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Mortality of workers employed at organochlorine pesticide manufacturing plants — an update

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BROWN DP. Mortality of workers employed at organochlorine pesticide manufacturing plants — an update. *Scand J Work Environ Health* 1992;18:155—61. A previous mortality study among four organochlorine pesticide manufacturers was updated through 1987. The organochlorine pesticides included chlordane; heptachlor and endrin; aldrin, dieldrin and endrin; and dichlorodiphenyltrichloroethane. The mortality for all causes and all malignant neoplasms at each of the plants was lower than expected. There was a statistically significant increase in liver and biliary tract cancer among workers at plant 3 (5 observed, standardized mortality ratio 393, 95% confidence interval 1.27—9.20). These results are somewhat consistent with experimental animal findings showing benign and malignant tumors of the liver after exposure to aldrin and dieldrin. However, the deaths were due to a mixture of intra- and extrahepatic tumors, and the dose-response analysis was limited because of the small number of deaths and lack of exposure data. Additional study of this group should include continued follow-up of the total cohort and a case-referent analysis of the deaths from liver and biliary tract cancer.

Key terms: aldrin, cancer, chlordane, dichlorodiphenyltrichloroethane, dieldrin, epidemiology, heptachlor, liver cancer, organochlorine pesticides.

In a previous study, the mortality of workers employed at four organochlorine pesticide manufacturing plants was reported (1). The report concluded that additional follow-up was necessary due to the small number of deaths and the relatively short period of observation. The mortality of the workers has now been updated from 1976 through 31 December 1987, and the results are presented in this report.

The primary purpose of the study was to assess the carcinogenic risk among workers exposed to the following organochlorine pesticides: chlordane (plant 1), heptachlor and endrin (plant 2), aldrin, dieldrin, and endrin (plant 3), and dichlorodiphenyltrichloroethane (DDT) (plant 4). Dibromochloropropane (DBCP), an organobromine pesticide, was also manufactured at plant 3. According to the latest information from the Integrated Risk Information System (IRIS) of the United States (US) Environmental Protection Agency (2), all of these pesticides have been classified as probable human carcinogens except DBCP, which has not been evaluated by IRIS, and endrin, which was considered "not classifiable." The International Agency for Research on Cancer (IARC) (3) has determined that DDT and DBCP are possible human carcinogens. The other compounds were determined not classifiable by IARC. The National Toxicology Program (4) has classified DDT and DBCP as animal carcinogens. Benign and malignant liver tumors were the most common tumors found in animal studies. The carcinogenic classification of these pesticides is summarized in table 1.

Some recent epidemiologic studies (5, 6, 7) designed to examine the carcinogenicity of several of these same pesticides have also been conducted. The studies have not demonstrated an association between exposure to these pesticides and an increase in cancer. However, most of the studies were based on small populations, and the power to detect risks for rare causes of death such as liver cancer was weak.

Subjects and methods

Each of the four study groups was defined as all white male workers who were employed for at least six months prior to 31 December 1964 at the plants under study. The personnel records from each of the plants were used to identify the groups. When the work history was provided in sufficient detail, workers in nonproduction jobs such as office workers were excluded. In most cases this was possible, but a few nonproduction workers who had limited access to the process areas were included in the study. Additional work histories for the workers who were active at the time the records were collected for the original study were not obtained for the update. No independent record systems were used to verify the completeness of the cohort. However, checks were run on the data

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Table 1. Review of the toxicity of aldrin, dieldrin, chlordane, heptachlor, endrin, dichlorodiphenyltrichloroethane (DDT), and dibromochloropropane (DBCP). (S = sufficient, I = inadequate, L = limited, D = not classifiable as to carcinogenicity to humans, ND = no data, B2 = probable human carcinogen, 2B = possible human carcinogen, 3 = not classifiable as to carcinogenicity to humans)

Pesticide	Integrated Risk Information System[a]			International Agency for Research on Cancer[b]			National Toxicology Program[c]	
	Animal	Human	Class	Animal	Human	Class	Animal	Human
Aldrin	S	I	B2	L	I	3	..	..
Dieldrin	S	I	B2	L	I	3	..	..
Chlordane	S	I	B2	L	I	3	..	..
Heptachlor	S	I	B2	L	I	3	..	..
Endrin	I	I	D	I	ND	3	..	..
DDT	S	I	B2	S	I	2B	S	I
DBCP	..	..	..	S	I	2B	S	I

[a] See reference 2.
[b] See reference 3.
[c] See reference 4.

to determine if there were missing records. No obvious gaps were found.

For this update, the follow-up of vital status was extended from the end of 1976 to 31 December 1987. Vital status for members of the cohort was determined from a search of the records maintained by the Social Security Administration, the Internal Revenue Service, and the National Death Index. Death certificates for deceased workers were obtained from the state vital records offices, and the underlying cause of death was coded by a qualified nosologist according to the revision of the International Classification of Diseases (ICD) in effect at the time of death.

The cohort was restricted to white male workers since they represented the vast majority of the work force at all of the plants. Those with unknown race were assumed to be white. The life-table analysis system of the National Institute for Occupational Safety and Health (NIOSH) (8) was used to calculate the values for the standardized mortality ratio (SMR) for specific causes of death. The system distributes the person-years at risk for each worker into strata by age and calendar year and further stratifies the person-years at risk by length of employment and time since first employment (latency). The person-years at risk for each worker were accumulated from the time the worker achieved six months of employment to the end of the study (31 December 1987) or the date of death, whichever occurred first. For those lost to follow-up, the person-years at risk were accumulated to the end of the study. The person-years at risk were multiplied by the corresponding age- and calendar-specific, white, male, US mortality rates to yield the expected numbers of death. For plant 3, Colorado state and county (Denver, Arapahoe, Jefferson, Douglas, and Adams County) mortality rates were also used for this purpose. The use of regional rates was added to the analysis for plant 3 because of the known high incidence rate for respiratory disease in the Denver area. The 95% confidence interval (95% CI) was computed for each cause-specific SMR with the use of the Byar approximation when the deaths were eight or more, or the Fisher exact method was used when the deaths were fewer than eight (9).

There were no historical exposure measurements available for the study. At each plant the workers were potentially exposed to multiple chemicals used in the manufacturing process, as well as to the pesticides themselves. A list of potential exposures was included in the original publication (1). Organophosphate pesticides and DBCP were also manufactured at plant 3 during part of the study period. However, aldrin and dieldrin were the predominant products of this plant.

Data from plant 4 were available on the levels of exposure to DDT among 35 workers employed in 1967. The DDT in the fat of workers ranged from 38 to 647 ppm compared with an average of 8 ppm for the general population. It was estimated that the average daily intake of DDT among the highly exposed group was 17.5 to 18 $mg \cdot man^{-1} \cdot d^{-1}$ compared with 0.04 $mg \cdot man^{-1} \cdot d^{-1}$ for the general population (10).

Results

The results of the vital status ascertainment are given in table 2. The total number of cohort members differed slightly from the original study because some workers that were previously excluded in plant 1 were included in the update, and workers who previously had an unknown race status were subsequently excluded if they were determined to be nonwhite. The increase in the number of deaths for each group of workers compared with the numbers in the initial study is given in table 2. For the 650 deaths, death certificates were obtained for all except eight persons. They were considered dead with an unknown cause of death.

Table 3 gives the cause-specific mortality by major cause and by individual plant. For all of the plants combined, the observed mortality for heart disease and for all causes combined was significantly less than expected. The cause-specific mortality was less than expected for all of the major causes of death except for cerebrovascular disease and respiratory disease.

The all causes mortality was less than expected for each of the four plants and significantly lower than expected at plant 3 (337 observed, SMR 0.87, 95% CI 0.78—0.97). The mortality for all malignant neoplasms was also equal to or lower than expected in each of the plants. Cerebrovascular disease was higher than expected in three of the plants. There was a statistically significant excess of deaths from this cause at plant 4, (11 observed, SMR 2.38, 95% CI 1.19—4.26), but a significant deficit at plant 3 (13 observed, SMR 0.56, 95% CI 0.30—0.97). Diseases of the respiratory system at plant 3 was significantly elevated when compared with US rates (37 observed, SMR 1.56, 95% CI 1.10—2.16). When Colorado state and the surrounding county rates were used to calculate expected deaths (table 4), the increase in nonmalignant respiratory disease (ICD 460—519) at plant 3 was substantially reduced and was no longer statistically significant, although it was still slightly elevated. The risks for cerebrovascular disease and heart disease were no longer significantly low when compared with the regional rates, and the risk for respiratory cancer was closer to the expected rate.

Table 5 gives the cancer-specific mortality for each plant separately and for all of the plants combined. When all of the plants were combined, the only excess risks by specific cancer site were for stomach and liver cancer. When examined by specific plant, stomach cancer was nonsignificantly elevated in three out of the four plants. Respiratory cancer was 33% higher than expected at plant 1. There was a significant increase in bladder cancer at plant 2. All of these bladder cancer deaths occurred after 10 years of employment, and two occurred after 20 years of latency and

Table 2. Vital status follow-up of the workers in the organochlorine pesticide plants as of 31 December 1987.

Vital status	Plant 1 (chlordane)		Plant 2 (heptachlor, endrin)		Plant 3 (aldrin, dieldrin)		Plant 4 (DDT)		Total	
Alive	245		240		803		230		1518	
Deceased[a]	159	(59)	64	(24)	337	(173)	90	(42)	650	(298)
Unknown	1		1		13		8		23	
Total	405		305		1158		328		2191	
Person-years[b]	13 191	(8354)	8477	(5672)	34 479	(24 939)	9797	(7601)	65 944	(46 566)

[a] Number of deceased in the original report in parentheses.
[b] Person-years in the original report in parentheses.

Table 3. Cause-specific mortality of the workers in the organochlorine pesticide plants, values based on United States mortality rates. (SMR = standardized mortality ratio, 95% CI = 95% confidence interval)

Cause of death[a]	Plant 1			Plant 2			Plant 3			Plant 4			Total		
	Observed (N)	SMR	95% CI	Observed (N)	SMR	95% CI	Observed (N)	SMR	95% CI	Observed (N)	SMR	95% CI	Observed (N)	SMR	95% CI
All malignant neoplasms (140—208)	35	0.87	0.61—1.22	18	1.00	0.60—1.59	72	0.86	0.67—1.08	18	0.87	0.52—1.39	143	0.88	0.74—1.04
Heart disease (390—429, except, 401, 403, 405, 415—417)	67	0.85	0.66—1.09	25	0.80	0.52—1.18	123	0.77	0.65—0.93	32	0.87	0.60—1.24	247	0.81	0.71—0.91
Cerebrovascular disease (430—438)	18	1.52	0.90—2.41	6	1.56	0.57—3.40	13	0.56	0.30—0.97	11	2.38	1.19—4.26	48	1.10	0.81—1.46
Respiratory disease (460—519)	10	0.83	0.40—1.54	5	1.11	0.36—2.60	37	1.56	1.10—2.16	5	0.93	0.30—2.19	57	1.25	0.95—1.62
Digestive disease (520—579)	6	0.68	0.25—1.48	2	0.47	0.06—1.70	18	0.93	0.55—1.48	7	1.44	0.58—2.98	33	0.89	0.61—1.24
Cirrhosis of the liver (571)	3	0.67	0.14—1.96	1	0.40	0.01—2.72	10	0.96	0.45—1.77	6	2.15	0.79—4.70	20	0.99	0.60—1.53
Genitourinary disease (580—629)	3	1.22	0.25—3.58	—	0	·	4	0.82	0.22—2.11	—	0	·	7	0.95	0.37—1.92
Accidents (E800—949)	8	0.80	0.34—1.59	3	0.52	0.11—1.53	20	0.81	0.50—1.26	5	0.73	0.24—1.72	36	0.76	0.53—1.05
Violence (E950—978)	3	0.67	0.14—1.96	—	0	·	13	1.13	0.61—1.95	2	0.62	0.08—2.26	18	0.94	0.56—1.48
All other	9	..	..	5	..	..	37	..	..	10	..	..	61	..	..
All causes	159	0.85	0.73—1.00	64	0.81	0.63—1.04	337	0.87	0.78— 0.97	90	0.98	0.79—1.21	650	0.87	0.80—0.94

[a] Code of the International Classification of Diseases, ninth revision, in parentheses.

Table 4. Cause-specific mortality for the workers from plant 3 on the basis of national, state, and county rates. (SMR = standardized mortality ratio, 95% CI = 95% confidence interval)

Cause of death[a]	National rates			State rates[b]			County rates[b]		
	Observed (N)	SMR	95% CI	Observed (N)	SMR	95% CI	Observed (N)	SMR	95% CI
All malignant neoplasms (140—208)	72	0.86	0.67—1.08	69	1.11	0.87—1.41	69	1.04	0.82—1.33
Liver biliary, gallbladder (155.0, 155.1, 156)	5	3.93	1.27—9.20	5	5.10	1.65—11.91	5	4.86	1.57—11.36
Respiratory (160—165)	20	0.66	0.40—1.02	19	0.92	0.56—1.45	19	0.87	0.52—1.36
Lymphatic and hematopoietic (200—208)	10	1.26	0.60—2.32	10	1.51	0.72—2.79	10	1.45	0.70—2.68
Heart disease (390—429, except 401, 403, 405, 415—417)	123	0.77	0.65—0.93	110	0.93	0.77—1.12	110	0.91	0.75—1.09
Cerebrovascular disease (430—438)	13	0.56	0.30—0.97	12	0.74	0.38—1.30	12	0.76	0.39—1.33
Respiratory disease (460—519)	37	1.56	1.10—2.16	36	1.21	0.85—1.68	36	1.11	0.78—1.54
Pneumonia (480—486)	14	1.73	0.95—2.91	13	1.36	0.73—2.34	13	1.14	0.61—1.95
Pneumoconiosis and other disease (470—478, 494—519)	15	1.72	0.96—2.84	15	1.29	0.73—2.14	15	1.20	0.67—1.98
All causes	337	0.87	0.78—0.97	307	0.98	0.87—1.10	307	0.98	0.84—1.06

[a] Code of the International Classification of Diseases, ninth revision, in parentheses.
[b] The state and county rates used in the analysis start in 1960; therefore the observed and expected deaths that occurred before this date were excluded.

20 years of employment (2 observed, SMR 15.38, 95% CI 2.58—50.82).

Probably the most important finding was the statistically significant increase in liver and biliary tract cancer (ninth revision ICD codes 155.0, 155.1, 156) among the workers at plant 3 (5 observed, SMR 3.93, 95% CI 1.27—9.20). The increased risk at plant 3 was statistically significant when state or county rates were used to calculate the expected deaths (table 4). According to death certificate information, three of the deaths from plant 3 were due to biliary tract or bile duct cancer, one from gall bladder, and one from hepatoma. Among the workers in plant 3, all of the liver cancer deaths occurred after 15 years of latency (1.03 expected, SMR 4.85). There were three observed versus 0.32 expected deaths (SMR 9.38) in the less than two years employment stratum and two observed versus 0.45 expected (SMR 4.44) in the greater than two years employment stratum. At plant 4, there were two deaths from liver or biliary tract cancer. However, for one of these deaths, an adenocarcinoma of the liver, the primary site was unspecified. The other death was due to gallbladder cancer. The expected number of primary and unspecified cancer deaths for this cause at plant 4 was 0.45. More details on the liver cancer deaths from plants 3 and 4 are given in table 6.

At plants 1 and 2 there were no observed deaths from liver or biliary tract cancer. However, only 0.64 deaths were expected at plant 1, and only 0.26 deaths were expected at plant 2.

Discussion

This update of a previously published study of pesticide manufacturers adds 11 years of follow-up, more than doubling the total number of deaths, and provides approximately 40 years of observation for the cohort. A minimum of 23 years (31 December 1964 to 31 December 1987) has elapsed since each cohort member was first employed at the study plants, and there was, therefore, time for diseases with long latency periods to develop.

The excess in liver and biliary tract cancer deaths observed in plants 3 and 4 is important because it may be relevant to the a priori disease of interest according to animal studies. In subchronic studies of rats and mice, the liver was the primary target organ. Both aldrin and dieldrin induced hepatocellular carcinomas and benign liver tumors in mice. Studies of rats resulted in effects on the liver, but no increase in malignant liver tumors (11). When these results are interpreted, several factors must be considered. First, there was a lack of quantitative information on exposure to the pesticides, as well as to precursor chemicals used in the manufacturing process. Second, since DBCP was manufactured at plant 3 between 1955 and 1976 and it is classified as an animal carcinogen, it has to be considered a potential confounding exposure. Two of the liver or biliary tract cancer deaths were included in the DBCP register kept by NIOSH. This is a national exposure register that includes plant 3 and is based on the voluntary submittal of the names of workers with at least 30 d employment in areas of the plant with potential exposure to DBCP. Third, the liver cancers were not a homogeneous type, but were a mixture of extrahepatic (biliary tract and gallbladder) and intrahepatic tumors, whereas the experimental animal studies resulted in intrahepatic tumors. Whether this is important etiologically is not known. Similar experimental and epidemiologic results have been found in studies of polychlorinated biphenyls (12) and

Table 5. Cause-specific cancer mortality of the workers in the organochlorine pesticide plants. (SMR = standardized mortality ratio, 95% CI = 95% confidence interval)

Cause of death[a]	Plant 1			Plant 2			Plant 3			Plant 4			Total		
	Observed (N)	SMR	95% CI	Observed (N)	SMR	95% CI	Observed (N)	SMR	95% CI	Observed (N)	SMR	95% CI	Observed (N)	SMR	95% CI
Buccal cavity or pharynx neoplasms (140—149)	—	0	·	—	0	·	3	1.19	0.25—3.49	—	0	·	3	0.61	0.16—1.67
Stomach neoplasms (151)	4	2.10	0.57—5.37	2	2.84	0.34—10.27	1	0.27	0.01—1.51	3	3.61	0.75—10.56	10	1.40	0.67—2.58
Intestinal neoplasms (152—153)	1	0.26	0.007—1.48	1	0.63	0.02—3.53	7	0.91	0.37—1.89	—	0	·	9	0.60	0.27—1.14
Rectal neoplasms (154)	—	0	·	—	0	·	3	1.36	0.28—4.00	—	0	·	3	0.70	0.18—1.92
Liver, biliary, gallbladder neoplasms (155.0, 155.1, 156)	—	0	·	—	0	·	5	3.93	1.27—9.20	1	3.27	0.08—18.17	6	2.42	0.88—5.27
Liver neoplasms, not specified (155.2)	—	0	·	—	0	·	—	0	·	1	7.17	0.18—39.88	1	0.85	0.04—4.18
Pancreas neoplasms (157)	2	0.93	0.11—3.38	—	0	·	4	0.91	0.25—2.33	1	0.93	0.02—5.20	7	0.82	0.33—1.68
Respiratory neoplasms (160—165)	19	1.33	0.80—2.08	6	0.88	0.32—1.92	20	0.66	0.40—1.02	8	1.03	0.45—2.04	53	0.90	0.67—1.17
Kidney neoplasms (189.0—189.2)	1	1.01	0.01—5.64	—	0	·	3	1.42	0.29—4.17	—	0	·	4	0.98	0.31—2.36
Bladder neoplasms (188, 189.3—189.9)	—	0	·	3	7.12	1.47—20.84	—	0	·	—	0	·	3	0.69	0.18—1.87
Lymphatic/hematopoietic neoplasms (200—208)	4	1.10	0.30—2.83	1	0.58	0.01—3.23	10	1.26	0.60—2.32	—	0	·	15	0.98	0.55—1.62
Other neoplasms	4	0.45	··	5	1.25	··	16	0.86	··	4	0.87	··	29	0.80	··
All malignant neoplasms (140—208)	35	0.87	0.61—1.22	18	1.00	0.59—1.59	72	0.86	0.67—1.08	18	0.87	0.52—1.39	143	0.88	0.74—1.04

[a] Code of the International Classification of Diseases, ninth revision, in parentheses.

Table 6. Detailed information on the liver cancer deaths at plants 1 and 3. (UCOD = underlying cause of death, DBCP = dibromochloropropane, NIOSH = National Institute for Occupational Health and Safety)

Case	Plant	Coded UCOD[a]	Cause on death certificate	Work history	Latency
1	3	156.1 (9th)	Hepatobiliary cancer	Laborer, plantwide — 1 year, 1952—1953	32 years
2	3	156.9 (9th)	Biliary tract cancer	Laborer, maintenance, plantwide — 9.5 years, 1952—1962 (in DBCP register)[b]	30 years
3	3	156.0 (8th)	Gallbladder cancer[c]	Operator, engineer, laborer — 17.5 years, 1951—1968 (in DBCP register)[b]	26 years
4	3	156.1 (8th)	Cholangitis, bile duct cancer[c]	Operator — insecticide — 1 year, 1951—1952	19 years
5	3	155.0 (8th)	Hepatoma, diffuse cancer[c]	Maintenance, construction — 6 months	21 years
6	4	155.1 (7th)	Gallbladder cancer	Laborer — 1.3 years, powder feeder — 1 month	15 years
7	4	197.8 (8th)	Adenocarcinoma of liver	Specific job unknown	20 years

[a] Revision used in parentheses.
[b] Included in the NIOSH register of workers with potential exposure to DBCP.
[c] The cause of death confirmed by hospital reports. Cases 3 and 4 were adenocarcinomas and case 5 was primary carcinoma of the liver.

dinitrotoluene (personal communication from Dr Leslie Stayner, NIOSH). Fourth, there does not appear to be a dose-response relationship for liver and biliary tract cancer when dose is measured as length of employment. However, this type of analysis is crude since there was no exposure data and a positive dose-response is difficult to demonstrate with so few deaths. There were only two deaths from liver cancer among the workers that had worked at the plant for more than two years.

The statistically significant excess in bladder cancer deaths at plant 2 was unexpected since no known bladder carcinogens were used at this plant. The small number of deaths (3 observed) makes it difficult to interpret these findings. It should be noted, however, that, since this is a mortality analysis and bladder cancer survival has improved, a better estimate of the true risk would require an analysis of incident cases rather than deaths. In other studies of occupationally induced bladder cancer, mortality alone did not detect a risk, whereas overall incidence revealed large excess risks (13, 14).

The findings for cerebrovascular disease mortality were of interest because three of the four plants had an excess risk, plant 4 having a statistically significant excess. This observation was not part of an a priori hypothesis and could have been due to chance or to differences among the study population in risk factors related to cerebrovascular disease. The potential exposures at these plants have not been previously associated with an increased risk for cerebrovascular disease. However, according to a recent report (15), a study of worker compensation claimants in California found a significant increase in deaths from cerebrovascular disease (proportionate mortality ratio 2.95, 95% CI 1.18—6.08) among workers in the agricultural industry. Since these claims were filed between 1945 and 1963, these workers had potential exposure to organochlorine pesticides.

Two epidemiologic studies of workers from pesticide manufacturing plants have been completed since the publication of the original study. Both of these studies were designed to evaluate the cancer risks among workers exposed to organochlorine pesticides. Shindell & Ulrich (5) performed a mortality analysis on the workers from plant 1, where chlordane was manufactured. This study included all of the workers with at least three months of employment between January 1946 and June 1985, and therefore there was considerable overlap between their study cohort, and plant 1 in this report. The results of the two studies are similar. In their study there was a deficit in cancer mortality (SMR 0.91) and an increase in cerebrovascular disease (SMR 1.71).

A mortality study of aldrin and dieldrin workers at a plant located in The Netherlands was recently completed (6). This study included 570 workers who were employed for at least one year between 1954 and 1970. There were only 75 deaths in this study, so it is difficult to draw any conclusions. There were 32 observed and 30.9 expected neoplasms, and no significant increases in specific cancer types were found. One death from liver cancer was observed, whereas 0.6 was expected. In addition no trends were seen when risk for various causes was examined by exposure groupings.

Wong et al (7) studied the mortality of chemical workers from three manufacturing plants where there was exposure to brominated chemicals (including DBCP) and DDT. There was a lack of historical exposure information, and many of the workers were exposed to multiple chemicals. Among a small group of 238 workers with potential exposure to DBCP in the Wong study, there was a significant excess in arteriosclerotic heart disease (6 observed and 2.17 expected). In the Wong study, there were also 740 workers exposed to DDT. There were 112 deaths among the DDT exposed workers, but there were no liver cancer deaths and no statistically significant excesses in cause-specific mortality. The authors pointed out that there were inherent deficiencies in the study, including a small sample size, multiple exposures, and a lack of information on historical exposure.

In summary, this updated analysis has provided additional information on the possible carcinogenicity of organochlorine pesticides. The most important result is the statistically significant increase in liver and biliary tract cancer among workers at plant 3, where aldrin and dieldrin were the primary organochlorine pesticides produced, and the nonsignificant increase at plant 4, which manufactured DDT. The study was limited by a lack of exposure data, included the potential for confounding exposures to other chemical compounds, and had a relatively small number of deaths with which to assess adequately mortality from rare diseases.

Since one of the primary limitations of this study was the lack of exposure information and the small number of liver cancer deaths, further follow-up and a subsequent nested case-referent study should be considered. Of course the feasibility of this type of study is dependent on the availability of at least qualitative exposure data.

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