modified life-table method. In this method of analysis, the age, race, cause, time-specific mortality rates in a standard population are applied to person-years classified by age, race, and time-specific subgroups of the worker population at risk (i.e. exposed) over the years of observation intervals. A standard mortality ratio will be calculated as the ratio of the sum of the observed deaths to the sum of the expected deaths x100.

The person-years of observation will be calculated by year of observation and age at observation as shown in Appendix A. Person-years of observation will be accumulated from date of first exposure to PCB's to the earliest of the following events: 1) date of death, 2) December 31, 1977, the cut-off ascertainment date, or 3) date at which the study member was lost-to-follow-up.

The expected number of deaths will be calculated using United States annual mortality rates, or county rates, if available, for every year from 1945-1977. If annual county mortality data is unavailable, the 1950-69 expected numbers of cancer deaths based on U.S. rates will be adjusted by cause for the local county death rates according to the ratio of the local county rate to the U.S. rate using U.S. Cancer Mortality by County: 1950-69. A standard mortality ratio will be calculated for certain selected causes of death (Appendix B).

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APPENDIX A

PERSON-YEARS OF OBSERVATION BY YEAR OF OBSERVATION AND AGE

AGE	1945-49	1950-54	1955-59	1960-64	1965-69	1970-74
15-24						
25-34						
35-44						
45-54						
55-64						
65-74						
75-84						
85 +						

APPENDIX B

Krummrich PCB Study

Cause of Death with I.C.D. Number (Seventh Revision)	Observed	Expected	P.M.R.
Malignant neoplasms (140-205)			
Buccal Cavity and Pharynx (140-148)			
Digestive Organs and Peritoneum (150-156A, 157-159)			
Biliary Passages and Liver (155-156A)			
Other Parts of Digestive System (Residual)			
Respiratory System (160-164)			
Bronchus, Lung, and Trachea (162-163)			
Other Parts of Respiratory System (Residual)			
Genito-Urinary System (177-181)			
Leukemia and Aleukemia (204)			
Lymphosarcoma and Other Neoplasms of Lymphatic and Hematopoietic Tissues (200-203, 205)			
All Other Neoplasms (Residual)			
Diseases of the Cardiovascular System (330-334, 400-468)			
Diseases of the Respiratory System (470-527)			
Diseases of the Digestive System (530-587)			
All Other Diseases (Residual)			
All External Causes (E800-E998)			

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