April 27, 1976

REPORT ON PAULSBORO, N.J.

MOBIL OIL PLANT STUDY

Department of Community Medicine

University of Pennsylvania

School of Medicine

Anita K. Bahn, M.D., Sc.D.
Professor of Community Medicine
(Epidemiology)*

* Assisted by I. Rosenwaike, M.A.; N. Hermann, Ph.D.; P. Grover, Ph.D.; J. Stellman, Ph.D., University of Pennsylvania - Fox Chase Cancer Center.

MONS 212748

OUTLINE OF REPORT

INTRODUCTION

Resume of Literature

METHODOLOGY

I. Data for the Research and Development Employees

II. Data for the Refinery Employees

FINDINGS

DISCUSSION OF FINDINGS AND LIMITATIONS OF THE DATA

RECOMMENDATIONS

TABLES

APPENDIX: LITERATURE REVIEW

MONS 212749

INTRODUCTION

In the Fall of 1975, the Medical Director and the management at Mobil oil became aware of possible health hazards due to exposure to polychlorinated biphenyls (PCBs) among two small groups of employees at their Paulsboro, New Jersey plant. Although PCB has not been in use for some time, the possibility exists that late effects such as cancer or liver disease could result from such exposure. The latter has been noted in experimental animals.

A thorough examination of available medical records was promptly made by Dr. J. Rodney Meredith, Medical Director of the plant. These records were supplemented with other sources of information with regard to exposure to PCB.

The report that follows is a preliminary epidemiologic analysis of the data furnished to us by Dr. Meredith. Suggestions for further epidemiological studies are also included in this report.

Resume of Literature

A detailed literature review has been included as an appendix. A brief summary is presented here.

Polychlorinated biphenyls (PCBs) describe a group of synthetic chlorinated organic compounds which have been manufactured in the U.S. since 1929 and have been widely used in industry. Commercial PCBs are generally mixtures of many different chlorinated biphenyls. Arochlor 1254, a trademark of the Monsanto Co., is a mixture of chlorinated biphenyls and contains 54% chlorine.

PCBs are not easily metabolized and tend to accumulate in human tissue. Polychlorinated biphenyls were found in measurable amounts in 31.1% of 637 samples of human adipose tissue collected from the general population in 38 U.S. cities.

It has been reported that workers engaged in the manufacture of arochlor were affected with acne-like condition on the face and neck and that fumes may penetrate the clothes and cause acne-like lesions to develop on the covered parts of the body.

In an outbreak of poisoning in Japan due to ingestion of rice bran oil which had been contaminated by PCB (Kanechlor 400) common symptoms included: pigmentation of the skin, acne-form eruptions and follicular accentuation, increased eye discharge and swelling of upper eyelids, and feeling of weakness. A dose-response relation was observed. Children born to mothers who had eaten the contaminated rice were smaller than average and had discolored skin, although as the children grew older the stained skin gradually faded.

Rats fed Arochlor showed more liver abnormalities including hepatocellular carcinomas than did control rats. No unusual features were noted in tumors of other organs, and there were no apparent differences in incidence in tumors between experimental and control animals.

The results of applying a mixture of isomers of chlorinated biphenyls to the skin of guinea pigs, rats and rabbits were: (1) changes of the liver among guinea pigs (2) liver and skin changes among rats and rabbits.

Reproductive failure has been noted in monkeys exposed to PCB.

METHODOLOGY

I. Data for the Research and Development Employees

A. Study group and exposure

Sixty-four Research and Development employees are reported to have been exposed to Arochlor 1254 in the interval between 1949 and 1957. Of the 64 men, 35 are still employed by Mobil; 29, including 3 deceased employees, are no longer employed (Table A). For 16 of the 29 not currently employed, medical information is missing on an average for only the last two to three years (Table B); therefore, these men are included in the analysis. For the remaining 13 men there is no Mobil medical record or follow-up information for the past 12 years or more; therefore, these 13 are excluded from this analysis.

Based on exposure data estimated by an employee, Bob Wilson, the 51 men included in the analysis were divided into two groups: (a) exposed to contact with forming oil, and (b) other ("probable", "unlikely", "unknown") exposure. Another observer, Ed Rosinski, developed a scale attempting to quantitate exposure. A summary of the total group (64) and the observed group (51) cross-classified on the two ratings (Wilson and Rosinski) is shown in Table C. It should be noted that the 13 persons excluded from the analysis are about evenly divided between the (a) and (b) exposure groups (7 and 6 respectively).

B. Observation period

R & D employees were exposed to PCB for various times during the years 1949-1957. The exact dates of exposure were not indicated in the material we used. For this analysis, therefore, observation time was assumed to be December 31, 1957 through December 31, 1975. This procedure understates the observation period (if the average beginning point is assumed to be midway between 1949 and 1957, i.e., 1953) but at the same time allows for an average minimum cancer induction period of about four years.

Information on age was available for all 51 employees. Person-years of observation by age category were constructed for the 51 employees for the 18-year interval between 1957 and 1975. (It was assumed that age reported for current employees is as of 12/31/75).

c. Expected number of new cancers

Expected incidence of cancer among the group under study during the period 1957-1975 was based on the Third National Cancer Survey Incidence Data (NCI Monograph 41, March 1975) which reports incidence rates by sex, race, and five year age groups for 1969-1971. Our expected values were based on rates for males (all races)*, by age, but are rough, for the following reasons:

(1) Incidence rates for males have tended to increase over time so the levels in 1969-71 may be slightly higher than that expected during the 1957-75 period. However, our use of the 1969-71 higher expected rates would tend to reduce any difference between observed and expected cancers.

(2) On the other hand, age-specific cancer mortality in New Jersey (as measured for the period 1950-69) was considerably higher than the national average; hence the expected levels in this New Jersey population probably should be higher than the national incidence level. The use of U.S. rates rather than New Jersey rates would tend to increase any difference between observed and expected. However, the New Jersey rates are believed to be a reflection of

---

* In calculating expected incidence of cancer the rates used were those for the "total" (white and black) population because (1) the exact racial distribution of the study population was not immediately available. An informed guess is that 0-1 of the 64 Research and Development employees and 2-3 of the 65 refinery employees were black; (2) the "total" population of the U.S. is 90% white. (All the carcinomas were found in white employees).

occupational-environmental factors and therefore the New Jersey population is a less desirable control group than the total U.S. population.

The expected cancer rates were applied separately to exposure classes (a) and (b) yielding the expected numbers of cancers shown in Table E.

II. Data for The Refinery Plant Employees

A. Study group and exposure

Sixty-five employees at the Bead Plant in Paulsboro are reported as exposed to Arochlor 1254 for varying lengths of time during the interval between October 1953 and June 1958. With the exception of one individual listed as exposed for one month, all exposures were from 6 to 56 months.

Of these 65 "exposed" men, 30 are still Mobil employees and 35, including 3 deceased, have terminated employment (Table A). Of these 35, 11 had current medical records yielding a total of 41 men (30 plus 11) for the study population (Table D). For 12 men (all terminated by 1960) no charts were available and for another 12 men charts are available only until the date of termination in 1961 or 1962. Therefore these 24 men have been excluded from the analysis.

It should be noted that no record was provided on extent of exposure of Refinery Plant employees but only months of exposure. Therefore no classification of this group was made in the analysis.

B. Observation period

Observation time was calculated from the end of 1957 thru the end of 1975 for the 41 men included in the analysis.

C. Expected number of new cancers

Person-years of observation and expected cancers were calculated as for the R and D employees (see Table E).

FINDINGS

The following is a resume of the preliminary analysis of this data (Table E):

1. Eight cancers were observed in the total population versus 5.7 expected. This difference is not statistically significant. However, of the 8 cancers, 5 (62.5%) were either melanoma (3) or cancer of the pancreas (2). This compares with an expected percentage of about 5 percent of all cancers in the general population.
2. One melanoma occurred among the refinery employees. The remaining two melanomas and the two cancers of the pancreas occurred only among the 31 (60%) of the R & D employees who were listed as exposed to contact with Arochlor 1254. The percentages that these cancers are to all cancers found, as compared with expected percentages based on the general population, are highly significant (Table F).
3. Looking at the data for all study employees on a rate basis or risk of developing cancer (the preferred type of analysis), 3 melanomas were observed versus only 0.1 expected, and 2 cancers of the pancreas observed versus only 0.2 expected (Table E). For the R & D employees classified as "yes" to exposure to Arochlor 1254, the respective P values are highly significant (Table F).

Other findings: For the three cases of melanoma of skin the site location and age at diagnosis were as follows: right upper arm (57 years), upper lumbar region (51 years) and left anterior chest (42 years). Time from the data of first exposure to Arochlor 1254 to time of diagnosis for the three cases were: 10-14 years (calculated, exact duration not given in memo), 17 years, and 10 years, respectively.

The two employees who developed cancer of the pancreas were ages 57 and 62 at the time of diagnosis. The times since first exposure were 13 years and 24 years. Both employees were non-smokers.

Carcinoma was also found in three other sites, among two R & D employees. Cancer of recto-sigmoid was diagnosed in a group (b) 56 year old employee approximately 21 years after exposure. Another employee in group (a) developed sarcoma of the right thigh at age 42 (14 years after exposure); ten years later he also developed multiple myeloma.

DISCUSSION AND LIMITATIONS OF THE DATA

These findings, although preliminary and excluding data on over one-third of the refinery workers and one-fifth of the R & D workers, suggest a probable causal relationship between exposure to Arochlor 1254 and melanoma. Even if all of the untraced men in the "Yes" exposure group were found to have not had melanoma the P value would be virtually unchanged (P= .0015 instead of .0010).

These findings are also coherent with biology (i.e. biological) plausibility). Chloracne is known to be a frequent acute dermatitis occurring upon exposure to volatile chlorinated hydrocarbons (See literature review.) In the Japanese women who ingested contaminated rice oil, both the women and their offpsring developed skin pigmentation. Histological examination of a stillborn fetus showed a "marked hyperkeratosis... a marked increase of melanin pigments in the basal cells of epidermis" (6). It should be pointed out also that melanoma on unexposed portions of the body are relatively rare.

As in the Japanese study, a dose-response gradient may be postulated as evidence of a causal relationship. Although unverified, it is believed that the R & D group had a much higher exposure to Arochlor 1254 than did the refinery group. This is consistent with the larger number of cancers among the R & D men.

The association of Arochlor 1254 with cancer of the pancreas is also statistically significant but weaker than that with melanoma. Furthermore, the possibility of cancer of the pancreas being associated with other chemical exposures in R & D employees must be considered. Li and Fraumeni in "Cancer Mortality Among Chemists" (Journal of the National Cancer Institute, November 1969) reported an excess of deaths from cancers of the pancreas and lymphatic tissue in professional chemists.

Arochlor 1254 is no longer being used at Mobil but PCBs are still being manufactured by Monsanto, are used in a number of industrial operations and have been dumped as a waste product into water supplies.

If, as seems likely, PCB is a causative agent of melanoma, this knowledge must be acted upon promptly. In terms of surveillance for melanoma it should be noted that early diagnosis of this malignancy greatly affects survival:

Stage of Disease at Diagnosis	Relative Survival (%)*	
	5 yrs.	10 yrs.
localized	73	67
regional	33	32

Our data on a small cohort shows a very high relative risk of developing melanoma upon exposure to this PCB. This study should be replicated in other industrial settings where other persons have been exposed to PCBs. The Japanese exposed to this agent in 1968 developed skin pigmentation (as did their offspring) and chloracne. Probably an insufficient time has elapsed for cancer to develop in the Japanese cohorts but surveillance for melanoma is essential.

Survival from cancer of the pancreas is less likely to be affected by early detection. Nevertheless, persons at high risk should be identified:

Stage of Disease at diagnosis	Relative Survival (%)*	
	3 yrs.	5 yrs.
Localized	7	4
Regional	2	2

* Source: End Results in Cancer, Report No. 4, NIH, 1972. These are relative survival rates, which adjust for "normal" mortality with respect to age and period of observation.

As stated, exposure to other chemicals may be implicated in cancer of the pancreas in particular.

Possibly other cancers may also be associated with PCB. Subsequent medical history of Paulsboro retired employees would be important in this regard, also. Data for a larger employee population probably would be necessary for assessing the risk of other cancers, however.

The major limitations of the data in our analysis should be mentioned:

1. Data on duration, age, and extent of exposure are limited. Also, no information is available on other chemical exposures.
2. No information is available on the occurrence of cancer in 37, or one fourth of all the employees in both groups. One or two missed diagnosed cancer cases of melanoma, pancreas, or other site could markedly affect conclusions.
3. The number of observed cancers among men included in the analysis may well be understated because there is no reported follow-up (other than death) for those study employees who were terminated. This includes for R & D employees three living employees terminated five to ten years ago and one 11 years ago. All are presently 69 years of age or older and therefore are in a high risk group for cancer in general. Similarly among the refinery employees information is lacking on several years of follow-up of recently retired employees. In effect, the methodology employed for all of these employees assumes that no cancers developed among them during this period.

4. Another major limitation is the relatively short observation period. Induction of cancer due to small doses of this agent may require more than 20 years to manifest itself. Current information indicates that for environmentally induced cancers in adults, in general, the average latency period between first exposure and disease is in the range of 10-30 years.

5. Our methodology (observation period beginning in 1958) understates the risk of cancer if there is a long latent period. For example, if the minimum latent period is ten years the entry period for the individual workers into the study cohort should begin at varying times between 1959 and 1967 (or 1968) rather than in 1958.

RECOMMENDATIONS

1. We urgently recommend that steps be taken immediately to insure prompt and periodic screening examinations for melanoma among all currently employed and terminated employees (both R & D and refinery) for whom there has been any possible exposure to PCB; i.e., all survivors of the potential total of 129 men exposed. We also urge prompt development and distribution of appropriate informational material for these employees. These recommendations are based upon (1) the data made available to us and our analyses (under the assumptions of our statistical models) which show a highly significant statistical association between "exposure" to Arochlor 1254 and subsequent incidence of melanoma (2) the biologically plausible relationship between Arochlor 1254 and melanoma in view of the frequency of reported chloracne dermatitis upon exposure to this agent and the Japanese study. Some evidence for a dose-response relationship is also present.

2. From an epidemiologic standpoint it is also of high priority to follow-up the 37 men (former R & D and refinery employees) for whom current records are not available to determine if they have had any cancers, whether or not currently alive. The follow-up could be in the form of a general health questionnaire by mail, telephone, or personal interview. Similar information should be obtained for 23 terminated employees who were included in the study but whose medical status for the last several years is unknown.

3. The above recommendation addresses the problem of "missed cancers". In addition the epidemiologic study needs sharpening up with respect to exposure data (who were exposed; dates and intensity of exposure-some of this information is already available in Dr. Meredith's records)

so that the appropriate classification of the employees by these parameters can be made. Also, this information will assist in better quantification of the dose-response relationship.

Therefore, we need to conduct a thorough epidemiologic study by obtaining exposure and other data via a questionnaire administered to all of the 64 R & D employees and 65 refinery employees (or the next of kin, if dead)*. Such query would include also history of cancer of any site (including squamous or basal cell carcinoma which might not be known to medical records), chloracne dermatitis, liver disease, and other significant medical conditions requiring hospitalization; smoking history; family history of cancer; fair skin color; exposure to other chemicals.

For this epidemiological study, in addition to the use of "internal" controls (the subgroup with minimal or zero exposure), it would be desirable to have another control group such as a sample of other R & D or refinery workers and/or of other types of workers. This procedure would have the additional advantage of "blinding" the real purpose of the study which if known might introduce bias in employee responses regarding intensity of PCB exposure.

5. To detect other possible cancers which may emerge, conduct in the near future, and periodically, health screening examinations of all exposed survivors (including retirees) for other skin cancers, other malignancies, and hepatic disease. A modified CANSCREEN questionnaire and CANSCREEN examination might achieve this and other stated objectives.

---

* Information on exposure should be obtained not only by the employees reporting for themselves but also by requesting them to indicate who else among the cohort may have been exposed, and the

6. If indicated perform fat biopsies for PCB as one indication of extent of exposure.

7. If possible we would like to also study employees in other plants, such as Monsanto, where a larger number of employees may have been exposed to PCB.

8. Study MRDC employees on hydraulic fluid program.

TABLE A

Employees by present status and by area of work:

Area of Work	Total	Living			Dead
		At Paulsboro	At other plants	Terminated	
R & D	64	32	3	26	3(2)
Refinery	65	28	2	32	3
	129	60	5	58	6

NOTE: Cancer deaths in parenthesis.

Table B

Medical Record Status of 64 Research & Development Employees

		Medical Records Available
	35	Current Employees
16	2	Died while employed
	14	Terminated at ages 57 to 65 - presumably retirement*
	51	Persons included in the analysis
		No Medical Records
	13	Terminated or transferred 1962 or earlier: excluded from the analysis.
	64	TOTAL

* The earliest retirement was 1964; the second earliest was 1969. Half of the retired left in 1973 or later.

Table C

Rating on Exposure to Arochlor 1254 of 64 Research and Development Employees

Rosinski Rating	Total	Wilson Rating (a) Yes	(b) Other (Probable, Unlikely, Unknown)
	64	38	26
Low to High	29	26	3
Slight	12	4	8
Negligible, questionable	10	6	4
No recollection	2	1	1
Zero	11	1	10

Rating on Exposure to Arochlor 1254 of 51 Research and Development Employees included in this study (Excludes 13 no-records available employees)

Rosinski Rating	Total	Wilson Rating (a) Yes	(b) Other (Probable, Unlikely, Unknown)
	51	31	20
Low to High	26	24	2
Slight	8	2	6
Negligible, questionable	9	5	4
No recollection	-	-	-
Zero	8	-	8

○ approximate concordance of ratings

Table D

Medical Record Status of 65 Refinery Employees

	Current Medical Records Available
30	Current Employees
2	Died either while employed or within a year after
9	Terminated in 1967 or later (6 were ages 57 to 64 - presumably retirement)-a majority left in 1971 or later.
41	Included in the analysis
	No Current Medical Records
12	No Medical Records - Terminated between 1955 and 1960.
12	Terminated in 1961-62
24	Excluded from the analysis
65	TOTAL

Table E

New Cases (Incidence) of Cancer among R & D Employees (by Exposure Class) and among Refinery Employees

Employee Group	Observed				Expected			
	All Cancer	Pancreas	Melanoma	Other	All Cancer	Pancreas	Melanoma	Other
R & D Employees								
Exposure to Arochlor 1254								
(a) "yes": 31 men (550 P.Y.)**	6	2*	2*	2	2.3	.07	.04	2.2
(b) other: 20 men (355 P.Y.)	1	-	-	1	1.2	.04	.02	1.1
Total R&D: 51 men (905 P.Y.)	7	2	2	3	3.5	0.1	0.05	3.3
Bead Plant 41 men (728 P.Y.)	1	-	1	-	2.2	0.1	0.05	2.1
TOTAL, Both Groups	8	2	3	3	5.7	0.2	0.1	5.4

* See Table F for levels of statistical significance

**P.Y. = Person-Years

MONS 212771

Table F

Levels of Statistical Significance among group (a) (Yes) R & D employees

	P Values	
	Observed number versus expected number	As a percentage of all cancers observed compared to expected percentages
*Pancreas	.0025	.0164
*Melanoma	.0010	.007

Assumes (1) that the data fit the Poisson distribution and (2) that there is independence of observations from year to year (this is not necessarily true of Person-year observations).

These P values are not based on tests of prior hypotheses but tests conducted after observation of the data.