Mortality of Workers Employed in the Manufacture of Chlordane and Heptachlor

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A retrospective mortality study has been carried out on workers employed in the manufacture of chlordane and heptachlor between 1946 and 1976. The study group was comprised of 1403 white males who worked for more than three months at either of the two plants in the United States now producing these compounds. Information on deaths among terminated employees was obtained from the Social Security Administration and supplemented by information collected by another investigator by individual follow-up. There were 113 deaths observed in the group, compared to 157 expected, giving a standardized mortality ratio (SMR) of 72. There was no overall excess of deaths from cancer, even among workers followed twenty or more years after entry into the occupation. There was one death from liver cancer. An excess of deaths from lung cancer (12 observed, 9.0 expected) was not statistically significant and was not distributed by duration of exposure or of latency in any pattern suggesting an etiologic role for chlordane-heptachlor exposure. Although diseases of the circulatory system as a whole showed fewer deaths than expected (SMR 83), there was a statistically significant excess of deaths from cerebrovascular disease (17 observed, 9.3 expected). This excess was not related to duration of exposure or latency and occurred exclusively after termination of employment.

Chlordane and heptachlor are chlorinated hydrocarbons which were widely used as agricultural and domestic pesticides until 1975, when the Environmental Protection Agency suspended their use for all but subterranean termite control and certain other limited applications. A complete ban for agricultural use is now being phased in.

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Central to the suspension proceedings and to the ban subsequently negotiated was concern that these compounds might be carcinogenic to man. The evidence is controversial and derives entirely from long-term feeding studies in laboratory animals. There are a few cross-sectional clinical studies of heavily exposed humans but essentially no data on long-term mortality associated with chronic or heavy exposure in man. A study of the mortality of workers engaged in the manufacture of these pesticides at the only two plants currently engaged in their production in the United States is reported here. While current levels of exposure are reasonably well characterized, the total exposure experienced by workers in these plants in the past cannot be reconstructed. However, it is very likely that a substantial proportion of workers has been exposed to levels well above those prevailing in the general population.

The study was undertaken at the invitation of the Velsicol Chemical Corporation which owns and operates the two plants.

Materials and Methods

Velsicol Chemical Corporation began producing chlordane in its plant at Marshall, Illinois, in 1946 and heptachlor and endrin in the plant at Memphis, Tennessee, in 1952. Personnel records are available for all of the 951 employees at Marshall and the 1425 employees at Memphis who had ever worked in these plants before the spring of 1976, when this study was initiated. After exclusion of females, males who worked for three months or less, and persons with inadequate identifying information, there remained 1403 eligible subjects. No information on race was available but all the deaths identified in the course of the study were of whites. Among the 973 employees excluded, approximately 7% were excluded because they were female, 64% because they worked for three months or less and 29% because of missing information.

Identifying information was submitted to the Social Security Administration (SSA) which provided, for those workers known dead, information on date of death and

Table 1. — Distribution of Study Subjects by Duration of Follow-up and by Plant.

Duration of Follow-up	Marshall	Memphis	Total No.	Total %
<10	129	352	481	34 3
10-19	99	324	422'	30 1
20-29	193	159	351'	250
30+	149	—	149	106
Total	570	835	1403	100 0

'Includes one subject who worked in both plants

the state in which the beneficiary filed a claim for benefits. A Social Security Administration search of its records identified 104 deaths in the study cohort through the end of 1975, for which death certificates were sought from the states and registration areas.

Contemporaneously, Dr. Sidney Shindell of the Medical College of Wisconsin had been conducting individual follow-up of terminated workers in these plants. He informed us of nine deaths in our cohort which had not been identified by SSA, four of which occurred in 1976 after the termination of the SSA search. These have been added to the known deaths and the closing dates of Dr. Shindell's follow-up — June 30, 1976, for Marshall employees and December 31,1976, for Memphis employees — were used as the termination dates for computing person-years of observation. Dr. Shindell also provided copies of some death certificates which had not been obtained by the authors. There remain two deaths for which certificates could not be found.

The distribution of deaths by cause was based on death certificate causes coded by one of the authors (HHW) to the 8th Revision of the International Classification of Diseases Adapted.[1] Expected numbers of deaths by cause were estimated using a computer program developed by Monson.[2] The program applies national mortality rates specific for sex, race and age and calendar time in five year groups to the comparable person-years accumulated during the period of observation. Since the publication of the reference cited, the program has been updated to use national mortality rates through 1975. The rates for white males were used for this analysis. For the computation of person-years, the beginning date was taken to be January 1, 1946, for Marshall and January1,1952, for Memphis if the employee was eligible on those dates, or at the end of three months employment if he was first employed later. Standardized mortality ratios (SMR) were estimated by dividing the observed deaths by the expected and multiplying by 100 An iterative method based on mid-p values' was used to compute 95% confidence intervals.

An attempt was made to examine the relationship between the intensity of exposure and mortality experience among these workers However, a complete occupational history was not available for each individual Moreover, serum pesticide levels of workers actively employed in the plants in 1975 and 1976' did not correlate with a classification of presumed exposure level based on job category Therefore, analyses according to presumed level of exposure are not presented.

Results

The distribution of the study group by plant and by duration of follow-up is given in Table 1. Table 2 gives observed and expected numbers of deaths by cause and estimates of the SMRs. The overall SMR is lower than 100

Table 2. — Observed and Expected Deaths from Selected Causes.

Cause of Death	Observed	Expected	SMR*	C.I. of SMR†
All causes	113	157 4	72	59 - 86
Malignant neoplasms	24	29 3	82	54 - 120
Digestive organs and peritoneum	7	a 2	86	38 - 170
Lung	12	9 0	134	73 - 228
Lymphatic and hematopoielic	1	3 3	30	2 - 151
Other	4	a a	45	14 - 109
Diseases of circulatory system	63	75 a	a3	64 - 106
schemic heart disease	37	53 9	69	49 - 94
Cerebrovascular disease	17	9 3	1a3	110 - 287
Other	9	12 6	71	35 - 131
Diseases of respiratory system	3	a l	37	9 - 101
Diseases of digestive system	4	a 5	47	15 - 114
External causes	14	22 a	61	35 - 101
All other causes	5‡	13 1	38	14 - a5

*SMR = Observed/Expected x 100 (computed from values expressed to two decimal places)
†95% exact confidence intervals computed by iteration based on mid-p values'
‡Including two with missing death certificates

Table 3. — Observed and Expected Deaths from Selected Causes According to Plant.

Cause of Oeath	Marshall Observed	Marshall Expected	Marshall SMR	Memphis Observed	Memphis Expected	Memphis SMR
All causes	76	107 1	71	37	50.1	74
Malignant neoplasms	13	20 1	65	11	9 1	121
Cancer of digestive organs and peritoneum	5	5 9	a5	2	2 3	88
Cancer of lung	7	6 1	115	5	2 9	174
Ischemic heart disease	26	38 1	68	11	15 6	70
Cerebrovascular disease	11	7 0	158	6	2 3	260
External causes	9	12 3	73	5	10 4	48

Table 4. — Observed/Expected Deaths from Lung Cancer According to Age at Observation and Age at Entry into Occupation.

Age at Observation	Age at Entry into Occupation <35	35-49	50+	Total
<50	5/1.2	1/0.5	—	6/1.7
50-64	2/1.4	1/2.8	0/0.4	3/4.7
65+	—	0/1.6	3/1.0	3/2.6
Total	7/2.6	2/4.9	3/1.4	12/9.0

Table 6. — Observed/Expected Deaths from Cerebrovascular Disease According to Age at Observation and Age at Entry into Occupation.

Age at Observation	Age at Entry into Occupation <35	35-49	50+	Total
<50	2/1 1	1/0 4	—	3/1 5
50-64	0/0.7	3/20	2/05	5/33
65+	—	3/18	6/27	9/4 5
Total	2/1 8	7/4 3	8/3 2	17/9 3

and significantly so, since its confidence interval does not include 100 However, the value (72) is typical of that observed in an employed population This deficit of observed deaths relative to expected seen in working populations is generally attributed to the selective factors associated with employment

Observed deaths from cancer are also fewer than expected, but not significantly so Only one type of cancer — cancer of the lung — shows more observed deaths than expected, but again the difference is not statistically significant There was one death attributed to carcinoma of the liver This occurred in a man who worked for the company for five years, beginning in 1944 when he was 68 years old, and who died in 1958, at the age of 81, of "carcinoma of the liver -- The carcinoma was not specified as primary but was so coded by us The expected number of deaths from cancer of the liver and biliary tract (ICD8 #155, 156) was 059 There was one death each from cancer of the bladder, the prostate and the central nervous system, and one with primary site unspecified

While diseases of the circulatory system as a whole account for fewer deaths than expected, there is a substantial and statistically significant excess of deaths due to cerebrovascular disease No other causes of death are in excess.

Table 3 gives similar data separately for the two plants The features outlined above are present in both sets of data

Table 4 shows observed and expected lung cancer deaths according to age at entry into occupation and age at observation Almost the entire lung cancer excess occurs among workers who were aged less than 35 at entry into occupation and less than 50 at observation In this particular category the difference between observed and expected is statistically significant ($p < 0.01$) Because of small numbers in the individual cells of this table it is not possible to tell whether the excess is a function of young age at entry, young age at observation, or both Relationships to duration of follow-up ("latency") and duration of employment are explored in Table 5 Again numbers are small but there is no pattern suggesting a real relationship with either variable For both variables the excess appears in the subgroup with intermediate durations. It is noteworthy that in the person-years with 20 or more years of latency there is a statistically significant deficiency of lung cancer deaths. The lack of any clear pattern in this table casts doubt on the meaningfulness of the relationship seen in Table 4.

Similar analyses of deaths from cerebrovascular disease are given in Tables 6 and 7. Within the variability inherent in the small numbers in these tables the excess appears to be distributed more or less evenly throughout and there is no clear relationship with any of the four variables. Although 3.2 deaths from cerebrovascular disease would have been expected among currently employed workers, there were none. Six deaths from this cause occurred within five years after termination; four occurred 5-9 years after termination; and seven, 10 or more years after termination. The expected values for the latter three periods were 1.7, 1.5 and 2.9.

The effects of worker selection are explored for deaths from two principal causes and from all causes in Table 8. All three categories show substantial deficits of observed deaths in the first 10 years of the follow-up period. For deaths from malignant disease, the effects of the selective factors which are presumed to be responsible for these deficits seem to have disappeared by 10 years after the beginning of the follow-up For deaths from ischemic heart disease and for all deaths, the deficits persist throughout all three categories of duration of follow-up, though not so markedly as in the first ten years.

Discussion

To the authors' knowledge this is the only published study of causespecific mortality among workers occupationally exposed to chlordane or heptachlor and there are, therefore, no other data with which these can be compared directly

The impetus to the study was a search for evidence of carcinogenicity of these compounds to man None has been found, although the study population is too small and the period of follow-up too short to translate this into a statement that there is no excess risk of cancer associated with exposure in man There was no excess of

Table 5. — Observed/Expected Deaths from Lung Cancer According to Duration of Employment and Duration of Follow-up.

Duration of Employment	Duration of Follow-up <10	10-19	20+	Total
<10	3/1.5	211.3	0/1 4	5/4.3
10-19	—	612 1	0/0.8	6/2.9
20+	—	—	111 8	1/18
Total	311.5	013.4	1/4.0	12/9.0

Tabb 7. — Observed/Expected Deaths from Cerebrovascular Disease According to Duration of Employment and Duration of Follow-up.

Duration of Employment	Duration of Follow-up <10	10-19	20+	Total
<10	3/2.0	311 4	3/1 3	914.7
10-19	—	212.1	611.3	813.4
20+	—	—	011.3	0/1.3
Total	3/2.0	5/3 5	9/3 9	17193

Table 8. — Observed/Expected Deaths from Selected Causes According to Duration of Follow-up.

Cause of Death	Duration of Follow-up <10	10-19	20+	Total
All causes	21/44.4	45/58.4	47/54.7	113/157.5
Malignant neoplasms	3/ 6.6	14/ 11.0	7/11.6	24/ 29.2
Ischemic heart disease	4/10.8	16/21.3	17/21.8	37/ 53.8

deaths from cancer compared to the number expected, even among persons followed 20 and more years after first employment. There was only one death from liver cancer — the tumor associated with chlordane exposure in mice.'

The only tumor in excess in these data is cancer of the lung. For this tumor the excess is not statistically significant and does not follow any pattern of association with duration of exposure or latency that suggests an etiologic relationship between occupational exposure and lung cancer. The fact that there are no data on cigarette smoking in this study group is further reason for caution in interpreting the observations on lung cancer.

A surprising observation is the statistically significant excess of deaths from cerebrovascular disease. This appears not to have been observed or suspected previously and should be confirmed in other data or further follow-up of these workers before it is accepted as evidence of a consequence of exposure to chlordane or heptachlor. There is, however, some equivocal evidence of increased blood pressure among pesticide workers. Thus, no increase in blood pressure was reported in three surveys of workers specifically exposed to chlordane.'[7,8] In one of these surveys two cases of hypertension were found among 24 workers but there was no control group and the finding was considered incidental.' Increased systolic and diastolic pressures have been reported among workers with mixed pesticide exposures[9,10] but lack of increase has also been reported." Hypertension was reported in two studies of workers exposed to DDT, another chlorinated hydrocarbon, but in the absence of a comparison group in either study the findings are difficult to interpret.'*[11] Obviously, research in this area is in an unsatisfactory state. The relationship of pesticide exposure to blood pressure and to cerebrovascular disease deserves more investigation.

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Warning on Intubation

Passing a nasogastric tube is such a common everyday task in medicine that physicians rarely stop to think that such an innocuous-looking catheter is a potentially lethal instrument. But indeed it is. There have been at least five reports in the last few years of catheters that went directly into the brain rather than into the stomach. What's more, the tubes went in so easily the clinicians passing them thought they were going right where they should.

. . . And all the reports in which the patients died — there were four deaths — had several things in common: massive frontal-impact injuries with nasal bleeding; blind insertion of a nasogastric tube through the nose; returns resembling gastric contents when the position of the tube was checked by aspiration; deterioration of neurologic status after intubation; discovery of the tube position on skull x-ray; and cribriform plate fractures noted at autopsy.

— From "When NC lubes Go To The Head." in *Emergency Medicine*, July 15, 1979