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Health Impacts of Pesticide Exposure in a Cohort of Outdoor Workers

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We compared mortality of 1,999 outdoor staff working as part of an insecticide application program during 1935–1996 with that of 1,984 outdoor workers not occupationally exposed to insecticides, and with the Australian population. Surviving subjects also completed a morbidity questionnaire. Mortality was significantly higher in both exposed and control subjects compared with the Australian population. The major cause was mortality from smoking-related diseases. Mortality was also significantly increased in exposed subjects for a number of conditions that do not appear to be the result of smoking patterns. Compared with the general Australian population, mortality over the total study period was increased for asthma [standardized mortality ratio (SMR) = 3.45; 95% confidence interval (CI), 1.39–7.10] and for diabetes (SMR = 3.57; 95% CI, 1.16–8.32 for subjects working < 5 years). Mortality from pancreatic cancer was more frequent in subjects exposed to 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane (SMR = 5.27; 95% CI, 1.09–15.40 for subjects working < 3 years). Compared with the control population, mortality from leukemia was increased in subjects working with more modern chemicals (standardized incidence ratio = 20.90; 95% CI, 1.54–284.41 for myeloid leukemia in the highest exposure group). There was also an increase in self-reported chronic illness and asthma, and lower neuropsychologic functioning scores among surviving exposed subjects when compared with controls. Diabetes was reported more commonly by subjects reporting occupational use of herbicides. These findings lend weight to other studies suggesting an association between adverse health effects and exposure to pesticides. ***Key words:*** **asthma, cohort study, DDT, diabetes, leukemia, neoplasms, pancreatic cancer, pesticides.** ***Environ Health Perspect*** **111:724–730 (2003). doi:10.1289/ehp.5885 available via *http://dx.doi.org/* [Online 30 October 2002]**

The widespread use of synthetic chemicals after the Second World War has revolutionized agricultural practice. Initial studies of the possible health effects of these substances on humans were small and reassuring (Cameron and Burgess 1945; Hayes and Durham 1956). During the 1960s, however, it became evident that persistent pesticides were having an adverse impact on ecologic communities (Ramade 1987; Ratcliffe 1970). This led to a number of more extensive epidemiologic investigations exploring the possible impact of these exposures on human health [International Agency for Research on Cancer (IARC) 1991; Pearce and Reif 1990). These studies faced numerous methodologic problems common to environmental epidemiology, and even today, our understanding of the relationship between pesticides and human health is limited (Blondell 1990).

In this paper we describe a historical cohort study undertaken to examine the health outcomes of a group of agricultural workers with high occupational pesticide exposures. The main group investigated in this study comprised all identifiable field staff employed by the New South Wales (NSW), Australia, Board of Tick Control between 1935 and 1995. The board constructed and operated over 1,600 cattle dips in a tick quarantine zone on the east coast of Australia, and over 3,000 staff worked on the program during the study period. Subjects interviewed during the course of the study report extremely high and recurrent exposures to the insecticides used in the dips. This is supported by limited evidence from an occupational monitoring program.

Methods

Identification of cohort. One of the methodologic challenges encountered by occupational cohort studies is the "healthy worker effect," characterized by a tendency for relatively healthy individuals to be more likely to gain employment and remain employed (Breslow and Day 1987). This may potentially bias studies toward finding lower mortality rates in an occupational cohort when compared with the general community and thus mask true increases in mortality. To deal with this problem, our study was designed to allow comparison of the exposed group with two reference populations: the Australian population as a whole, and a control group of outdoor workers drawn from a similar socioeconomic background but not occupationally exposed to insecticides.

The study population comprised a dynamic cohort divided into exposed and control subcohorts. To facilitate matching with death registries, the cohort was restricted to male workers with known dates of birth.

The exposed subcohort was made up of all male staff identified by a search of NSW government records as having worked as field officers or laboratory staff for the NSW Board of Tick Control at any time since 1935. A total of 1,999 subjects met these criteria.

The control subcohort was made up of all male staff identified by local governments from the same region as having worked as outdoor field officers at any time since 1935. A small group of office staff who had worked for the Board of Tick Control were also included in this group. A total of 1,984 subjects met these criteria.

Subjects were followed from 1 January 1935, or their subsequent entry to the study, until their death, loss to follow-up, or study completion on 1 January 1996.

Ascertainment of vital status. Vital status was ascertained by matching the cohort with national death registers and health insurance records. This matching was generally undertaken using probabilistic record linkage.

Australian citizens are required to register with the Australian Health Insurance Commission to receive a universal health care rebate (Medicare). Medicare commenced operation in October 1983, and the cohort was matched with commission records for registration at any time after this date. Subjects with current Medicare registration were considered alive. The cohort was also matched with the Australian National Deaths Index (operating from 1980) and with the NSW and Queensland Deaths Registers for 1945–1979.

Survey of surviving cohort members. We also attempted to locate all cohort members who were thought to still be alive. Possible contact addresses were found for a total of 1,533 subjects, who were sent a questionnaire by mail. Questions focused on factors that might potentially confound the broader study, such as smoking or alcohol consumption, pesticide exposure history, a validated neuropsychologic score, and a range of nonfatal outcomes that may potentially be related to pesticide exposure.

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Analytical methods. To compare the exposed subcohort with the general Australian population, we calculated standardized mortality ratios (SMRs) using person-years analysis, based on a published model allowing stratification by year at risk, length of follow-up, age at risk, and cumulative duration of employment (Pearce and Checkoway 1987). Exact Poisson 95% confidence intervals (CIs) were estimated around these SMRs.

A range of models was used for this analysis. The default model followed all subjects from 1935 to 1995 inclusive, incorporating a lag period of 10 years and excluded all subjects for whom complete information was not available.

We also employed a person-years method, using Poisson regression, to calculate standardized incidence ratios (SIRs) to compare deaths in the exposed subcohort, or its different exposure subgroups, with deaths in the control subcohort. To allow for the sampling variability resulting from small numbers in the denominator, CIs were calculated using likelihood ratio-based methods, considered to be more robust than classical approaches when the sample size is small (Venzon and Moogavcar 1988).

Questions in the survey distributed to surviving cohort members were analyzed using logistic regression. The model included log of subject age and was adjusted for possible confounding from smoking. For analysis of continuous outcome variables, we used analysis of variance, adjusting for age.

Exposure assessment. Board of Tick Control records indicate that chemical usage followed defined patterns over the study period (Table 1). For the purposes of analysis, these periods were categorized into periods of arsenic use (1935–1955), 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane (DDT) use (1955–1962), and modern chemical use (1963–1996). The number of subjects working during each exposure period is shown in Table 2.

A subject's period of employment was used to estimate both the type of chemical he was likely to have been exposed to and the duration of this exposure. This was categorized into exposure groups: "All" equates to any employment during a particular period, "Dose 0" relates to exposed subjects not yet past 10 year exposure lag, "Dose 1" equates to < 5 years employment, "Dose 2" equates to ≥ 5 to < 15 years of employment, and "Dose 3" equates to ≥ 15 years of employment. For the DDT period, "Dose 1" represents < 3 years and "Dose 2" represents ≥ 3 years of employment.

Results

Results of an occupational monitoring program undertaken during the early 1980s by the NSW Health Department support subject reports of high occupational pesticide exposure. Sampling in that program included total serum DDT levels. Although DDT use had stopped at least 18 years before this sampling period, DDT has a long half-life in humans, and the DDT metabolite DDE (1,1,dichloro-2,2-bis(*p*-chlorophenyl)ethylene; included in total DDT results) is a good indicator of past exposure (Mussalo-Rauhamaa 1991). The total serum DDT levels of cohort members are shown in Table 3. Only three exposed subjects who had worked during the DDT era could be matched with subjects in the sampling program. However, the serum mean level in these three DDT-exposed subjects was over five times that of the 14 matched members of the control subcohort and eight times that of the 8 exposed subjects who did not work during the DDT era.

Subjects in the exposed subcohort who responded to the study survey were also significantly more likely to report using pesticides occupationally [odds ratio (OR) = 10.39; 95% CI, 6.15–17.54].

Exposed and control subjects did, however, offer similar survey responses on key lifestyle indicators, suggesting they were drawn from comparable populations (Table 4). The average years at school was significantly different ($p < 0.01$), but this value was only 0.4 years. When age-adjusted responses were compared using logistic regression, there was no significant difference between either current smoking or alcohol consumption patterns. Respondents from the exposed subcohort were, however, significantly more likely to report ever having smoked (OR = 1.66; 95% CI, 1.21–2.28).

Table 5 illustrates the determination of vital status for cohort members. Of the 3,983 cohort members, 2,913 enrolled with Medicare after its commencement in 1983. Enrollment ceased for 337 of these subjects, and death certificates were found for 328 of these, leaving 9 lost to follow-up.

A further 1,070 subjects never enrolled with Medicare. Employment records indicate that 154 of these subjects were alive after 1983, and they were considered to have chosen not to enroll or to have escaped matching. For analysis, these subjects were considered alive until their last contact with the study. Of the remaining subjects who never enrolled with Medicare, there were 666 death register matches. The remaining 261 subjects were considered to have been lost to follow-up, giving a total of 270 (6.8%) subjects lost to

Table 1. Chemicals used in cattle dips during different periods and the classification used in this study.

Tickicide	Period of use
Period of arsenic use	
Arsenic (trioxide)	1935–1955
Period of DDT use	
DDT	1955–1962
Benzene hexachloride	1955–1962
Early period of modern chemical use	
Coumaphos	1962–1965
Carbophenothion	1962
Carbaryl	1963–1970
Chlorpyrifos	1969–1974
Bromophos ethyl	1969
Dioxothion	1962–1976
Ethion	1962–1976
Chlordimeform	1973–1976
Cymyazole	1977–1986
Late period of modern chemical use	
Chlormethiuron	1977
Amitraz	1976–present
Promacyl	1977–present
Cypermethrin	1979–present
Chlorfenvinphos	1979–present
Flumethrin	1986–present

Table 3. Results of biological monitoring for DDT of study subjects, 1980–1987.

	Serum DDT		
	No.	Mean total (ppb)	Range
Controls	14	6.7	0–14
DDT-exposed subjects	3	39.3	10, 28, 80[a]
Other exposed subjects	8	4.25	0–11

[a]Actual results for three subjects.

Table 4. Odds of self-reported behaviors in exposed subjects compared with controls.

	OR	95% LCL	95% UCL
Ever drinker	1.47	0.85	2.54
Current smoker	1.16	0.80	1.68
Ever smoker	1.66*	1.21	2.28

Abbreviations: LCL, lower confidence limit; UCL, upper confidence limit.
*Significant at $p < 0.05$.

Table 5. Vital status by exposure group.[a]

	Exposed	Controls
Total subjects	1,999	1,984
Medicare match	1,353	1,560
Medicare enrollment ended	204	133
Death register match	776	392
Lost to follow-up	145	125

[a]Numbers do not add up because some subjects were matched with death registry before Medicare enrollment ceased.

Table 2. Number of subjects working during different chemical periods.

	No. of subjects	
Period	Working exclusively during this period	Working at all during this period
Arsenic use	5 (1 control, 4 exposed)	528 (199 controls, 329 exposed)
DDT use	144 (24 controls, 120 exposed)	579 (185 controls, 394 exposed)
Modern chemical use	2,100 (1,257 controls, 843 exposed)	2,949 (1,586 controls, 1,363 exposed)

follow-up. Vital status ascertainment for the study is therefore estimated at 93.2%, a figure considered acceptable in large cohort studies (Checkoway et al. 1989).

The initial response to the questionnaire mailout was poor. Nonresponding subjects were then followed up by telephone. The total response rate for the questionnaire was 54.9%, with a further 17% choosing the option of returning a blank questionnaire. The percentage of exposed subjects and controls choosing to return a blank questionnaire was almost identical. However, exposed subjects (60.9%) were more likely to respond than controls (51.6%), and this difference was significant after adjusting for age using Mantel-Haenszel analysis ($p < 0.001$). Because a large proportion of the subjects failing to return a questionnaire could also not be contacted by phone, the low response rate may largely reflect incorrect contact addresses. A total of 1,167 (391 control, 776 exposed) deaths were identified among cohort members.

Outcomes with significant results in SMR and SIR analysis using the default model are shown in Tables 6 and 7, and these findings are expanded on in the "Discussion." Significant increases in mortality were identified in at least one exposure group for total deaths, asthma, diabetes, ischemic heart disease, respiratory disease, total cancers, pancreatic cancer, and leukemias. There were no significant increases in SMR or SIR in any exposure group for cancers of the bladder, brain, colon, prostate, lung, rectum, or stomach, nor for melanoma, multiple myeloma, non-Hodgkin lymphoma (NHL), or emphysema (Table 8). There was no significant change in SMR for circulatory disease, although the most exposed group working during the arsenic period showed an increased SIR. Full results of analysis are available on request from the authors.

Numerous other analyses were undertaken using different models such as varying

Table 6. Significant SMRs of subjects compared with the Australian population (adjusted for age and period of follow-up).

		All chemical periods			Arsenic period			DDT period			Modern chemical period		
Exposure group	OBS	SMR	LCL	UCL	SMR	LCL	UCL	SMR	LCL	UCL	SMR	LCL	UCL
All deaths													
Controls	331	1.08	0.96	1.22	1.00	0.81	1.23	1.07	0.92	1.24	1.24*	1.01	1.50
All	607	1.10*	1.01	1.20	0.97	0.83	1.12	1.09	0.98	1.20	1.28*	1.06	1.53
Dose 0	72	1.00	0.78	1.26									
Dose 1	104	1.03	0.84	1.24	1.00	0.75	1.30	1.03	0.78	1.33	1.09	0.81	1.44
Dose 2	177	1.04	0.90	1.21	0.80	0.60	1.04	1.10	0.98	1.23	1.39*	1.07	1.77
Dose 3	228	1.19	1.04	1.35	1.16	0.89	1.49				2.13	0.97	4.04
Asthma													
Controls	2	1.61	0.19	5.81	0.00	0.00	7.48	1.40	0.04	7.81	2.22	0.06	12.37
All	7	3.45*	1.39	7.10	3.94	0.81	11.51	2.27	0.47	6.64	6.44*	1.33	18.82
Dose 1	2	3.87	0.47	14.00	3.61	0.09	20.09	0.00	0.00	12.11	4.36	0.11	24.31
Dose 2	3	3.89	0.80	11.38	6.09	0.74	21.99	2.80	0.58	8.17	9.31*	1.13	33.62
Dose 3	2	2.69	0.33	9.71	0.00	0.00	19.23				0.00	0.00	136.9
Diabetes													
Controls	2	0.52	0.06	1.87	0.85	0.02	4.73	0.40	0.01	2.21	0.77	0.02	4.31
All	12	1.49	0.71	2.74	0.85	0.02	4.73	1.22	0.45	2.65	2.70	0.74	6.91
Dose 1	5	3.57*	1.16	8.32	1.47	0.04	8.18	1.30	0.03	7.26	2.96	0.36	10.71
Dose 2	4	1.66	0.45	4.26	0.00	0.00	3.43	1.20	0.39	2.80	2.76	0.33	9.95
Dose 3	1	0.34	0.00	1.92	0.00	0.00	4.18				0.00	0.00	36.71
Ischemic heart disease													
Controls	115	1.38*	1.13	1.68	1.80*	1.29	2.45	1.38*	1.08	1.74	1.31	0.91	1.83
All	205	1.37*	1.18	1.59	1.36*	1.02	1.78	1.31*	1.09	1.56	1.28	0.91	1.76
Dose 1	43	1.70*	1.24	2.29	0.85	0.44	1.48	2.09*	1.37	3.07	1.32	0.79	2.06
Dose 2	57	1.25	0.95	1.62	1.56	0.98	2.37	1.20	0.98	1.45	1.14	0.65	1.85
Dose 3	71	1.32*	1.03	1.66	1.79*	1.07	2.79				2.55	0.53	7.46
Respiratory disease													
Controls	33	1.50*	1.02	2.12	1.29	0.59	2.44	1.43	0.87	2.21	1.92	0.99	3.36
All	72	1.61*	1.24	2.07	1.72*	1.10	2.55	1.60*	1.16	2.13	1.87*	1.02	3.14
Dose 1	8	1.09	0.47	2.14	2.36*	1.08	4.49	0.45	0.06	1.64	1.52	0.49	3.54
Dose 2	19	1.39	0.84	2.17	1.67	0.76	3.17	1.81*	1.31	2.43	1.83	0.73	3.76
Dose 3	34	2.03*	1.41	2.84	1.25	0.46	2.73				5.68	0.69	20.52
All cancer													
Controls	85	1.07	0.83	1.35	1.01	0.61	1.57	1.01	0.73	1.38	1.30	0.88	1.84
All	148	1.18	0.99	1.41	1.01	0.70	1.40	1.15	0.92	1.42	1.29	0.89	1.80
Dose 1	26	1.06	0.69	1.56	1.16	0.64	1.95	1.07	0.57	1.83	1.21	0.68	1.99
Dose 2	43	1.12	0.81	1.51	0.66	0.30	1.26	1.16	0.92	1.46	1.20	0.67	1.97
Dose 3	59	1.30	0.99	1.68	1.31	0.68	2.29				2.75	0.75	7.03
Pancreatic cancer													
Controls	2	0.67	0.08	2.41	0.00	0.00	3.25	0.54	0.01	2.99	0.94	0.02	5.22
All	8	1.61	0.69	3.16	1.78	0.37	5.19	1.98	0.79	4.07	0.00	0.00	2.53
Dose 1	1	0.88	0.02	4.91	3.39	0.41	12.23	5.27*	1.09	15.40	0.00	0.00	5.26
Dose 2	2	1.12	0.14	4.05	0.00	0.00	4.51	1.35	0.37	3.44	0.00	0.00	5.45
Dose 3	5	2.43	0.79	5.66	2.30	0.06	12.83				0.00	0.00	47.70
Leukemia (all types)													
Controls	4	1.93	0.53	4.94	1.69	0.04	9.39	1.61	0.19	5.80	2.61	0.32	9.44
All	7	1.79	0.66	3.89	0.92	0.02	5.11	1.69	0.46	4.34	3.70	0.76	10.81
Dose 1	2	2.51	0.30	9.08	2.59	0.07	14.43	2.57	0.06	14.29	5.20	0.63	18.79
Dose 2	1	0.83	0.02	4.61	0.00	0.00	7.08	1.52	0.31	4.45	0.00	0.00	7.82
Dose 3	3	2.22	0.46	6.48	0.00	0.00	10.71				22.89	0.58	127.53

Abbreviations: LCL, lower confidence limit; OBS, number of deaths observed; UCL, upper confidence limit.
*Significant at $p < 0.05$.

the exposure lag or using an average duration of employment to include subjects without a known final date of employment. In general, these made little difference in the study findings. One notable exception was removing the exposure lag for analysis of leukemia. When the exposure lag was removed, the SMR for leukemia in exposed subjects working during the modern chemical period was of borderline significance (SMR = 3.62; 95% CI, 0.99–9.26), and the SMR for the lowest exposure group became statistically significant (SMR = 6.41; 95% CI, 1.32–18.73).

Default analysis of the modern chemical period excluded subjects who had worked at other times in the study. Using this approach, there was only a small increase in mortality from NHL. When subjects who had also worked in other periods were included in the analysis, both the SMR and lower confidence limit for NHL increased (SMR = 2.22; 95% CI, 0.72–5.18). When NHL mortality among this group was compared with controls, the increase in SIR for all exposed subjects was of borderline significance (SIR = 8.71; 95% CI, 0.97–78.12), and this was statistically significant for exposed subjects working 5–15 years (SIR = 11.60; 95% CI, 1.11–121.74).

Results of comparisons of self-reported morbidity between the exposed and control subcohorts after adjusting for age and smoking are shown in Table 9. Because a number of control subjects reported occupational use of herbicides, morbidity was also compared by subject's reported herbicide exposure. Subjects reporting herbicide use had significantly increased odds for diabetes (OR = 2.26; 95% CI, 1.15–4.43) and hay fever (OR = 1.82; 95% CI, 1.23–2.69) after adjusting for age and smoking status.

Discussion

Methodologically, this study has a number of strengths. The study is of a moderately sized cohort followed over a prolonged period (over 82,000 person-years of follow-up), with good outcome ascertainment. The healthy worker effect also appears to have been largely overcome by the study's long follow-up period.

Including a control group allows some assessment of the degree of confounding by smoking and other lifestyle factors on the cohort outcomes. Although these two subcohorts were not drawn from the same

Table 7. SIRs of mortality in exposed subjects and controls by exposure group (adjusted for log age).[a]

	All periods			Arsenic period			DDT period			Modern period		
Dose	SIR	LCL	UCL	SIR	LCL	UCL	SIR	LCL	UCL	SIR	LCL	UCL
All deaths												
All	1.13	0.98	1.30	1.11	0.94	1.32	1.17*	1.01	1.36	1.14	0.89	1.45
Dose 1	0.96	0.77	1.20	1.07	0.85	1.35	1.10	0.83	1.45	0.93	0.67	1.28
Dose 2	1.12	0.93	1.35	0.96	0.74	1.23	1.18*	1.01	1.38	1.34	0.98	1.81
Dose 3	1.25*	1.05	1.49	1.53*	1.16	2.02				1.65	0.84	3.25
Asthma												
All	3.09	0.62	15.52	2.79	0.44	17.72	1.62	0.30	8.85	4.38	0.42	45.78
Dose 1	3.16	0.44	22.45	–	–	–	–	–	–	3.05	0.18	50.38
Dose 2	3.53	0.57	21.81	–	–	–	–	–	–	6.71	0.52	86.70
Dose 3	2.46	0.31	19.23	–	–	–					0.00	0.00
Diabetes												
All	3.95	0.84	18.44	0.91	0.08	10.61	4.88	0.90	26.45	4.71	0.50	44.44
Dose 1	7.68*	1.49	39.61	–	–	–	4.51	0.40	51.31	–	–	–
Dose 2	4.06	0.74	22.42	–	–	–	4.98	0.87	28.36	–	–	–
Dose 3	0.93	0.08	10.52	–	–	–				–	–	–
Circulatory disease												
All	1.08	0.89	1.32	1.09	0.86	1.39	1.16	0.94	1.43	0.98	0.68	1.42
Dose 1	0.99	0.73	1.34	0.91	0.64	1.29	1.18	0.81	1.73	0.90	0.56	1.44
Dose 2	1.08	0.84	1.40	0.92	0.65	1.32	1.15	0.92	1.44	1.07	0.67	1.70
Dose 3	1.13	0.89	1.45	1.82	1.27	2.60				1.08	0.34	3.44
All cancers												
All	1.24	0.93	1.66	1.11	0.78	1.58	1.21	0.89	1.64	1.29	0.80	2.07
Dose 1	1.03	0.66	1.61	1.21	0.76	1.91	1.07	0.60	1.92	1.13	0.62	2.06
Dose 2	1.16	0.80	1.69	0.95	0.57	1.60	1.24	0.90	1.70	1.30	0.70	2.41
Dose 3	1.49*	1.05	2.13	1.21	0.65	2.26				2.94*	1.03	8.34
Leukemia												
All	1.24	0.36	4.29	–	–	–	–	–	–	3.02	0.54	16.96
Dose 1	1.34	0.26	6.96	–	–	–	–	–	–	3.33	0.52	21.38
Dose 2	0.57	0.06	5.02	–	–	–	–	–	–	–	–	–
Dose 3	2.06	0.43	9.92	–	–	–				27.44*	2.23	337.99
Lymphocytic leukemia												
All	1.42	0.18	11.54	–	–	–	0.90	0.07	11.45	7.45	0.33	170.74
Dose 1	1.86	0.16	21.11	–	–	–	–	–	–	9.74	0.46	205.45
Dose 2	1.79	0.14	22.14	–	–	–	–	–	–	–	–	–
Dose 3	–	–	–	–	–	–				–	–	–
Myeloid leukemia												
All	1.15	0.25	5.39	0.60	0.06	6.05	1.64	0.30	8.98	1.94	0.25	15.39
Dose 1	1.15	0.12	11.21	1.62	0.16	15.83	2.99	0.30	29.76	1.83	0.16	21.13
Dose 2	0.00	0.00	–	0.00	0.00	–	1.32	0.20	8.69	–	–	–
Dose 3	3.92	0.65	23.63	0.00	0.00	–				20.90*	1.54	284.41
Pancreatic cancer												
All	2.89	0.60	13.85	3.13	0.56	17.62	2.72	0.67	11.01	–	–	–
Dose 1	1.54	0.14	17.01	–	–	–	7.00*	1.39	35.32	–	–	–
Dose 2	2.07	0.29	14.93	–	–	–	1.82	0.39	8.49	–	–	–
Dose 3	4.79	0.86	26.59	–	–	–				–	–	–

Abbreviations: –, failure to converge; LCL, lower confidence limit; UCL, upper confidence limit.
[a]Poisson regression adjusting for log age with likelihood ratio confidence limits, 10-year exposure lag. For all deaths, analysis was also adjusted for whether the year of death occurred before or after 1960. *Significant at $p < 0.05$.

occupational population, a range of evidence suggests they shared similar but not identical lifestyles. This includes their similar area of residence, similarity of occupation, and self-reported alcohol, smoking, and schooling experience.

As with much environmental or occupational epidemiology, exposure assessment remains a problem, although limited biological monitoring supports assumptions about high pesticide exposures in the exposed subgroup. A number of pesticides were used during the study period, and this allows for analysis of the impact of specific chemicals in different periods. However, not all exposed subjects working at a particular point in time used the same chemicals. This may mask true associations, as the experience of subjects exposed to that chemical are pooled with other exposed subjects using different pesticides.

Although it is common practice to use duration of exposure as a surrogate for exposure dose, it is also possible that the first years of employment were periods of relatively high exposure, as newly employed staff may have been given the dirtiest jobs and were less skilled at avoiding exposure. It is also possible that staff with the most difficulty tolerating these early high exposures, possibly due to genetic variance in their ability to metabolize, tend to leave employment after shorter periods. Such a trend has been identified in at least one small study of genetic susceptibility and has even been suggested as an explanation for the healthy worker effect (Au et al. 1999). A number of positive associations identified in this study were found in the shortest exposure group.

This study also undertook a large number of statistical analyses for a wide range of outcomes. SMR and SIR analysis were undertaken on over 20 separate conditions, with further analysis of a number of separate exposure groups and exposure periods for each condition. This needs to be considered when assessing the results as, by chance, a statistically significant result might be expected for every 20 analyses.

To avoid the risk that significant results are simply a consequence of multiple comparisons, the study findings should be interpreted using a weight-of-evidence approach. Factors that might add weight to a positive finding include consistency in results from both internal and external analysis, supporting evidence from the survey of surviving cohort members, the size of the association, the number of subjects involved, trends in exposure categories, evidence from other research, and whether the identified association is physiologically plausible.

The identified increase in all-cause mortality in both exposed and nonexposed subcohorts is somewhat surprising, given the general experience in occupational studies of a healthy worker effect—sometimes amplified in studies on pesticides by the otherwise healthier lifestyles of farmers (Alberghini et al. 1991). The main cause of the increase in this study is excess mortality from circulatory disease, respiratory disease, and lung cancer.

There is considerable evidence to suggest that these findings reflect smoking patterns in both the exposed and control subcohorts. Although some authors have suggested that the potential confounding effect of smoking is modest unless the smoking habits of a study population are quite extreme (Blair et al. 1988), a number of methods have been proposed for assessing the impact of smoking in epidemiologic research (Axelson and Steenland 1988). If smoking rates are high, a consistent increase in all smoking related diseases might be expected. Not only is this the case in this study, but the increase also occurs across the total study period, arguing against it being the result of a particular chemical exposure. Deaths from smoking-related diseases are also increased in the control subcohort and in exposed subjects not yet past the 10-year exposure lag. These disease patterns suggest both subcohorts had increased smoking rates compared with the Australian population. This is supported by the lower, nonsignificant incidence ratios when smoking-related disease rates are compared between the two groups.

The increases in mortality from respiratory and ischemic heart disease observed in this study are therefore likely to relate to smoking patterns. However, it is unlikely that smoking is also responsible for the identified increases in mortality from two other smoking-related diseases: pancreatic cancer and asthma. This remains high when exposed subjects are compared with controls, and both SMRs and SIRs are clearly higher than those for lung cancer, which is an indicator of any difference in smoking habits between the two compared subcohorts.

All exposed subjects dying from pancreatic cancer worked during the period of DDT use, and mortality during this period was elevated compared with both the Australian population and controls. For those working less than 3 years, this increase was statistically significant compared with both controls and the Australian population.

Table 8. Outcomes not reaching statistical significance: SMRs of exposed subjects compared with the Australian population (adjusted for age and period of follow-up) and SIRs of mortality in exposed subjects compared with controls adjusted for log age.

Disease	EXP	OBS	SMR	LCL	UCL	SIR	LCL	UCL
Emphysema	4.62	6	1.30	0.48	2.82	0.54	0.17	1.69
Bladder cancer	3.73	3	0.80	0.17	2.35	0.40	0.09	1.84
Brain cancer	3.30	3	0.91	0.19	2.65	3.13	0.29	33.43
Colon cancer	11.23	6	0.53	0.20	1.16	0.52	0.18	1.54
Lung cancer	37.24	49	1.32	0.97	1.74	1.15	0.72	1.83
Melanoma	ND	ND	ND	ND	ND	0.62	0.10	3.72
Multiple myeloma	ND	ND	ND	ND	ND	0.59	0.04	9.87
NHL	3.66	6	1.64	0.60	3.57	4.57	0.53	39.39
Prostate cancer	12.11	16	1.32	0.76	2.15	1.05	0.46	2.39
Rectal cancer	4.94	8	1.62	0.70	3.19	2.02	0.52	7.86
Stomach cancer	9.11	11	1.21	0.60	2.16	2.12	0.66	6.87

Abbreviations: EXP, number of deaths expected; LCL, lower confidence limit; ND, no Australian data; OBS, number of deaths observed; UCL, upper confidence limit. Includes subjects employed at any time during this period.

Table 9. ORs for self-reported outcomes in exposed subcohort compared with controls.[a]

Outcome	Controls	Exposed	OR	LCL	UCL
Asthma	53	55	1.59*	1.05	2.43
Child with asthma	92	71	1.45*	1.01	2.09
Hay fever	93	56	0.98	0.67	1.45
Eczema/dermatitis	42	47	1.62*	1.02	2.56
Bronchitis	60	53	1.32	0.87	2.01
Emphysema	8	14	1.99	0.80	4.93
Skin cancer	259	168	0.86	0.64	1.16
Depressed	55	43	1.22	0.73	2.05
Birth defect	28	19	1.01	0.53	1.92
Difficulty achieving pregnancy	22	20	1.37	0.72	2.61
Miscarriage	90	74	1.40	0.98	2.00
Recurring ill health	21	35	2.73*	1.54	4.84
Chronic fatigue syndrome	8	12	2.66*	1.01	7.02
Diabetes	23	21	1.13	0.59	2.16
Arboviral infection	30	30	2.14*	1.21	3.78
Circulatory disease	95	83	1.23	0.86	1.75
Parkinson disease	1	2	3.30	0.28	38.94

Abbreviations: LCL, lower confidence limit; UCL, upper confidence limit.
[a]Logistic regression by group (exposed subject or control) adjusted for log age, ever smoked. *Significant at $p < 0.05$.

Although DDT was first used in 1955, it was introduced slowly into the dipping program and was not used in the majority of dips until 1961. This may have resulted in misclassification bias toward the null, as in the early years of the DDT period, many exposed subjects may have used DDT infrequently, if at all. If there was a true association between DDT exposure and pancreatic cancer, it might therefore be expected that this relationship would be stronger for subjects working in the later years of the DDT era, when exposure to the chemical was more likely. Members of the exposed subcohort working during the later part of this period do show both increased standardized mortality rates and increasing lower confidence limits. However, mortality rates still remain short of statistical significance (for subjects working during 1962, SMR = 2.41; 95% CI, 0.89–5.25; SIR = 4.73; 95% CI, 0.89–25.15). When exposed subjects not yet past the 10-year exposure lag were added to the control group to increase study power, this increase is statistically significant (SIR = 6.44; 95% CI, 1.22–34.13).

These findings are consistent with a causative association between DDT exposure and pancreatic cancer and are consistent with the results of other studies. There is, however, still no general agreement on whether pesticides as a whole, or DDT in particular, are associated with pancreatic cancer (Garabrant et al. 1992; Hoppin et al. 2000; Porta et al. 1999).

When compared with the Australian population, members of the exposed group working in the modern chemical period had an increase in mortality from diabetes (type unspecified) of borderline statistical significance (SMR = 3.00; 95% CI, 0.97–7.00). This association was statistically significant when all exposure lag models other than the 10-year default used in analysis were applied. For exposed subjects as a group working in the early period of modern chemical use (1963–1976), the increase was also significant (SMR = 3.08; 95% CI, 1.00–7.20). There was also significantly increased mortality from diabetes for exposed subjects as a group over the total study period in the < 5 years exposure group, and this persisted when exposed subject were compared with controls. There were also large increases in mortality when exposed subjects were compared with controls over different chemical periods, particularly the modern era, although none of these were statistically significant.

Although the increased death rates from diabetes are based on a total of only 14 deaths, a number of factors suggest this association may be real. Firstly, the association is relatively large and seems to relate to a specific chemical period (post-1963), suggesting a specific exposure during this time exerted an effect. Mortality is not raised for the control group, suggesting the outcome was not influenced by an underlying lifestyle difference. A true association is also supported by the finding in the survey of surviving subjects of a higher prevalence of diabetes among those reporting herbicide use, although it is not known what type of herbicides were used.

There is evidence from other studies that supports a possible association between pesticide exposure and diabetes. A study of veterans of Operation Ranch Hand during the Vietnam War found increased diabetes prevalence with increasing exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, a contaminant of the herbicide Agent Orange (Henriksen et al. 1997). Before 1980, a wide range of pesticides were used by subjects of our own study, including 2,4-D and 2,4,5-T, substances present in Agent Orange.

Little other research has been done on diabetes and pesticides, although a 1967 study of 59 highly exposed workers at the Montrose chemical factory in the United States found high DDT levels in fat and an 8.6% prevalence of diabetes (Laws et al. 1967). A study of 3,579 U.S. workers involved in the production of DDT found increased mortality from diabetes, but not in those thought to be exposed to DDT (Wong et al. 1984). An early cohort study of 2,620 pesticide-exposed workers suggested a higher prevalence of diabetes in subjects with high DDT levels, although the study had a low response rate and may have been subject to reporting bias (Morgan et al. 1980). Another study calculated proportionate mortality ratios from 748 deaths among corn wet-milling workers and found increased mortality from diabetes and a 3-fold excess of pancreatic cancer deaths among some workers (Thomas et al. 1985).

Several case studies of diabetes induced by pesticide poisoning have been reported (Takahashi et al. 2000), and one study of 23 subjects admitted to an Indian intensive care unit with carbamate or organophosphate poisoning found 69% of subjects demonstrated transient glycosuria (Shobha and Prakash 2000).

Diabetes has also been suggested as a risk factor for pancreatic cancer (Calle et al. 1998) and is a well-known risk factor for circulatory disease. Mortality from both these conditions was elevated in this study.

Although the findings of our study are not conclusive, they are consistent with an increase in diabetes prevalence and mortality as a result of pesticide exposure. Whether this increase relates to a particular chemical, class of chemicals, or multiple chemical exposures is unclear. On the other hand, the findings may simply result from the large number of analyses undertaken in this study. Diabetes warrants further investigation as an outcome in studies exploring the impact of pesticide exposure.

Evidence was also found for both increased mortality from asthma and increased prevalence of atopic conditions among surviving members of the exposed subcohort and their offspring. Although it is possible mortality ratios might be confounded by the influence of smoking, mortality from asthma was also significantly increased in exposed subjects when they were compared with the control group, suggesting the influence of smoking was limited. The association was not evenly distributed over the study period, suggesting it was also not the result of other occupational exposures such as cattle dander. Both asthma and diabetes relate to immune function, and there is some evidence this can be compromised by pesticide exposure (Krzystyniak et al. 1995).

Comparison of cohort mortality from leukemia with the Australian population is hampered by the lack of Australian data on specific leukemia types for the majority of the study period. The two main forms of leukemia, lymphocytic and myeloid, may be thought of as different diseases and are best examined separately. If a toxic agent such as a pesticide exerted its effect only on a specific form of this disease, aggregating this information would make it more difficult to identify a real relationship.

We identified a nonsignificant increase in SMR for leukemias as a group when exposed subjects working during the era of modern chemical use were compared with the Australian population. When the exposure lag was removed, this increase was of borderline significance (SMR = 3.62; 95% CI, 0.99–9.26), and the SMR for the lowest exposure group became statistically significant (SMR = 6.41; 95% CI, 1.32–18.73). There is considerable empirical and biological logic for removing the lag period from this analysis, as leukemia risks may rise soon after leukemogenic exposure.

Mortality for subjects working during this period was also increased compared with the control group, and this increase was statistically significant for subjects in the highest exposure category (SIR = 27.44; 95% CI, 2.23–337.99). Large SIRs were observed for both lymphatic and myeloid leukemia, and the increase in mortality for myeloid leukemia was also statistically significant (SIR = 20.90; 95% CI, 1.54–284.41). There is a suggestion of a dose–response relationship during this period, with a tendency for mortality to be higher in subjects working for longer terms.

Several epidemiologic studies have suggested an association between pesticide exposure or farming and leukemia (Brown et al. 1990; Kristensen et al. 1996; Viel and Richardson 1993). Increased mortality from leukemia has also been identified in gardeners (Hansen et al. 1992) and aerial pesticide applicators (Cantor and Silberman 1999),

suggesting the identified associations are not the result of other farm-related exposures such as bovine viruses. In our study, the increase in mortality from leukemia across the different chemical periods is uneven, also suggesting an effect independent of bovine exposure.

Our findings are based on a small number of events in each leukemia category and may simply reflect the multiple comparisons undertaken during analysis. However, they are also consistent with the relationship between exposure to pesticides and leukemia identified by other researchers.

The default analytical model also identified nonsignificant increases in mortality from a number of other conditions previously associated with pesticide exposure. These include NHL, brain cancer, and prostate cancer. Failure to identify these increases as significant may reflect the methodologic limitations and power of the study, and the findings do not conflict with the possibility these may in fact be true associations.

Although the survey of surviving cohort members identified possible associations between several self-reported outcomes and membership of the exposed subcohort, methodologic limitations, including a low response rate and the potential for recall bias, limit the weight that can be put on this evidence. Possible associations identified in the survey included neuropsychologic dysfunction, chronic fatigue syndrome, and atopic conditions.

In conclusion, this study identifies associations between a number of adverse outcomes and pesticide exposure. These findings warrant further investigation and reinforce the need to minimize exposure to pesticides in both occupational settings and the broader environment.

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