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Mortality study of workers employed at organochlorine pesticide manufacturing plants

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DITRAGLIA D, BROWN DP, NAMEKATA T, IVERSON N. Mortality study of workers employed at organochlorine pesticide manufacturing plants. *Scand j work environ health* 7 (1981): suppl 4, 140—146. A retrospective cohort study was conducted to examine the mortality of workers employed in the manufacture of the chlorinated hydrocarbon pesticides, chlordane, heptachlor, dichloro-diphenyl-trichloro-ethane (DDT) and aldrin/dieldrin/endrin. Four manufacturing plants were selected for study, and each cohort included all workers employed for at least six months prior to January 1964. The entire study group totaled approximately 2,100 individuals. Vital status ascertainment for these cohorts ranged from 90 to 97 % complete; the cut-off date for follow-up was 31 December 1976. In general there were too few deaths in this study on which to draw any meaningful conclusions. The standardized mortality ratio (SMR) for all causes in each cohort was below the expected level (100) and ranged from 66 to 82, probably a reflection of the "healthy worker effect." For "all malignant neoplasms" the SMRs ranged from 68 to 91 and for respiratory cancer from 55 to 132. In the aldrin/dieldrin/endrin cohort observed deaths due to pneumonia and "other respiratory diseases" were significantly above the expected number of deaths. For several other specific cancer sites (stomach in plant 1, esophogus, rectum, liver and lymphatic/hematopoietic system in plant 3), the observed deaths were more than the expected number and should be examined in more detail. It is recommended that these cohorts be followed for several more years and the mortality patterns be reexamined.

Key terms: aldrin, cancer, chlordane, dichloro-diphenyl-trichloro-ethane (DDT), dieldrin, endrin, epidemiology, heptachlor.

The organochlorine (OC) pesticides such as dichloro-diphenyl-trichloro-ethane (DDT), aldrin, dieldrin, lindane, chlordane, heptachlor, toxaphene, and mirex have been an important class of compounds in terms of production volume and use. Due to the widespread use of these pesticides during the past 30 a, there has been an opportunity for the potential exposure of workers who manufacture, formulate, and apply these compounds, and ultimately to those in the general population through ingestion of contaminated food and general environmental pollution.

There has been a great deal of concern about the long-term, latent health effects of exposure to OC pesticides. These chemicals have a tendency to penetrate cell membranes and to be stored in body fat (14). Some of these chemicals have been shown to be toxic to the liver and kidney in exposed humans (9, 10) and benign and malignant tumors have been induced in the liver of experimental animals chronically exposed to several of the OC compounds (1, 5, 7, 8, 11, 15). There are also reports of effects on the hematopoietic system of individuals exposed to chlordane (4), DDT (13), dieldrin (13), and lindane (3, 12, 17).

In order to determine whether or not exposure to certain OC pesticides is as-

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sociated with an increased risk of mortality due to chronic diseases, a retrospective cohort mortality study was initiated by the National Institute for Occupational Safety and Health (NIOSH) and carried out under contract by the University of Illinois, School of Public Health.

The original intent of this study was to examine the mortality of workers employed in OC pesticide formulating plants. However, after visits had been made to numerous formulating plants around the country, it was determined that this part of the pesticide industry was not suitable for an epidemiologic study. The formulating plants are usually small operations, where work is seasonal, the turnover rate is high, exposures are multiple, and the records needed to conduct an epidemiologic study are generally unavailable. Therefore, the emphasis of the study was shifted to OC pesticide manufacturing plants. These plants offered a more suitable population for the investigation. However, the exposures at these plants are probably lower than at formulating plants, and they also include the chemical precursors of the final technical grade pesticide.

An attempt was made to include OC pesticide manufacturing plants which began operation in the United States at least 25—30 a ago, which had relatively large work forces, and which had records available to identify a study cohort. A list of the major OC pesticide manufacturing plants was assembled from sources such as the Farm Chemical Handbook, trade commission reports, and the US Environmental Protection Agency. Based on accumulated information, a number of potential facilities were contacted and walk through surveys were conducted before the final selection into the study.

Four facilities were eventually chosen for the study. Table 1 gives a description of the four plants. Plant 1 was located in Illinois and had manufactured chlordane since 1946. Plant 2, located in Tennessee, had produced heptachlor since 1951. Also, in 1953, endrin was manufactured in a pilot operation at this plant, and by 1955 full-scale commercial production of endrin had begun. Other products which had been manufactured at plant 2 included hydrogen gas, chlorine, and chlorendic anhydride. Plant 3, located in Colorado, had manufactured a variety of pesticides. In 1946 production of aldrin and dieldrin began and continued until the 1970s. Endrin production began in 1953 and continued until 1965. In 1955 this plant started manufacturing an organobromine pesticide, and in 1956 the production of organophosphates was started. Plant 4 was located in California, and DDT had been its sole product since 1947.

Methods

The study population consisted of four separate cohorts representing the four pesticide plants. The cohorts were defined as all workers at each plant who

Table 1. Description of plants included in the study of organochlorine (OC) pesticide manufacturers.

	Plant 1	Plant 2	Plant 3	Plant 4
Date began OC pesticide production	1946	1951	1946	1947
OC pesticides produced	Chlordane	Heptachlor, endrin	Aldrin, dieldrin, endrin	Dichloro-diphenyl-trichloroethane (DDT)
Other pesticides produced	None	None	Organobromines, organophosphates	None
Other chemicals at plant	Chlorine, dicyclopentadiene	Chlorine, chlorendic anhydride, hexachlorocyclopentadiene, vinyl chloride	Numerous precursors	Tri-chloroacetaldehyde, sulfuric acid, monochlorobenzene
Location	Illinois	Tennessee	Colorado	California

had achieved at least six months' employment prior to 31 December 1964. This cutoff date was selected to allow for an accrual of sufficient time from the date of initial employment (latency) for manifestation of disease.

An effort was made to determine the vital status (alive or deceased) of each member of the study cohorts as of 31 December 1976. Vital status was ascertained through records maintained by federal and state agencies, including the Social Security Administration and state motor vehicle offices. For those individuals whose vital status could not be determined through these sources, the US Postal Mail Correction Services was consulted, and other follow-up searches were used. For all those known to be deceased, death certificates were obtained and causes of death were coded by a nosologist according to the International Classification of Disease, Adapted (ICDA) in effect at the time of death. Those who had an unknown vital status were assumed to be alive as of 31 December 1976 so that the true risk of mortality would not be overestimated. Those who died after 31 December 1976 were considered alive for the purposes of this analysis.

In each cohort, person-years at risk of dying were accumulated for each worker starting when six months of employment were completed and ending either at the date of death or at the study end date of 31 December 1976, whichever occurred first. With the use of a modified life table analysis program similar to that described by Cutler (2), the person-years for each cohort were combined into 5-a calendar time periods and 5-a age groups and multiplied by the corresponding US white male cause-specific mortality rates to yield the expected number of deaths. Person-years were additionally distributed by 5-a exposure and 5-a latency (number of years from date first employed) categories. The observed and corresponding expected deaths were compared, and differences were tested with the Poisson distribution.

Results

The results of the vital status ascertainment and the total number of person-years for each cohort are given in table 2. Even with the efforts previously described, the vital status of 10 % of the cohorts from plants 3 and 4 was unknown.

Table 3 summarizes the observed and expected deaths by specific cause. For the category of "all causes," the standardized mortality ratios (SMR = observed deaths/expected deaths $\times$ 100) ranged from 66 to 86. Under the assumption that the record systems used to identify the cohorts were complete, these low SMRs probably reflect the healthy worker effect which has been noted in other studies of occupational groups (6), and possibly the lack of complete vital status ascertainment. Mortality due to all malignant neoplasms was also lower than expected, the SMRs ranging from 68 to 91. Other major causes of death, including diseases of the circulatory system, were also generally lower than expected. The only major category where observed deaths were significantly greater than expected was "nonmalignant respiratory system disease" at plant 3 (22 observed vs 10.4 expected; SMR = 212), specifically for pneumonia (ICDA = 490—493) (11 observed vs 4.3 expected, SMR = 255, $p < 0.01$) and for "other respiratory diseases" (ICDA = 500—527) (11 observed vs 5.2 expected deaths, SMR = 213, $p < 0.05$).

Table 4 summarizes the observed and expected deaths by specific type of cancer. As stated previously, there was a deficit in observed deaths due to "all malignant neoplasms" in each plant studied. Although there were no statistically significant excesses or deficits in mortality for any specific cancer site, there were several noteworthy ones. In plant 1 there were three observed deaths due to stomach cancer when 0.99 were expected. In plant 3 there were slight excesses of cancer of the esophagus (2 observed vs 0.85 expected), cancer of the rectum (3 observed vs 1.24 expected), liver cancer (2 observed vs 0.57 expected), and cancer of the lymphatic and hematopoietic system (6 observed vs 4.09 expected). There was a deficit for respiratory cancer (7 observed vs 12.64 expected) at plant 3.

An analysis by latency is presented in table 5 for "all malignant neoplasms." In this type of analysis, one looks for trends to examine whether or not the risk of mortality as measured by the SMR is associated with any particular latency

period. Plants 2 and 4 showed a consistent increase in the risk of cancer mortality with an increase in the latency period; however the numbers involved in this analysis were small.

Since nonmalignant respiratory disease was greater than expected at plant 3, latency was also examined for this cause of death. As shown in table 6 there was a statistically significant increase in mortality due to nonmalignant respiratory disease during the 10- to 20-a latency period (12 observed vs 4.51 expected, $p < 0.05$,) but a nonsignificant increase during the greater-than-20-a latency period (8 observed vs 3.96 expected, $0.05 < p < 0.1$).

Discussion

Plants 1 and 2 have been previously studied by Wang (16). In that study, the definition of the cohort included workers from both plants who were employed for at least three months between 1946 and 1975. Therefore, although there was an overlap in definition between that cohort and plants 1 and 2 included in the present study, the cohorts were not exactly alike. In Wang's study, there was no observed excess mortality due to specific cancer sites except for a small increase in respiratory cancer, and the only major cause of death with a significant excess was cere-

Table 2. Vital status follow-up of workers in the study of organochlorine pesticide manufacturers.

	Plant 1	Plant 2	Plant 3	Plant 4
Known to be alive	259 (79 %)	265 (87 %)	870 (75 %)	278 (79 %)
Known to be deceased	59 (18 %)	24 (8 %)	173 (15 %)	42 (11 %)
Unknown vital status	9 (3 %)	16 (5 %)	112 (10 %)	34 (10 %)
Total	327	305	1,155	354
Person-years of observation	8,354	5,672	24,939	7,601

Table 3. Cause-specific mortality according to major cause among workers in the study of organochlorine pesticide manufacturers (SMR = standardized mortality ratio).

Cause of death [a]	Plant 1		Plant 2		Plant 3		Plant 4	
	Observed	SMR [b]	Observed	SMR [b]	Observed	SMR [b]	Observed	SMR [b]
All malignant neoplasms (140—205)	11	69 (35—124)	6	91 (33—198)	31	82 (56—116)	6	68 (25—247)
Nervous system diseases (330—334)	7	116 (47—239)	1	54	9	68 (31—128)	0	—
Circulatory system disease (400—468)	28	70 (46—101)	12	78 (40—137)	69	77 * (60—97)	17	82 (48—132)
Nonmalignant respiratory system disease (470—527)	1	22	0	—	22	212 ** (133—320)	1	44
Accidents (800—962)	6	96 (35—208)	1	25	11	60 (30—107)	4	73 (20—188)
Suicide (963, 970—979)	1	47	0	—	10	167 (80—307)	0	—
All other causes	5	42 * (13—97)	4	47 (13—119)	21	71 (44—108)	14	119 (65—199)
All causes	59	68 ** (52—87)	24	66 * (42—98)	173	84 * (72—98)	42	86 (62—116)

[a] International Classification of Disease, seventh revision, numbers in parentheses.
[b] 95 % confidence limits in parentheses.
* $p < 0.05$, ** $p < 0.01$.

brovascular disease. Neither of these findings was seen in the present study — deaths from cerebrovascular disease in plants 1 and 2 combined were 8 observed vs 7.88 expected and those from respiratory cancer were 9 observed vs 7.87 expected. As noted previously, there was an increase in stomach cancer observed in plant 1; however, the small numbers involved in this study preclude any clear association.

In the plant 3 cohort there was a significant increase in deaths due to nonmalignant respiratory disease, especially among those with at least 10 a of latency. In contrast to this finding there was a deficit in deaths due to respiratory cancer. These findings need to be examined further to determine whether there is a true association between nonmalignant respiratory disease and employment at this plant or whether there has been some misclassification of cause-specific mortality.

There was no noteworthy excess of the cause-specific deaths examined in the plant 4 cohort. However, when the deaths from malignant neoplasms were examined by latency, there was an increase in risk with an increase in the length of the latency period. The numbers in this analysis were small, and this trend could have been due to chance alone.

Due to the small number of workers included in this study the statistical power does not enable one to conclude that no association exists between cause-specific mortality and employment at the study plants. The primary reason for these small numbers is due to the rapid turnover at these plants, and thus most workers who were hired left before they achieved six months of employment, especially at plant 4, where approximately 70 % of the employees worked less than six months.

Since the vital status was unknown for 10 % of the plant 3 and 4 cohorts, the risk

Table 4. Cause specific mortality according to specific cancer causes among workers in the study of organochlorine pesticide manufacturers (SMR = standardized mortality ratio).

Cause of death [a]	Plant 1		Plant 2		Plant 3		Plant 4	
	Observed	SMR [b]	Observed	SMR [b]	Observed	SMR [b]	Observed	SMR [b]
All malignant neoplasms (140—205)	11	69 (35—124)	6	91 (33—198)	31	82 (58—116)	6	68 (25—147)
Esophagus (150)	0	—	0	—	2	235 (26—850)	0	—
Stomach (151)	3	303 (61—885)	0	—	1	48	1	227
Intestine exp rectum (152, 153)	0	—	1	175	1	30	0	—
Rectum (154)	1	178	0	—	3	242 (49—707)	0	—
Liver (155, 156A)	0	—	0	—	2	225 (39—1,267)	0	—
Pancreas (157)	1	110	0	—	1	48	1	204
Respiratory system (160—164)	6	110 (40—241)	3	122 (25—358)	7	55 (22—114)	4	125 (34—321)
Bladder and urinary system (180—181)	0	—	1	666	1	91	0	—
Other and unspecified (156B, 165, 190—199)	0	—	1	114	6	125 (46—272)	0	—
Lymphatic and hematopoietic system (200—205)	0	—	0	—	6	147 (54—319)	0	—
Others	0	—	0	—	1	—	0	—

[a] International Classification of Disease, seventh revision, numbers in parentheses.
[b] 95 % confidence limits in parentheses.

Table 5. Observed and expected deaths due to malignant neoplasms (ICDA [a] = 140—205) according to latency [b] among workers in the study of organochlorine pesticide manufacturers (SMR = standardized mortality ratio).

Years since first employed	Observed	Expected	SMR	95 % confidence limits
Plant 1				
< 10	1	1.52	66	—
10—19	4	4.43	90	25—231
≥ 20	6	9.94	60	22—131
Plant 2				
< 10	0	1.46	—	
10—19	3	3.30	91	18—266
≥ 20	3	1.85	162	33—474
Plant 3				
< 10	4	7.55	53	14—136
10—19	18	16.25	111	66—175
≥ 20	9	14.00	64	29—122
Plant 4				
< 10	0	1.40	—	—
10—19	1	3.68	27	—
≥ 20	5	3.78	132	43—309

[a] ICDA = International Classification of Disease, Adapted.
[b] Latency = number of years from date first employed.

Table 6. Observed and expected deaths from nonmalignant respiratory disease (ICDA [a] = 470—527) according to latency among workers at plant 3 in the study of organochlorine pesticide manufacturers (SMR = standardized mortality ratio).

Years since first employed	Observed	Expected	SMR	95 % confidence limits
< 10	2	1.07	187	23—675
10—19	12	4.51	266 *	149—505
≥ 20	8	3.96	202	87—398

[a] ICDA = International Classification of Disease, Adapted.
* $p < 0.05$.

assessments for these two cohorts may be underestimated. This underestimation would occur if there were additional deaths within these unknown groups that should be included as observed deaths in the analysis. Secondly, it was assumed in the analysis that all those with an unknown vital status were alive as of the cut-off date. This procedure may give an overestimation of the actual number of person-years at risk which would produce an inflated number of expected deaths. Therefore, the actual number of observed deaths was probably more than those included in the analysis, while the actual number of expected deaths was probably less, and thus the reported analysis probably yields an underestimate of the actual risk.

Although this study has not identified a specific cancer risk associated with employment at certain types of OC pesticide manufacturing plants, it points to several causes (stomach cancer in plant 1; esophagus, rectum, liver and lymphatic/hematopoietic cancer in plant 3) that should be examined further. An attempt should be made to determine if there were common exposures among those who died from these causes of death. Additional analyses are also necessary to determine, if possible, whether or not the excess in

respiratory disease is associated with specific occupational exposure at plant 3. Finally, the mortality experience in each of these cohorts should be followed for several more years, and a better ascertainment of vital status made, to increase the statistical power of the analysis so that more definite conclusions can be drawn.

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