An Update of Mortality Among Chemical Workers Potentially Exposed to the Herbicide 2,4-Dichlorophenoxyacetic Acid and Its Derivatives

Louis J. Bloemen, MPH
Jack S. Mandel, PhD
Gregory G. Bond, PhD
Alex F. Pollock, MS
Robert P. Vitek, MD
Ralph R. Cook, MD, MPH

Four years of additional mortality follow-up through 1986 are reported for a previously studied cohort of 878 chemical workers who were potentially exposed to 2,4-dichlorophenoxyacetic acid (2,4-D) and its derivatives between 1945 and 1983. Observed mortality was compared with expected levels based on death rates of the U.S. population and of 36,804 "unexposed" workers from the same manufacturing location. Non-Hodgkin's lymphoma (NHL) was a particular focus of the study because of a suggested association with 2,4-D exposure in some case-control studies. For the total observation period, the standardized mortality ratios for all causes and for malignant neoplasms were 92 and 91, respectively. Analyses using the internal comparison group yielded virtually identical results. The initial study had found two deaths from NHL, both of which occurred under circumstances (ie, short latency and modest exposure) which made it less plausible that they were related to 2,4-D exposure. No new deaths from NHL were observed in the extended follow-up period and mortality for this cause showed a nonstatistically significant excess (standardized mortality ratio, 196; 95% confidence interval 24 to 708) for the total observation period. Analyses by production area, and by two different measures of exposure, combined with two different approaches to account for latency, did not show patterns suggestive of a causal relationship between exposure to 2,4-D or its derivatives and any particular cause of death.

From Dow Benelux NV Biomedical Research, 4530 AA Terneuzen, The Netherlands (Dr Bloemen); The University of Minnesota School of Public Health, Division of Environmental and Occupational Health, Minneapolis, Minnesota (Dr Mandel). The Dow Chemical Company Epidemiology Midland, Michigan (Dr Bond and Dr Cook); Dow Chemical USA Michigan Division, Medical and Industrial Hygene Departments Midland, Michigan (Dr Pollock Dr Vitek)

0096-1736/93/3512-1208$03.00/0

Epidemiologic studies of populations with occupational exposure to phenoxy herbicides have generated inconsistent evidence of associations with various cancers, including soft-tissue sarcomas and the malignant lymphomas.[1-26] Recent reviews have concluded that there is currently not enough coherent evidence to confirm that the phenoxy herbicides in general, or 2,4-dichlorophenoxyacetic acid (2,4-D) in particular, represent a carcinogenic hazard to humans.[27-29] Additional follow-up of cohorts was suggested to help clarify the issue.

In 1988, two of the authors (GGB and RRC) first reported a study[23] of the cause-specific mortality experience of a cohort of 878 employees who had been engaged in the manufacture, formulation, or packaging of 2,4-D and its amines and esters. The current study provides 4 years of additional mortality follow-up of this cohort through 1986.

December 31, 1982 were identified from plant rosters. Employees' work

ston records were compiled and their job assignments were classified to three categories of potential time-weighted average exposure (ie. less than 0.1, 0.1 to 1.0, or more than 1.0 mg/m³). Cumulative exposures were calculated for each worker by multiplying the time spent on each job by the weight assigned to its respective time-weighted average value (ie, 0.05, 0.5, or 5 mg/m³) and summing across all jobs.

Vital status was successfully ascertained for all cohort members through 1986 using records of the company, the Social Security Administration, and the National Death Index. Death certificates were coded according to rules of the International Classification of Diseases (ICD) revision in effect at the time of death. Cause of death codes were then grouped according to the categories of the 8th ICD Revision for analyses using a modified life-table program.[11] To calculate expected numbers of deaths from non-Hodgkin's lymphoma (NHL), US rates for 1940 to 199 were obtained from the National Center for Health Statistics. Exact, test-based, two-sided confidence intervals (95% CI) were calculated according to the method of Miettinen using the programs of Rothman and Boice.[12] Analyses were done by production area, and by two measures of exposure: duration and cumulative dose. Analyses by duration of exposure considered latency categorized in 5-year intenals. Cumulative dose was analyzed with either no latency period or lagging exposures by a fixed interval of 15 years.[13] Examination for trends across standardized mortality ratios (SMRs) was done using a χ^2 test with 1 degree of freedom."

Using a method of direct standardization,[14] mortality among the 2,4-D cohon was also compared with that Jf other workers who were also actively employed at this manufacturing location at any time during 1945 through 1982. Adjustment was made for age, calendar year, and pay status (ie, hourly or salary). The internal comparison group differed slightly from the one used for the original study as some temporary workers were excluded, as were foundry, Admus from 3 satellite operation

Results

During the additional 4 years of idlo\\-up there occurred fewer deaths than were expected from all causes and from total cancer, uith the latter difference achieving statistical significance (Table 1) Overall, for the total follow-up period the all causes SMR was 92 (95% CI, 77 to 109), and the total cancer SMR was 91 (95% CI, 61 to 131). For no cause of death did employees experience a statistically significant increased risk compared to the US population, or to other, "unexposed" workers from the same location (Table 2).

No new deaths from NHL were identified in the additional follow-up period. Overall, there were two deaths from NHL compared with approximately one expected (SMR, 196: 95 5 CI. 24 to 208).

When allowance was made for a 15-year minimum latency period, there were only small changes in the SMRs. An exception was the SMR for NHL, which became zero because, as discussed in the original publication, both cases occurred within a relatively shon time after first exposure (3 and 10.5 years, respectively).

Analyses of the four individual production plants continued to show a statistically significantly elevation (SMR, 351: 95% CI, 116 to 833) in the category of "cancer of other and unspecified sites" among employees who worked in one of the four plants referred to as the "2,4-D Plant," hut revealed no new findings of note. Analyses by duration of exposure or by estimated cumulative dose of exposure did not show any statistically significant trends. Tables summarizing these analyses are available from the authors upon request.

TABLE 1
Observed and Expected Deaths,* SMRs, and 95% Confidence intervals for Selected Causes of Death, Cohort of 878 Workers Exposed to 2,4-D

Cause of Death (ICDA-8)	Updated Follow-up Period, 1983-1986				Total Follow-up Period, 1945-1986			
	Obs	Exp	SMR	95% CI	Obs	Exp	SMR	95% CI
All causes (001-999	21	32.2	65	40-100	132	143.3	92	77-109
malignant neoplasms (140-209)	2	8 3	24	3-87	28	309	91	61-131
Digestive organs and peritoneum (150-159)	0	2.0	-†	0-184	5	7.8	65	21-150
Respiratory system (160-163)	0	2.3	-†	0-160	9	11 4	79	36-150
Genitourinary system (185-189,	1	0 9	111	3-619	3	3.2	94	19-274
Brain and other CNS tissues (191 192	0	0 2	-†	0-1844	0	1 1	-†	0-326
Lymphatic and hematopoietic system (200-209)	0	0 7	-†	0-527	5	3 2	157	51-367
Non-Hodgkin s lymphoma (200 202)	0	0 3	-†	0-1230	2	1 0	196	24-708
Other and unspecified sites (171, 173, 194-199)	1	0 6	167	4-929	7	3 2	In,	98-583
Arteriosclerotic heart disease (410-413)	9	10 3	87	40-166	46	46 1	100	73-133
Cerebrovascular disease (430-438,	2	1 6	125	15-452	9	6 9	131	60-248
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Person-years at risk		3,068				19,365		

* Number of expected deaths are based on U.S. white mortality rates.
† Values are inestimable.

TABLE 2
Mortality Comparison of Study Cohort With Internal Comparison Group, Total Follow-Up Period, 1945–1986

Causa of Death (ICDA-8)	Obs	Exp	Relative Risk	95% Confidence Interval
All causes (001–9991	132	1271	104	0.88–1 24
All malignant neoplasms (140–209)	28	294	095	0.66–1 39
Digestive organs and peritoneum (150–159)	5	7 1	071	0 29–1 21
Respiratory system (160–163)	9	106	0.85	0 44–1 64
Genitourinary system (185–189)	3	2 7	111	0 35–3 46
Brain and other CNS tissues (191. 192)	0	1 3	-†	-†
Lymphatic and hematopoietic system (200–2091	5	3 2	157	0 65–3 78
Non-Hodgkin s lymphoma(200 202)	2	0 7	303	0 78–11 85
Other and unspecified sites (171 175 194–199)	*6*	3	*201*	0 91–4 46
Arteriosclerotic heart disease (410–413)	46	44 9	103	0 77–1 37
Cerebrovascular disease (430–438)	9	6 3	142	0 73–2 75
Accidents (E800–E949)	17	123	139	0 86–2 25

* Number of expected deaths *are* basad on Michigan Division male mortality rates. adjusted for *age.* calendar year. and pay status
† Values are inestimable

Discussion

Mortality was updated an additional 4 gears. through 1986. for 878 employees who manufactured 2.4-D and who had been studied originally by Bond et al.[23] A variety of causes of death were examined but special focus was directed at NHL because of a possible association with the use of phenoxy herbicides. such as 2.4-D. reponed from several case-control studies,[3,12,19,25] but not supported by similar studies done elsewhere."[13,14,16]

A criticism of the case-control approach has been the potential for a differential misclassification of exposure arising from either "recall" or 'interviewer" bias." Methodological questions have been raised about whether farmers' next-of-kin can recall their past use of pesticides in sufficient detail to permit valid estimates of exposure." Questions have also been raised about uncontrolled confounding due lo other farm exposures,[17] and the implausibility of infrequent. farm environment exposures causing substantial increases in cancer risks, as suggested by some of the case-control studies."

Welldesigned cohort studies of workers who manufactured the phenoxy herbicides offer the advantage of documented records of exposure. uhich presumably makes these studies less prone to misclassification errors.[27–29] Additionally, the workers are likely to have received more frequent and intense exposures relative to farmers or other herbicide applicators, especially during the early years of production when industrial hygiene controls were not as sophisticated. The manufacturing environment also offers a different set of potential confounding exposures than those found on the farm. thus providing a useful contrast.

Overall mortality in this group of 2.4-D production workers was o b served to have been comparable with the US population (SMR, 92) and to other workers from this manufacturing site. and was slightly lower than that reponed initially" (SMR, 100). Similarly, mortality from total cancer was comparable to expected levels and showed no trends with duration of exposure. a measure of cumulative dose or latency. This suggests that these workers have. at least thus far. not experienced a substantial cancer hazard associated with their occupational exposure to 2.4-D.

The interpretation of findings for specific types of cancer. including NHL. is complicated by the small number of observed and expected events which restricts *the* statistical power of the study to detect or rule-out modest increases in risk. Although no new cases of NHL were found, the two cases observed originally compare with about one expected in this cohort. Taken at face value, this slight excess could be interpreted as being in accord with other studies suggesting that any risk of NHL from exposure to phenoxy herbicides is small.[1–28] Moreover, an expert group recently concluded[29] that these two NHL deaths occurred ". . . under circumstances [modest exposure. short latent). and in the presence oi confounding exposures] which seem unlikely to implicate 2.4-D exposure."

An excess of deaths in the category of 'cancer of other and unspecified sites" was observed for employees on one of the four production plants, This category of death has been consistently elevated among the general work force at this manufacturing site,[30] and was found *to* be partially due to historical death certification practices." A review of the death certificates and job titles of the affected workers in the current study revealed no further information useful for interpreting whether they might be related to workplace exposures.

S o deaths were observed from soft-tissue sarcoma, although again the cohort is small and fewer than one case was expected. Nor were there any deaths observed from brain cancer, the cancer type that was statistically significantly elevated in male rats, but not female rats or mice of either sex, fed the highest dose levels of 2,4-D.[41,42] Brain cancer has not been found in excess in any of the cohort studies of phenoxy herbicide-exposed workers conducted to date,[4–9,11,15,21–26] and *docs* not now seem likely to be a consequence of human exposure to 2.4-D.

In summary, this 4-year update of mortality among workers who manufactured 2.4-D did not show patterns suggestive of a causal association with any particular cause of death. including cancer.

Acknowledgments

We gratefully acknowledge technical E sistance provided by Kenneth M. Bodner.

B. Cartmill, Diana L. Diamond, A. Kravat, and Elsie 4. McLaren.

References

1. Hardell L. Sandstrom A. Case-control study: soft tissue sarcomas and exposure to phenoxyacetic acids or chlorophenols. *Br J Cancer.* 1979;39:711–717.
2. Eriksson M. Hardell L. Berg NO. Moller T. Axelson O. Soft tissue sarcomas and exposure to chemical substances: a case-referent study. *Br J Ind Med.* 1981;38: 27–33.
3. Hardell L. Eriksson M. Lenner P. Lundgren E. Malignant lymphoma and exposure to chemicals, especially organic solvents, chlorophenols and phenoxyacids: a case-control study. Br *J Cancer.* 1981: 43:169–176.
4. Ott MC. Holder BB. Olsen RD. 4 mortality analysis of employees engaged in the manufacture of 2,4,5-trichlorophenoxyacetic acid *J Occup Med* 1980;22 47–50.
5. Riihimaki V. Asp S. Herberg S. Mortality of 2,4-dichlorophenoxyacetic acid and 2,4,5-trichlorophenoxyacetic acid herbicide applicators in Finland. *Scand J Work Environ Health.* 1982;8:37–42.
6. Wolfe WH. Michalek JE. Miner JC. Rahe 4. et al. Health status of Air Force veterans occupationally exposed to herbicides in Vietnam. I. Physical health. JAW.4 1990;264:1824–1831.
7. Smith AH. Pearce NE. Fisher DO. Giles HJ. Teague CA. Houard JK. Soft tissue sarcoma and exposure io phenoxy herbicides and chlorophcnols in Sew Zealand. *JNCI* 1984;73:1111–1117.
8. Lynge E. A follow-up study of cancer incidence among workers in manufacture of phenoxy herbicides in Denmark. *Br J Cancer.* 1985;52:259–270).
9. Coggon D. Pannet B. Winter PD. Acheson ED. Bonsall J. Mortality of workers exposed io 2-methyl-4-chlorophenoxyacetic acid. *Scand J Work Environ Health.* 1986;12 448–454
10. Coggon D. Pannet B. Winter P. Mortality and incidence of cancer at four factories making phenoll herbicides. *Br J Ind Med.* 1991;48:173–178.
11. Cantor KP. Blair A. Agricultural Chemicals. Drinking Water. 3nd Public Health An Epidemiologic Review. Bethesda, MD National Cancer Institute, 1986
12. Hoar SK. Blair A. Holmes FF. et al. Agricultural herbicide use and risk of lymphoma and soft tissue sarcoma ... also correction. *JAMA* 1986;256:3351).
13. Pearce NE. Sheppard RA. Smith AH. Teague C.4. Non-Hodgkin's lymphoma and fanning. an expanded case-control study. *Br J Cancer* 1987 39:155–161
14. Pearce NE. Phenoxyherbicides and non-Hodgkin's lymphoma in New Zealand: frequency and duration of herbicide use. *Br J Ind Med.* 1989;46:143–144.
15. G m n LM. Mortality analysis of Ontario Hydro forestry tradesman cohon 1950–1982. Toronto. Ontario, Canada: Health and Safety Division, Ontario Hydro. November 1986.
16. Woods JS. Polissar L. Severson RK. Heuser LS. Kulander BG. Soft tissue sarcoma and non-Hodgkin's lymphoma in relation to phenoxy herbicide and chlorophenol exposure in western Washington *JNCI* 1987;78:899–910
17. Veneis P. Terracini B. Ciccone G. et al. Phenoxy herbicides and soft tissue sarcomas in female rice weeders: a population-based case-referent study. *Scand J Ubrk Environ Health.* 1987;13:9–17
18. Vineis P. Faggiano F. Tedeschi M. Ciccone G. Incidence rates of lymphomas and soft tissue sarcomas and environmental measurements of phenoxy herbicides *JNCI* 1991;83 362–363
19. Persson B. Dahlander 4. Fredriksson M. Brage HN. Ohlson CC. Axelson O. Malignant lymphomas and occupational exposures. *Br J Ind* .Wed. 1989;45: 516–520.
20. Hardell L. Eriksson 51. The association between wit tissue sarcomas and exposure to phenoxyacetic acids: a new case-referent study. *Cancer.* 1988;62: 652–656.
21. Ott MC. Olson RA. Cook RR. Bond GG. Cohon mortality stud) of chemical workers with potential exposure io the higher chlonnatcd dioxins. *J Occup Med.* 1987;29:422–429
22. BondGG. McLaren EA. Lipps TE. Cook RR. Update of mortality among chemical workers uith potential exposure to the higher chlorinated dioxins *J Occup Med.* 1988;31121–123
23. Bond GG Wetterstroem NH. Roush GJ. McLaren EA. Lipps TE. Cook RR Cause specific mortality among employees engaged in the manufacture, formulation. or packaging of 2,4-dichlorophenoxyacetic acid and related salts. *Br J Ind Med.* 1988;45:98–105.
24. Fingerhut MA. Halperin WE. Marlow DA. et al. Cancer mortality in workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin *N Engl J Med* 1991;324 212–218
25. Zahm SH. Weisenberger DD. Babbitt et al. A case-control study of non-Hodgkin's lymphoma and the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) in eastern Nebraska *Epidemiology* 1990; 1349–356
26. Wigle DT. Semenciw RM. Wilkins K. Riedel D. Ritter L. Morrison HI, Mao Y. Mortality study of Canadian male farm operators: non-Hodgkin's lymphoma mortality and agricultural practices in Saskatchewan. *JNCI.* 1990:82: 575–582.
27. Bond GG, Bodner KM, Cook RR. Phenoxy herbicides and cancer: insufficient epidemiologic evidence for a causal relationship. *Fund Appl Toxicol* 1989:12: 172–188.
28. Johnson ES. Association between soft tissue sarcomas, malignant lymphomas and phenoxy herbicides/chlorophenols: evidence from occupational cohon studies. *Fund Appl Toxicol.* 1990:14: 219–234.
29. Harvard School of Public Health The weight of the evidence on the human carcinogenicity of 2,4-D Report on workshop. Boston, MA: Program on Risk Analysis and Environmental Health: 1990.
30. Monson RR. Analysis of relative survival and proportional mortality. *Comput Biomed Res.* 1974;7:325–332.
31. Rothman KJ. Boice JD Epidemiologic analysis with a programmable calculator Boston. MA: Epidemiology Resources Inc: 1982.
32. Enterline PE. Marsh CM. Cancer among workers exposed to arsenic and other substances in a copper smelter. *Am J Epidemiol* 1981.116:895–911
33. Breslow SE. Lubin JH. Marek P. Langholz B Multiplicative models and the analysis of cohort data. *J Am Stat Assoc.* 1983;78:1–12.
34. Hakulinen Th. 4 Mantel-Haenszel statistic for testing the association between a polychotomous exposure and a rare outcome. *Am J Epidemiol.* 1981:113: 192–196.
35. Blair A. Zahm SH. Cantor KP. Stewart PA. Estimating exposure to pesticides in epidemiologic studies of cancer In. Wong RGM, Franklin CA. Honeycutt RC. Reinert JC. eds. Biological Monitoring for Pesticide Exposure—Measurement, Estimation and Risk Reduction ACS Symposium Series Washington, DC: American Chemical Society: 1989; 382:38–46.
36. Johnson RA, Mandel JS. Gibson RW, Mandel JH. Bendor AP. Gunderson PD. Renier CM. Data on pnor pesticide use collected from self- and proxy respondents. *Epidemiology* 1993;4:157–164
37. Smith 4H. Bates MN Epidemiologic studies of cancer and pesticide exposure In: Wong RGM, Franklin CA. Honeycutt RC. Reinert JC. eds. Biological Monitoring for Pesticide Exposure—Measurement, Estimation and Risk Reduction. ACS Symposium Series. Washington DC American Chemical Society: 1989.382.207–222
38. Pearce N, Reif JS. Epidemiologic studies of canar in agricultural workers. *Am J Ind Med.* 1990; 18 133–148

39. Bond GG, McLaren EA, Cartmill JB. Wymer KT. Sobel W, Lipps TE, Cook RR. Cause-specific mortality among male chemical workers. *Am J Ind Med.* 1987;12.353–383.
40. Bond GG, Cartmill JB. Cook RR. Investigation of excess cancer of other and unspecified sites among chemical workers. *Am J Ind Med.* 1990;18:617–619. Letter to the Editor.
41. Combined toxicity and oncogenicity nub? in rats, 2.4-dichlorophenoxyacetic acid, final report. Volume 1. Vienna, V.4: Hazelton Laboratories America; 1986.
42. Oncogenicity audy in mice with 2,4-dichlorophenoxyacetic acid (2,4-D), final report. Volume 1. Vienna, VA: Hazelton Laboratories America, 1985.

Erratum

Several paragraphs of text were inadvertently omitted from the **ACOEM** Position Statement on National Health Care Reform. published in the **June** 1993 issue. page 623. The missing text. which should have appeared after the fifth paragraph. reads as follows:

The ACOEM Proposal

The American College of Occupational and Environmental Medicine proposes changes in six key areas related to health care reform: coverage, financing, supply, demand, administration, and information management.

Coverage

A basic package of benefits that emphasizes prevention, primary *care,* and continuity of care should be provided. The basic benefits package should be defined to meet medical practice guidelines. process efficiency standards. and outcome specifications rather than to cover types of service. Only proven, cost-effective. and appropriate technology. services. and pharmaceuticals would be covered. Resources should be directed away from terminal care or low yield to more productive uses.

Worksite-based primary care and health-promoting and preventive services should be reimbursed. These services *are* often more cost effective and less disruptive to workers' and supervisors' schedules when provided at the worksite.

To improve the quality of *care* and manage the disability of work-related illnesses and injuries, and to stop con shifting, we feel it is critical to create a uniform reimbursement and medical management system for occupationally related illness and injury that provides the same quality. efficiency. and effectiveness as general medical senices. One option is a merger of the two systems and disability coverage uith a focus on the appropnate care of the worker and appropnaie and *effective management* of disability, especially the provision of modified duty to accommodate impairments. This might require a Federal law preempting state laws. The 'work relatedness" test would become irrelevant, as would legal issues of compensability. Disability coverage for any absence would be combined.

Financing

All Americans should be required to purchase or obtain basic medical insurance for medically necessary *care* from an employer-provided benefits plan or from another (possibly government-organized) financing pool. Low-income Americans would receive tax credits or vouchers for this purchase. This is not intended io create a separate but unequal system of care for those in small business or for the unemployed. The government pian is a nsk-pooling mechanism.

We sincerely regret the omission.