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Mortality in a Cohort of Orchard Workers Exposed to Lead Arsenate Pesticide Spray

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ABSTRACT. During the period from 1890 to 1940, lead arsenate was the major pesticide used in apple orchards to control the coddling moth. In the Wenatchee area of Washington State, lead arsenate spray was used for longer periods and in larger quantities than in other areas of the United States. In 1938, a cohort of 1 231 people who lived in this area was selected for a study to determine the effects of exposure to lead arsenate spray and residue. This same cohort was re-examined to determine whether there was excess mortality that could be attributed to the lead arsenate exposure. Three levels of exposure (i.e., orchardist, intermediate, consumer) were defined, based upon the use of lead arsenate pesticide spray before and during the 1938 apple growing season. Age-adjusted hazard ratios for all causes of mortality were elevated for both male orchardists and male intermediates. The only significantly increased age-adjusted hazard ratio (1.94) was heart disease in male intermediates. No significantly elevated age-adjusted hazard ratios were observed for women in any exposure group. The lack of evidence that supported an increase in mortality from respiratory cancer in this cohort may have resulted from the lower cumulative concentration of arsenic exposure, the type of arsenical compound, and the small number of study subjects.

BOTH LEAD AND ARSENIC are known toxic substances. In spite of their toxicity, occupational exposure to both these compounds has been common in agricultural and smelting occupations. Many epidemiologic studies of workers exposed to lead and arsenic have documented serious health problems and an excess risk of cancer and mortality.[1–16] Exposure to lead in various settings, including lead smelters, storage battery factories, and residential areas adjacent to lead smelters, has been associated with elevated blood lead levels, clinical symptoms of lead poisoning, and impairment of central nervous system functioning.[1–3] Elevated blood-lead levels have also been associated with increases in blood pressure, especially in men[4]; exposure to lead may also increase the risk of death from cerebrovascular disease.[5] Several epidemiologic studies have suggested a higher incidence of digestive and respiratory cancers in lead smelter and battery plant workers.[6,7]

Numerous other studies of smelter and factory workers have shown that occupational exposure to arsenical compounds is associated with excess cancers, particularly respiratory cancers.[8–17] A clear dose-response relationship between arsenic levels and respiratory cancers has been observed in smelter workers.[8–14] Respiratory cancer rates are also higher in employees who are involved in the manufacture of arsenic-containing pesticides.[15–17] Several studies have also reported an association between arsenic exposure and nonrespiratory cancers. Studies of arsenic ingestion via drinking water in Taiwan and Japan suggest that arsenic is associated

with cancers of the bladder, kidney, lung, and liver.[18–20] Elevated relative risks for nonrespiratory cancers (e.g., cancers of the urinary tract, gastrointestinal tract, and liver) have also been observed in smelter workers in the United States, Japan, and Sweden, as well as in Japanese refinery and mine workers.[13,20–22]

Arsenic is often used in (a) insecticides to control the cotton bollworm and tobacco pests; (b) organic herbicides, such as MSMA and DMSA, to control weeds in cotton fields; and (c) desiccants, such as arsenic acid. During the period from 1890 to 1940, lead arsenate was the major pesticide used in apple orchards to control the coddling moth. Other compounds have since replaced lead arsenate, and it is no longer used widely. However, as a consequence of lead arsenate use, orchardists have been exposed to a potentially harmful substance over a long period of time.

Results of studies that have examined exposure to arsenic in agricultural settings have varied.[23–28] An association between exposure to arsenates in vineyards and respiratory cancer has been suggested in two studies.[23,24] Barthel[25] reported a twofold excess of lung cancer in male German agricultural workers, but he was unable to show an association with any specific pesticide. A study of orchardists in Washington State was also inconclusive as to whether exposure to lead arsenate increased the risk of lung cancer.[26] The long-term health effects of lead arsenate spray on individuals who lived in an apple-growing region in Washington State were examined in two additional studies.[27,28]

In 1938, a cohort of 1 231 individuals who lived in the Wenatchee area of Washington State was selected for a study that was designed to determine effects of inhalation or ingestion of lead arsenate spray and residue.[27] This group was known as the Neal Study Cohort. The Wenatchee area was originally chosen because lead arsenate spray had been used there for a longer period of time (i.e., more than 25 y) and in larger quantities than in other areas of the United States. People who lived in this area were also isolated from industrial sources of both lead and arsenic. This early study noted no significant increase in clinical symptoms of lead arsenate intoxication in individuals exposed to the pesticide during the 2 y of the study. A follow-up study in 1968 re-examined the Neal Study Cohort to determine whether there was excess mortality that could be attributed to lead arsenate exposure.[28] There was no overall excess in mortality and no excess deaths from cancer, heart disease, or stroke. In 1968, however, only 37% of the cohort had died, and many of the study members had not reached high-risk mortality ages. Sufficient time may not have elapsed since the exposure to lead arsenate for mortality differences to appear.

The current study examined mortality risks in the Neal Study Cohort 22 y after the first follow-up mortality study and 52 y after the original morbidity study. Mortality effects, if they existed, should have been more evident than in the earlier follow-up study. The goals of this second follow-up study were to determine (a) whether there was an overall increased risk of dying as a result of exposure to lead arsenate and (b) whether there was an increased risk of dying from lung and digestive cancers, which have been associated with exposure to arsenic.

Method

The study cohort included 1 225 individuals who had lived in the Wenatchee area of Washington State during the 1938 apple growing season and who had participated in the 1938 Neal study and the 1968 Nelson study.[27,28] The cohort excluded 4 individuals who had died in 1938, prior to the end of the original recruitment period for the Neal study, and 2 individuals for whom no names were available in the 1968 Nelson follow-up study.

The original assignment to an exposure group used in 1938 was retained. Three levels of exposure were defined, based upon use of lead arsenate pesticide spray before and during the apple-growing season in 1938. Consumers included individuals whose occupations did not bring them into contact with lead arsenate spray (e.g., school teachers, store clerks, housewives). Orchardists were individuals who prepared and applied lead arsenate spray during the 1938 growing season. Intermediates included individuals who had not used lead arsenate spray during 1938 or who had infrequent exposure to lead arsenate spray. This group included retired orchardists who had long histories of using the spray prior to 1938, as well as warehouse workers who had experienced infrequent exposures.

In 1938, blood lead and urinary arsenic measurements were taken for most of the participants. However, by 1968, the individual measurements had been lost in a warehouse flood. Mean values for each exposure group were published by Neal et al.[27] (Table 1). Arsenic and lead levels of consumers were lower than those for orchardists and intermediates. Levels in men were consistently higher than those identified in women. Mean urinary arsenic levels for the consumers were similar to those published for other control groups studied in the 1940s and 1950s.[8,9,29] Mean blood-lead levels for the consumers were higher than mean levels reported for the rural U.S. population in 1965 (i.e., men: 16 μg/dl; women: 10 μg/dl).[30]

Table 1.—Average Concentrations of Blood Lead and Urinary Arsenic in Selected Members of the Neal Study Cohort in 1938[27]

	Blood lead (μg/d)			Urinary arsenic (μg/L)		
	n	$\bar{x}$	*SD*	*n*	$\bar{x}$	*SD*
Adult males						
Consumers	148	26.3	11.1	140	62.0	88.0
Orchardists	329	43.9	11.0	305	140.5	176.4
Intermediates	108	29.5	13.2	123	71.0	103.5
Adult females						
Consumers	124	25.8	9.5	121	56.3	69.4
Orchardists	58	34.4	13.2	58	97.9	118.1
Intermediates	27	21.9	9.6	25	58.0	69.3

Table 2.—Arsenic and Lead Concentrations in the Orchard Air in 1938 during Various Orchard Activities[19]

Orchard activity	Length of exposure		Arsenic concentration		Lead concentration	
	h/d	wk/y	$\bar{x}$	Range	$\bar{x}$	Range
Mixing insecticide	1	8–12	18.5	0.2–110.7	57.4	0.9–467.3
Burning containers	NA	NA	166.7	48.6–261.2	35.8	10.2–76.5
Spraying orchard	8–14	8–12	1.4	0.4–4.8	4.5	1.3–14.3
Thinning fruit	8–14	2–3	0.8	0.1–3.2	3.0	0.4–17.0
Picking fruit	8–14	6–10	8.8	2.6–19.0	29.3	7.7–75.2
Dumping fruit	8–12	8–12				
October	NA	NA	0.6	0.1–1.9	1.9	0.4–6.9
December	NA	NA	0.1	0.02–0.2	0.3	0.01–1.1
Sorting and packing						
October	8–12	4–12	0.06	0.03–0.08	0.16	0.07–0.22

*NA = data were not available.

In the original 1938 study, the ambient air levels of arsenic and lead were monitored during various orchard activities (Table 2). The usual hours per day and weeks per year spent in these activities were also calculated for the orchardists.

Although the original list of Neal Study members and their assignment to exposure group were available, extensive information was obtained from the 1968 follow-up records. The 1968 records included name in 1938 and name in 1968; age at time of exposure in 1938; age in 1968; and birthdate, exposure group, and vital status in 1968. If the study member had been alive in 1968, an address at which the member resided in 1968 had been recorded. Copies of the death certificates were also available for most study members who had died during or prior to 1968. In the 1968 study, a questionnaire was used to gather information on duration of use of lead arsenate and other pesticides during the time period from 1938 to 1968. Unfortunately, this information had been lost for some of the study members during the ensuing years.

A list of the 777 study members who were not known to be deceased in 1968 was used to search the 1969–1990 death records of Washington State and to locate any deaths. The search included the 54 people who had been lost to follow up in 1968. Copies of death certificates were then obtained for individuals who had died in Washington State.

The vital status of 507 individuals was still unknown after searching the death records. Letters that explained the purpose of the study and a questionnaire were mailed to these study members at their 1968 address or, if a current address could be found in the local telephone directory, it was used. The questionnaire included information on current name, current address, age, birthdate, and whether the study member was still alive. If deceased, a relative or close friend was asked to provide date and place of death. A total of 380 individuals were found to be alive.

Death certificates were obtained for those study members who were identified from the questionnaire as having died. Death certificates were not obtained for 35 of the deaths, of which 5 resulted from World War II injuries; however, information provided on the questionnaires for the remaining 30 cases was not sufficiently specific to allow the death certificates to be located. Twenty-one of the remaining 30 cases were reported to have died outside of Washington State. These names were matched to the National Death Index so that death certificates could be located. Information on cause of death, date of death, and birthdate was obtained from the death certificates. Regardless of the date of death, the cause of death was coded for all decedents, using the International Classification of Diseases (9th revision). Despite the fact that the ICD cause-of-death code was written on most death certificates, the cause of death for deaths that occurred between 1939 and 1975 was recoded, using the ICD-9 conventions.

The Neal Study Cohort originally included 128 children who were less than 18 y of age. The majority (81.3%) were classified as consumers. Given that the long-term effects of lead and arsenic exposure in children may differ from those in adults, the children were removed from the analysis. Therefore, 1 097 study members who were 18 y of age or older were included in the survival analysis.

Survival time was calculated in months; January 1, 1939, was the beginning of the study period, and December 31, 1984, served as the endpoint. Survival time for those who were lost to follow up in 1938 (i.e., not located after the original study period) was set at 1 mo. Survival time for all others was calculated as time (mo) (a) to death, (b) to date of loss to follow up, or (c) to the end of the study. Survival endpoints for the different analyses included death from all causes; from all cancers (ICD-9 codes 140–208, 230–239); from digestive cancers (ICD-9 codes 150–159); from stomach cancer (ICD-9 code 151); from pancreatic cancer (ICD-9 code 157); from respiratory cancers (ICD-9 codes 160–165); from lung cancer (ICD-9 code 162); from breast cancer (ICD-9 code 174); from lymphatic and hematopoietic cancers (ICD-9 codes 200–208); from coronary heart disease (ICD-9 codes 410–414); from other heart disease (ICD-9 390–398, 401–405,

415–417, 420–429); and death from stroke (ICD-9 codes 430–438).

Crude mortality rates for cancers associated with arsenic exposure and other major causes of death were calculated for each sex and each exposure group. Person-months of follow up or person-months to death were used as the denominator.

Survival experiences of each of the two exposed groups (intermediates and orchardists) were compared with the unexposed group (consumers), using a Cox proportional hazards model that estimates the effects of explanatory variables (i.e., sex, age at exposure, exposure category) on mortality rates. This model is appropriate for cohort survival analysis because it allows the use of censored observations (those individuals lost to follow up and not failing), provides for varying lengths of observations, and produces estimates of the hazard (mortality) rate ratio (exposed versus unexposed mortality rates). The consumers served as the internal baseline group.

Results

The follow-up status of the entire study cohort (1 225 members) is summarized and compared with the 1968 status in Table 3. At the conclusion of the study period, the vital status of 1 123 members (91.6%) was known: 380 were alive and 743 were deceased. There were four ways that the remaining study members were lost to follow up: (1) 25 individuals were last contacted in 1938 and were not located in either of the two follow-up studies, (2) 24 individuals were last known to be alive at some point in time between 1938 and 1968, (3) 1 individual was last known to be alive between 1969 and 1984, and (4) 52 individuals were contacted in 1968 but were not located in 1984. The characteristics of the 102 study members lost to follow up are compared with those of known vital status in Table 4. Study members lost to follow up were more likely to be female (in the consumer group) and were 18-34 y of age in 1938.

The age and sex distributions of each of the exposure groups are shown in Table 5. Most of the children (81.8%) were consumers. Once the children were excluded, a lower percentage of orchardists and intermediates were in the youngest adult age group (18–34 y), compared with consumers. The overall age distributions of the two sexes were similar. However, there were proportionately more male intermediates (37.4%) and orchardists (20.3%), compared with consumers (17.2%) in the oldest age group (55 y and older); and there were proportionately more female consumers (36.8%), compared with intermediates (26.9%) and orchardists (27.9%) who were 18–34 y of age. A large percentage of orchardists were men (88.8%), whereas more consumers were women (56.8%). There were approximately equal numbers of male and female intermediates (males: 50.8%; females: 49.2%).

Crude mortality rates for the causes of death of interest were calculated per 100 000 mo of follow up (Tables 6 and 7). A total of 728 study members had died, of whom 84 men and 39 women died of some type of cancer. There was only 1 female lung cancer death that occurred in a consumer, and no other respiratory cancer deaths occurred in women. Two women orchardists and 1 woman intermediate died of pancreatic cancer.

The age-adjusted hazard ratios for deaths from selected causes are also given in Tables 6 and 7. Risk of dying during the follow-up period was increased significantly for both male orchardists and intermediates (hazard ratios of 1.36 and 2.00, respectively). The only significantly increased specific cause of death was coronary heart disease in the male intermediates (hazard ratio of 1.94). Overall mortality was not elevated for women.

Discussion

There is much experimental and epidemiologic evidence that suggests that exposure to lead and arsenic has adverse effects on health and mortality.[1-17] In this study of Wenatchee orchardists we found an increased risk of dying of all causes in male orchardists and intermediates. Almost a twofold increased risk of dying of coronary heart disease was observed in men in the intermediate group, but this risk was not observed in the orchardist group. This is consistent with other studies that have shown a dose-response relationship between

Table 3.—Follow-up Status of Neal Study Cohort in 1968 and in 1990

	All ages				1990			
	1968		1990		Adults		Children	
Follow-up status	*n*	%	*n*	%	*n*	%	*n*	%
Alive	723	59.0	380	31.0	277	25.2	103	80.4
Deceased	448	36.6	743	60.6	728	66.4	15	11.7
Lost to follow up								
Not found after 1938	28	2.3	25	2.0	25	2.3	0	0.0
Last alive 1938–1967	26	2.1	24	2.0	21	1.9	3	2.3
Last alive 1969–1990			1	0.1	1	0.1	0	0.0
Alive 1968, not found in 1990			52	4.2	45	4.1	7	5.5
Total	1 225		1 225		1 097		128	

arsenic exposure and death from cardiovascular disease in smelter workers,[11,13,31] as well with studies in which increases in cardiovascular mortality have been correlated with exposure to lead.[5] In smelter workers exposed to arsenic at the Ronnskar smelter in Sweden, there was a twofold risk increase for death from cardiovascular disease.[31] However, a more recent study of this cohort did not support the findings of the earlier study.[15] Lead exposure may have also contributed to the excess in cardiovascular deaths. There is some evidence to suggest that elevated blood-lead levels are associated with hypertension and heart disease. Analyses of the NHANES II data have demonstrated an increase in systolic pressure in men exposed to lead.[4,32,33] However, after important confounding factors have been adjusted for, other large-population studies have not demonstrated such an association.[34,35]

It is surprising that there was not an increase in mortality from respiratory cancer in this cohort, given the amount of evidence that supports an association between arsenic exposure and lung cancer. Previous studies have documented increased standardized mortality ratios (SMRs) from lung cancer, ranging from 1.68 to 3.43, in copper smelter, insecticide, and agricultural workers exposed to arsenic.[6-17] The results of this follow-up study, however, are consistent with the results of two other studies, as well with the earlier follow-up study in 1968. Barthel examined a cohort of male German agricultural workers who were exposed to pesticides between 1948 and 1972.[25] Prior to 1960, arsenical dusts were the primary pesticide used by these agricultural workers. The SMR for lung cancer for men exposed to arsenicals did not differ appreciably from the SMR for men who were not exposed to arsenicals. Wicklund et al. completed a case-control study of white male orchardists who died from respiratory cancer in Washington State during the time period 1968–1980.[26] The presence, intensity, and duration of lead arsenate exposure did not differ among case and control subjects. Information on smoking habits was also available and used in the analysis.

Three factors might explain the absence of increased respiratory cancers in the Wenatchee orchard workers: (1) amount of exposure, (2) type of arsenical compound used, and (3) the low number of cancer deaths in the cohort. During certain time periods, orchardists and intermediates were exposed to high concentrations (i.e., up to 26 120 μg/m³) of lead arsenate as spray and residue. Nonetheless, the total amount of lead and arsenic that they encountered each year may have been less than that experienced by constantly employed industrial workers in smelters and insecticide factories. The concentrations of arsenic in the air during orchard operations were generally lower than those encountered in a pesticide factory. Ott et al. measured air arsenic levels that ranged from 180 to 40 800 μg/m³ in a pesticide factory.[36] Body arsenic levels of the Neal Cohort intermediates (mean urinary arsenic of 71.0 μg/l) and orchardists (mean urinary arsenic of 140.5 μg/l) were also much lower than those of smelter workers (mean urinary arsenics ranging from 174 to 820 μg/l) in whom excess cancer neoplasms have been noted.[9,29,37] Body arsenic levels in female orchardists and intermediates were even lower than those of men. Studies of Swedish copper smelter workers have suggested that, with respect to increased cancer risk, the intensity of the

Table 4.—Characteristics of the Study Members Lost to Follow Up

	Lost to follow up		Known vital status	
	n	%	*n*	%
Age group (y)				
0–17	11	10.8	117	10.4
18–34	43	42.2	295	26.3
35–54	40	39.2	456	40.6
≥ 55	8	7.8	255	22.7
Sex				
Male	43	42.2	757	67.4
Female	59	57.8	366	32.6
Exposure group				
Consumer	41	40.2	292	26.0
Orchardists	28	27.4	535	47.6
Intermediates	33	32.4	296	26.4

Table 5.—Age and Sex Distribution of Each Exposure Group in the Neal Study Cohort

	Group							
	Consumer		Orchardist		Intermediate		All	
	n	%	*n*	%	*n*	%	*n*	%
Age group								
0–17	104	31.2	20	3.6	4	1.2	128	10.4
18–34	84	24.9	168	29.8	86	26.1	338	27.6
35–54	95	28.5	266	47.2	135	41.0	496	40.5
≥ 55	50	15.0	109	19.4	104	31.6	263	21.5
All ages	333		563		329		1 225	
Sex								
Males	143	42.9	500	88.8	167	50.8	810	66.1
Females	190	57.1	63	11.2	162	49.2	415	33.9
Males and females	333		563		329		1 225	

Table 6.—Crude Mortality Rates per 100 000 Person-Months of Follow Up and Cox Proportional Hazards Survival Analysis for Male Orchardists and Intermediates Who Were 18 y and Older in 1938, Compared with Male Consumers

	Consumer	Orchardist			Intermediate		
Cause of death	Crude mortality rate	Crude mortality rate	Hazard ratio	95% CI	Crude mortality rate	Hazard ratio	95% CI
All causes	143.78	192.28	1.36	1.01–1.85	282.23	2.00	1.42–2.81
All cancers (140–208, 230–239)	26.96	30.91	1.20	0.59–2.44	43.58	1.74	0.78–3.85
Digestive cancers (150–159)	5.99	13.16	2.23	0.52–9.52	16.60	2.61	0.55–12.5
Pancreatic cancer (157)	3.00	4.01	1.42	0.17–11.60	2.08	1.01	0.06–18.53
Respiratory cancers (160–165)	11.98	8.01	0.69	0.23–2.16	12.45	1.47	0.41–5.31
Lung cancer (162)	11.98	6.30	0.59	0.19–1.85	12.45	1.35	0.37–4.90
Lymphatic and hemato. cancers (200–208)	3.00	2.28	0.78	0.08–7.00	4.15	0.79	0.06–9.76
Coronary heart diseases (410–414)	50.92	64.67	1.23	0.73–2.06	89.23	1.94	1.08–3.48
Other heart diseases (390–398, 401–405, 415–417, 420–429)	14.98	17.74	1.40	0.54–3.62	35.28	1.87	0.66–5.34
Stroke (430–438)	14.98	24.61	1.65	0.65–4.20	24.90	2.18	0.72–6.57
Person-months of follow up	33 385		174 744			48 122	
No. deaths	48		336			136	

Table 7.—Crude Mortality Rates per 100 000 Person-Months of Follow Up and Cox Proportional Hazards Survival Analysis for Female Orchardists and Intermediates Who Were 18 y and Older in 1938, Compared with Female Consumers

	Consumer	Orchardist			Intermediate		
Cause of death	Crude mortality rate	Crude mortality rate	Hazard ratio	95% CI	Crude mortality rate	Hazard ratio	95% CI
All causes	154.65	152.67	1.07	0.71–1.61	164.79	1.03	0.76–1.39
All cancers (140–208, 230–239)	23.79	25.44	1.31	0.48–3.61	36.81	1.63	0.79–3.34
Digestive cancers (150–159)	3.97	12.72	3.09	0.52–18.79	12.27	2.92	0.61–14.16
Pancreatic cancer (157)	0.00	8.40	—	—	1.75	—	—
Respiratory cancers (160–165)	1.98	0.00	—	—	0.00	—	—
Lung cancer (162)	1.98	0.00	—	—	0.00	—	—
Breast cancer (157)	5.95	4.24	0.75	0.08–7.25	14.02	2.38	0.62–9.00
Lymphatic and hemato. cancers (200–208)	7.93	4.24	0.55	0.06–4.97	0.00	—	—
Coronary heart diseases (410–414)	31.72	25.44	0.80	0.31–2.11	31.56	0.98	0.49–1.94
Other heart diseases (390–398, 401–405, 415–417, 420–429)	23.79	16.96	0.93	0.29–3.00	15.78	0.63	0.26–1.54
Stroke (430–438)	31.72	29.68	0.95	0.38–2.36	73.96	1.02	0.52–1.98
Person-months of follow up	50 435	23 581			57 043		
No. deaths	78	36			94		

arsenic exposure may be more important than its duration.[14] The orchard workers in our cohort may not have been exposed to sufficiently intense levels of arsenic to produce an increase in lung cancer.

The toxicity of arsenic varies according to its chemical form.[38] Lead arsenate is a pentavalent form, and arsenic trioxide is a trivalent form. The LD_{50} for lead arsenate is 100 mg/kg, whereas the LD_{50} for arsenic trioxide ranges from 15 to 110 mg/kg.[39] Both the pentavalent and trivalent forms are well absorbed via inhalation. In the body, arsenite is partially oxidized to arsenate, and arsenate is partially reduced to arsenite. The blood contains a mixture of As(+3) and As(+5). Smelter and sheep dip workers in whom excess lung cancers were noted were exposed to arsenic trioxide.

Despite the fact that 66.3% of the cohort of adults had died, there may have been too few cancer deaths to detect any association between lead arsenate exposure and death resulting from a specific type of cancer. There was, however, a suggestion of a twofold increase in digestive cancers in both men and women in our exposure categories. This observation deserves further follow up, given the results of other studies that have found excess digestive cancers in smelter, mine, and refinery workers.[20,21]

The observed increased risk of dying of all causes in the male orchardists and intermediates in this study contradicted the results of the earlier follow-up study by Nelson et al.,[28] who found no overall excess mortality in either male or female orchardists and intermediates. This may have resulted from the increase in total number of deaths in the cohort, the many years that followed exposure to lead arsenate, and from the choice of the comparison group. In 1968, only 37% of the study cohort had died, and most had not reached the age at which mortality begins to increase. In our study, 66.4% of the study members who were adults in 1938 had died. It has been suggested that arsenic has a latency period of up to 51 y between exposure and appearance of cancers and other diseases.[36] Hence, in the 1968 follow up, 30 y may not have been sufficient time to observe excess mortality.

There were several factors that could not be controlled for in this study. Ideally, the actual amount of exposure (i.e., blood-lead and urinary arsenic levels) for each individual should be known in order to assign each individual to an exposure group. In this study, however, participants were assigned to the exposure group, based on their use of lead arsenate spray prior to and during the 1938 apple-growing season. Blood-lead and urinary arsenic levels were measured after the participants were assigned to the exposure group. Different amounts of lead and arsenic were encountered in the various jobs in the orchards (Table 2). Thus, an orchardist who spent relatively more time burning containers would have had greater exposure to lead arsenate than an orchardist who spent less time in this activity. Nonetheless, both would have been classified in the same exposure group. A more accurate measure of exposure would have included the number of years each study member was engaged in each specific job as well as measures of blood lead and urinary arsenic levels. The lack of this information resulted in misclassification from using such broadly defined occupations.

It was not possible to control for additional exposure to lead and arsenic after 1938. Exposure to large concentrations of lead arsenate probably did not occur often after 1938. In 1938, the Department of Agriculture recommended that other pesticides replace the use of lead arsenate. After the 1940s, the major routes of exposure to lead and arsenic would have been expected to be through the soil and water. Neal et al., however, determined that the local water supply did not provide an additional source of arsenic.[27] The possibility that lead and arsenic were present in locally grown produce (other than apples) was not addressed.

The healthy-worker effect can often explain reduced mortality risks in occupational studies that use the general population as a comparison group. The healthy-worker effect, however, disappears as the length of the follow-up time increases. In this study of orchardists, the follow-up time of 50 y was of sufficient duration that the healthy-worker effect did not affect the results.

Smoking habits may also have been a modifying or confounding factor, because smoking is known to be associated with several of the diseases common to arsenic exposure. It was not possible to obtain an accurate account of the smoking habits of this cohort for several reasons. The amount of time since the participants were first identified was substantial (52 y), and a majority of the participants were deceased. An informant or close relative would have been needed to provide information about the decedent's smoking habits. Any information on the smoking habits of an individual who died many years previously would most likely lack accuracy. In fact, even living individuals found it difficult to recall their own smoking habits for a period of similar duration (i.e., 52 y). Many of the study members who were alive and who were between the ages of 80 and 100 y had difficulty recalling past events. Wicklund et al. examined the smoking habits of orchardists who were living in this same area of Washington State[26] (some of their cases were also members of the Neal Study). No differences in smoking habits between orchardists and nonorchardists were observed. This suggests that the smoking habits of the three groups of this study may not have been very different. If smoking were more common in the two exposed groups (i.e., orchardists and intermediates), a higher excess of lung cancer mortality should have been observed.

Our ability to observe differences in mortality in this study was limited by the small number of study subjects. Although the length of follow up was long, the power of the study remained limited because of the small sample size.

Consistency in the coding of cause of death over such a long time period may also have affected our ability to detect differences in mortality in our study. However, in an effort to reduce inconsistencies in coding, all of the earlier death certificates were recoded, using ICD-9. Accuracy of the cause of death has always been dependent upon the ability of the attending physician to

determine the reason(s) for the death, especially if an autopsy is not completed. There is no reason to believe the attending physicians for individuals in each exposure group differed in their ability to determine cause of death.

In summary, this study has demonstrated an increased risk of dying of all causes of death in male orchardists and intermediates, as well as an increased risk of dying of coronary heart disease in male intermediates who were exposed to lead arsenate pesticide spray. The study size was too small to determine if there were other elevated risks for specific causes. No increased risk of death from cancer was found in any of the groups exposed; however, our power to detect these differences was low. The study cohort was of lower occupational levels and exposed at different forms of arsenic than were workers in whom excess cancers have been noted. These two factors may explain why no overall increased risk of death from cancer was observed in the Neal Cohort.

Authors' Note

One reviewer suggested that we confer with a toxicologist to calculate estimates of expected excess risk of lung cancer in this cohort. We did so, and we think that this approach would be the same as that of a standard mortality ratio analysis. We did not select this approach initially because the Cox proportional hazards analysis is a much more powerful method to use when follow-up times vary considerably. We were also able to control for other explanatory variables, such as age at exposure, using the proportional hazards method. Although we realize that many occupational studies use the SMR method, we think that more powerful analytic methods are available and should be used. The calculation of SMRs would also require an extensive amount of additional time and probably would not add much to the results of the study. Another reviewer suggested that we calculate cumulative exposure values. We were also unable to do this because we were unable to determine the number of years each individual spent at work in orchards.

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