

Soft Tissue Sarcoma and Non-Hodgkin's Lymphoma in Workers Exposed to Phenoxy Herbicides, Chlorophenols, and Dioxins: Two Nested Case-Control Studies

Manolis Kogevinas,^{1,2} Timo Kauppinen,³ Regina Winkelmann,¹ Heiko Becher,⁴ Pier Alberto Bertazzi,⁵ H. Bas Bueno-de-Mesquita,⁶ David Coggon,⁷ Lois Green,⁸ Eric Johnson,⁹ Margareta Littonin,¹⁰ Elsebeth Lynge,¹¹ David A. Marlow,¹² John D. Mathews,¹³ Manfred Neuberger,¹⁴ Trevor Benn,¹⁵ Brian Pannett,⁷ Neil Pearce,¹⁶ and Rodolfo Saracci¹

We examined the effect of exposure to chemicals present in the production and spraying of phenoxy herbicides or chlorophenols in two nested case-control studies of soft tissue sarcoma and non-Hodgkin's lymphoma. Eleven sarcoma and 52 lymphoma cases occurring within an international cohort were matched for age, sex, and country of residence with 55 and 158 controls, respectively. Exposures to 21 chemicals or mixtures were estimated by three industrial hygienists who were blind to the subject's case-control status. Excess risk of soft tissue sarcoma was associated with exposure to any phenoxy herbicide [odds ratio (OR) = 12.3; 95% confidence interval (CI) = 1.2-91] and to each of the three major classes of phenoxy

herbicides (2,4-dichlorophenoxyacetic acid, 2,4,5-trichlorophenoxyacetic acid, and 4-chloro-2-methylphenoxyacetic acid), to any polychlorinated dibenzodioxin or furan (OR = 5.6; 95% CI = 1.1-28), and to 2,3,7,8-tetrachlorodibenzo-p-dioxin (OR = 5.2; 95% CI = 0.85-32). Sarcoma risk was not associated with exposure to raw materials or other process chemicals. In the non-Hodgkin's lymphoma study, associations were generally weaker than those found in the study on sarcoma. These findings indicate that workers exposed to phenoxy herbicides and their contaminants are at a higher risk of soft tissue sarcoma (Epidemiology 1995;6:396-402).

Keywords: soft tissue sarcoma, non-Hodgkin's lymphoma, phenoxy herbicides, dioxin, case-control study.

Studies of cancer risk have revealed excesses of soft tissue sarcoma and non-Hodgkin's lymphoma in popu-

lations exposed to phenoxy herbicides, chlorinated phenols, and dioxins during manufacture, while spraying, or after accidents.¹⁻⁴ Dioxins, present as contaminants in some types of phenoxy herbicides, have been suggested as a causal factor, although excess risks have also been associated with exposure to those herbicides not considered to have been contaminated with dioxins.⁵⁻⁹ Chronic bioassays and mechanistic data have indicated that contaminants of the herbicides, and in particular 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), are extremely potent carcinogens.¹⁰ Other chemicals in the same occupational environment (herbicides, chlorophenols, dioxin congeners other than TCDD, polychlorinated dibenzofurans, solvents) are not inert compounds and have been associated in epidemiologic studies and/or chronic bioassays with adverse health effects, including cancer.¹¹⁻¹⁷

The International Agency for Research on Cancer (IARC) maintains an international register of workers exposed to phenoxy herbicides, chlorophenols, and dioxins. In a cohort mortality analysis, excess risk was found among exposed subjects for soft tissue sarcoma [standard mortality ratio (SMR) = 196], while only a

From the: International Agency for Research on Cancer, Lyon, France; Institut Municipal d'Investigació Mèdica, Barcelona, Spain; Institute of Occupational Health, Helsinki, Finland; German Cancer Research Center, Heidelberg, Germany; Clinica del Lavoro Luigi Devoto, Milan, Italy; National Institute of Public Health and Environmental Protection, Bilthoven, the Netherlands; MRC Environmental Epidemiology Unit, University of Southampton, Southampton, England; National Institute for Environmental Health Sciences, Durham, North Carolina; Tulane University Medical Center, New Orleans, LA; Lund University, Lund, Sweden; Institute of Public Health and Hygiene, University of Vienna, Austria; University of Graz, Graz, Austria; University of Vienna, Vienna, Austria; Health and Safety Executive, Research Unit, London, United Kingdom; National Cancer Institute, Bethesda, MD, USA.

Address correspondence to: Manolis Kogevinas, Department of Epidemiology and Public Health, Institut Municipal d'Investigació Mèdica (IMIM), Doctor Aiguader 82, Barcelona 28003, Spain.

This study was supported by Grant No. 01-68-25276 from the National Institute of Environmental Health Sciences, USA. This work was conducted in part during the tenure of M. Kogevinas of a fellowship of the Ministry of Education and Science, Spain (CGL-7-SAR94/212).

Submitted February 11, 1994; final version accepted December 11, 1994.

© 1995 by Epidemiology Resources Inc.

slightly elevated risk was observed for non-Hodgkin's lymphoma (SMR = 129).²¹ We undertook a case-control study on soft tissue sarcoma and one on non-Hodgkin's lymphoma, nested within the international cohort, to examine exposure to various chemicals occurring in the work place, applying an exposure model approach. In contrast with the cohort mortality analysis (which was based on underlying cause of death), information on all cases diagnosed with soft tissue sarcoma and non-Hodgkin's lymphoma in the international register could be examined in the nested case-control studies, irrespective of vital status or cause of death as recorded on the death certificate.

Subjects and Methods

COHORT DESCRIPTION

At the time of the cohort mortality analysis in 1991,² the international register included 18,390 workers from 20 cohorts in 10 countries (Australia, Austria, Canada, Denmark, Finland, Italy, the Netherlands, New Zealand, Sweden, and the United Kingdom). On the basis of job history information, 13,898 workers were assessed as exposed to any phenoxy herbicide, 7,410 as chlorophenol, 3,951 workers as nonexposed, and 541 workers as of unknown exposure because of incomplete job history information. Since 1991, four production cohorts from Germany have been added to the register, and follow-up time has been updated for some cohorts. Information is currently incorporated on 21,153 workers from 24 cohorts in 11 countries.

CASE IDENTIFICATION

Cases of the two index neoplasms were sought in death certificates (underlying and contributing causes of death) for all cohorts in the register and in cancer registration records in cohorts for countries with cancer registration schemes (Austria, Denmark, Finland, New Zealand, Sweden, and the United Kingdom). We identified 11 male cases with soft tissue sarcoma from cohorts in Australia (1 case), Denmark (5 cases), New Zealand (2 cases), and the United Kingdom (3 cases). We identified 32 cases with non-Hodgkin's lymphoma (31 male, 1 female) from cohorts in Australia (2 cases), Denmark (11 cases), Finland (1 case), Germany (5 cases), the Netherlands (2 cases), New Zealand (1 case), Sweden (1 case), and the United Kingdom (9 cases). No case was registered with sarcoma or lymphoma in the Italian, Canadian, and Austrian cohorts.

Four sarcoma and 20 lymphoma cases (of which 15 were already included in the cohort mortality analysis) were identified through death certification. Additionally, 7 sarcoma and 12 lymphoma cases were identified only through cancer registration records; these cases were either alive at the end of mortality follow-up, had been lost to follow-up, or had died from another cause, or had died with a sarcoma but, similar to other studies,²² were coded in the death certificate under a cause code other than the specific rubric "Sarcomas of connective

and other soft tissue" (*International Classification of Diseases*, 9th revision, code 171).²³

Independent verification of diagnosis was not conducted, but evidence of histologic diagnosis was available for all but one case of soft tissue sarcoma and two cases of non-Hodgkin's lymphoma.

SELECTION OF CONTROLS

Incidence density sampling was applied for the selection of controls, which involves selecting controls from the person-time experience that generated the cases, that is, the study base.²⁴ We selected five controls per case, matched for age, sex, and country of residence at the time of employment. Matching by country was done to avoid potential confounding by country of residence, since both exposure and occurrence or recognition of disease may differ by country. In the six countries enrolling more than one cohort, matching was done by country rather than by cohort, to avoid potential over-matching of cases and controls. We excluded two controls in the study on non-Hodgkin's lymphoma because of missing information on job histories, leaving a total of 158 controls in the lymphoma study and 55 controls in the sarcoma study. A SAS program was used for the sampling of controls.

ASSESSMENT OF EXPOSURE

We constructed a list of chemicals to which workers may have been exposed during production or spraying, on the basis of recorded information in company exposure questionnaires and company records. Exposure was evaluated specifically for the major phenoxy herbicides and chlorophenols, polychlorinated dibenzodioxins and furans, raw materials, process chemicals, and also some chemicals commonly used in the production of phenoxy herbicides and chlorophenols. A panel of three industrial hygienists (TK, DAM, BP) carried out the assessment of exposure to 21 chemicals or mixtures. The hygienists were unaware of the subject's case-control status. They used criteria previously agreed upon, as described in detail elsewhere.²⁵ Exposure of workers was reconstructed through the use of individual job records and a detailed company exposure questionnaires and company reports. The information made available to the industrial hygienists on the job history of cases and controls was retrieved from the cohort database. The selection of chemicals to be examined was based on previous associations with health effects (mainly cancer) in human and animal experiments^{26,27} or on the prevalence of the compounds in the occupational environment.²⁸ Level of exposure was evaluated using a relative scale, since few actual measurements of past exposure were available. A cumulative exposure score was calculated for each subject and chemical, on the basis of estimated level of exposure and duration of exposure (in years). The model that we used as the conceptual framework in deriving levels of exposure included variables related to department, duration of chemicals contact with chemicals, personal protection, and other relevant determi-

nants of exposure. Within each matched set, exposures occurring less than 5 years before the date of selection into the study were ignored. For each chemical examined, subjects were grouped into those nonexposed (having a cumulative exposure score (CE) of less than 0.005, corresponding to an exposure of less than 1 day), and those ever exposed ($CE \geq 0.005$). Ever-exposed workers were further classified into those with low exposure ($0.005 \leq CE < 1$, corresponding, for most subjects, to an exposure of less than 1 year); medium exposure ($1 \leq CE < 10$); and high exposure ($CE \geq 10$).

In addition, two alternative classifications of exposure were used. In the first, cumulative exposure score was examined without time lagging. In the second, subjects in each matched set were ranked according to cumulative exposure score (rank 1 corresponding to the lowest CE, rank 6 to the highest).¹³ Rank within each matched set was entered in the regression equations as a continuous variable. Results for these two exposure classifications were similar to those obtained for the main analysis (based on cumulative exposure using a 5-year lag), and are not reported here. Results are available from the authors upon request.

Exposure to six other pesticides (or classes of pesticides) was also examined (arsenicals, dichlorodiphenyl-trichloroethane (DDT), dinoseb, lindane, organophosphates, triazines). These were produced in the same or adjacent departments to those producing the phenoxy herbicides or were sprayed by the same workers spraying phenoxy herbicides. Apart from the phenoxy herbicides and related chemicals, these six pesticides constituted the most commonly occurring chemicals among the cohorts with cases of sarcoma or lymphoma. A dichotomous classification of exposure was applied which, however, may encompass considerable misclassification, since information on dates and quantities of production and spraying of the six pesticides was not available in all cohorts.

STATISTICAL ANALYSIS

We used conditional logistic regression analysis.¹⁴ Conditional exact inference was used in the soft tissue sarcoma study whenever cumulative exposure was entered in the models as a categorical variable with four levels, using the statistical package LogXact-Turbo.¹⁵ Years from first exposure until disease or selection as control (as a dichotomous variable, less or more than 10 years) and year of first exposure (as a dichotomous variable, before or after 1970) were examined as potential confounding variables.

Results

SOFT TISSUE SARCOMA

We found excess risks (Table 1) for exposure to any phenoxy herbicide [odds ratio (OR) = 10.3; 95% confidence interval (CI) = 1.2-90.6], exposure to 2,4-dichlorophenoxyacetic acid (2,4-D) (OR = 5.7; 95% CI = 1.1-29), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) (OR = 4.3; 95% CI = 0.7-26), 4-chloro-2-

methylphenoxyacetic acid (MCPA) (OR = 11.5; 95% CI = 1.3-98), exposure to any polychlorinated dibenzodioxin or furan (OR = 5.6; 95% CI = 1.1-28), and exposure to TCDD (OR = 5.2; 95% CI = 0.9-32). Exposure to chlorophenols and to all other chemicals examined (raw materials and process chemicals) was not associated with risk of soft tissue sarcoma (Table 1). Odds ratios for exposure to different chemicals were only minimally modified when adjusted for period of first employment and time since first employment.

The odds ratios shown in Table 2 for selected major chemicals are based on cumulative exposure score in four categories (nonexposed, low, medium, high exposure). We observed an increasing risk with exposure for 2,4-D (OR for highest category = 13.7; 95% CI = 3.9-309; P-value for trend = 0.01), 2,4,5-T (OR for highest category = 7.7; 95% CI = 0.5-477; P-value for trend = 0.07), any polychlorinated dibenzodioxin or furan (OR for highest category = 19.0; 95% CI = 1.3-1236; P-value for trend = 0.008), and TCDD (OR for highest category = 10.6; 95% CI = 0.6-671; P-value for trend = 0.04).

A model including exposure both to 2,4-D and 2,4,5-T (as dichotomous variables) resulted in lower ORs than those obtained in the univariate analysis (2,4-D: OR = 4.8; 95% CI = 0.8-28; 2,4,5-T: OR = 1.7; 95% CI = 0.2-13.2). Similarly decreased ORs were found for a model including 2,4,5-T (OR = 1.4; 95% CI = 0.2-11.3) and MCPA (OR = 9.9; CI = 1.0-100), a model including 2,4-D (OR = 1.5; 95% CI = 0.1-16.1) and MCPA (OR = 8.0; 95% CI = 0.4-180), and a model including the three herbicides (2,4-D: OR = 1.4; 95% CI = 0.1-15.8; 2,4,5-T: OR = 1.4; 95% CI = 0.2-11.0; MCPA: OR = 7.3; 95% CI = 0.3-172). The decrease in ORs when multiple exposures are fitted concurrently is largely the result of correlation between different exposures.

Of 11 cases with sarcoma, 7 were production workers, and 4 were sprayers. The OR for exposure to any phenoxy herbicide in production workers was 3.5 (CI = 0.9-80), for exposure to any chlorophenol was 2.3 (CI = 0.4-19.3), and for exposure to any polychlorinated dibenzodioxin or furan was 4.5 (CI = 0.8-25). Repression models limited to sprayers were based on very small numbers. All four sprayer cases were exposed to at least one phenoxy herbicide. Of the 12 sprayer controls in the four matched sets, eight were exposed, and four were nonexposed to any phenoxy herbicide.

Exposure to dinoseb (OR = 5.4; 95% CI = 0.7-45) and DDT (OR = 3.3; 95% CI = 0.4-30) was associated with increased risk, whereas smaller or no excess risks were observed for triazines (OR = 0.7; 95% CI = 0.04-11.8), arsenicals (OR = 0.6; 95% CI = 0.07-4.6), organophosphates (OR = 1.5; 95% CI = 0.3-6.5), and lindane (OR = 0). Adjustment for exposure to any phenoxy herbicide reduced the OR for dinoseb (OR = 2.4; 95% CI = 0.3-22.1) and for DDT (OR = 0.8; 95% CI = 0.1-9.7). ORs for phenoxy herbicides, chlorophenols, and their contaminants were little modified when adjustment was made for exposure to dinoseb (OR for

TABLE 1. Odds Ratios and 95% Confidence Intervals (CI) for Soft Tissue Sarcoma and Non-Hodgkin's Lymphoma by Cumulative Exposure to Specific Chemicals. Cumulative Exposure Is Lagged by 5 Years. Risks Are Relative to That among Nonexposed

Chemical*	Soft Tissue Sarcoma†			Non-Hodgkin's Lymphoma‡		
	Exposed Cases/Controls	OR	95% CI	Exposed Cases/Controls	OR	95% CI
Phenoxy herbicides						
Any phenoxy herbicide	10/30	1.25	1.18-90.56	19/85	1.25	0.54-2.90
2,4-D/DP/DB	9/24	5.72	1.14-28.65	12/56	1.11	0.46-2.65
2,4,5-T/TP	5/14	4.31	0.71-26.27	10/35	1.85	0.71-4.80
MCPA/P/B	10/29	11.27	1.30-97.92	15/76	0.88	0.36-2.18
Chlorophenols						
Any chlorophenol	2/8	1.29	0.24-6.91	9/38	1.26	0.52-3.08
PCP	0/0			3/9	2.75	0.45-17.00
2,3,4,6-TeCP	0/0			1/7	—§	
2,4,5-TCF	0/3	—§		2/15	0.65	0.12-3.41
2,4,6-TCF	0/2	—§		3/24	1.03	0.34-3.09
2,4,6-TCF	1/1	5.3	0.11-79.94	2/11	0.80	0.08-8.04
Contaminants						
Any dioxin or furan	9/24	5.56	1.12-27.70	20/78	1.84	0.80-4.26
TCDD	5/13	5.19	0.85-31.56	11/39	1.93	0.74-5.07
Process chemicals, raw materials						
MCA	2/13	0.71	0.13-3.84	8/47	0.78	0.31-1.91
<i>o</i> -Cresol	2/11	0.88	0.15-5.07	5/38	0.53	0.18-1.59
P/C/C	3/9	1.97	0.42-9.36	7/43	0.68	0.25-1.88
TeCB	0/3	—§		2/13	0.70	0.13-3.72
Phenol	1/4	0.28	0.03-2.78	6/28	1.17	0.36-3.79
Chl. one	2/11	0.88	0.15-5.07	8/53	0.61	0.24-1.59
Chlorobutyl lactone	1/1	5.20	0.31-29.94	2/3	3.20	0.52-18.12
Aliphatic chlorinated hydrocarbons	1/9	0.39	0.03-4.44	3/18	0.55	0.09-3.40
Other solvents	2/8	1.31	0.23-7.30		1.22	0.48-3.09

* 2,4-D: 2,4-dichlorophenoxyacetic acid; 2,4-DP: 2,4-dichlorophenoxypropionic acid; 2,4-DB: 2,4-dichlorophenoxybutyric acid; 2,4,5-T: 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TP: 2,4,5-trichlorophenoxypropionic acid; MCPA: 4-chloro-2-methylphenoxyacetic acid; MCTP: 4-chloro-2-methylphenoxypropionic acid; MCTB: 4-chloro-2-methylphenoxybutyric acid; 2,4,6-T: 2,4,6-trichlorophenoxyacetic acid; 2,4,6-TP: 2,4,6-trichlorophenoxypropionic acid; 2,4,6-DB: 2,4,6-trichlorophenoxybutyric acid; 2,3,4,6-TeCP: 2,3,4,6-tetrachlorophenol; PCP: pentachlorophenol; MCA: monochloroacetic acid; P/C/C: *p*-chloro-*o*-cresol; TeCB: tetrachlorobenzene; TCDD: 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.

† Total number of cases = 14; total number of controls = 35.

‡ Total number of cases = 32; total number of controls = 158.

§ Regression model did not converge.

phenoxy herbicides = 7.2; 95% CI = 0.7-72), DDT (OR for phenoxy herbicide = 11.9; 95% CI = 0.9-155), or any of the other four pesticides.

Analysis by location and histology of the sarcomas was not possible owing to small numbers. The locations and histology of the sarcomas were as follows: a neurofibrosarcoma of the lower limb, a leiomyosarcoma of the larynx, a leiomyosarcoma of the prostate, a fibrosarcoma of the lower limb, a neuroblastoma, a hemangiopericytoma of the back, a spindle cell neuroblastoma, a Kaposi angiosarcoma of the lower limb, a leiomyosarcoma of the small bowel, a liposarcoma of the trunk, and a sarcoma of the lower limb (histology not available).

Non-Hodgkin's Lymphoma

In the non-Hodgkin's lymphoma study, associations were generally weaker than those observed in the study on sarcoma (Table 1). We observed a nearly twofold excess risk for exposure to 2,4,5-T (OR = 1.9; 95% CI = 0.7-4.8), any polychlorinated dioxin or furan (OR = 1.8; 95% CI = 0.8-4.3), and TCDD (OR = 1.9; 95% CI = 0.7-5.1). A threefold increased risk for exposure to pentachlorophenol and chlorobutyl lactone was based

on few exposed cases (Table 1). Adjusting for latency reduced the OR for exposure to any phenoxy herbicide from 1.25 to 0.85.

The odds ratios shown in Table 3 are based on cumulative exposure scores grouped in four categories (non-exposed, low, medium, high exposure). We observed a three- to four-fold increased risk for subjects in the medium or high exposure groups for 2,4,5-T, TCDD, and pentachlorophenol. Increasing risk with exposure was observed for 2,4,5-T (*P*-value for trend = 0.09), TCDD (*P*-value for trend = 0.1), and any polychlorinated dibenzodioxin or furan (*P*-value for trend = 0.08).

ORs in the model including the three major herbicides were 1.05 for 2,4-D (95% CI = 0.26-4.28), 2.09 for 2,4,5-T (95% CI = 0.67-6.46), and 0.67 for MCPA (95% CI = 0.18-2.49). ORs for phenoxy herbicides, chlorophenols, and contaminants did not markedly differ between production workers and sprayers.

Exposure to lindane was associated with a small excess risk (OR = 1.6; 95% CI = 0.3-8.8), whereas no excess risk was observed for triazines (OR = 0.7; 95% CI = 0.1-3.1), arsenicals (OR = 0.9; 95% CI = 0.2-3.9), organophosphates (OR = 1.1; 95% CI = 0.4-2.6), DDT

TABLE 2. Odds Ratios for Soft Tissue Sarcoma by Level of Exposure to Selected Chemicals: Cumulative Exposure Has Been Lagged by 5 Years

Chemical* and Exposure	Number of Cases/Controls	OR	95% CI
Any phenoxy herbicide			
Nonexposed	1/25	1.0	Referent
Low	2/4	16.99	0.65-1327.5
Medium	3/13	7.60	0.54-434.9
High	5/13	11.96	1.03-701.9
2,4-D/DP/DB			
Nonexposed	2/31	1.0	Referent
Low	4/12	4.55	0.61-33.41
Medium	2/7	6.13	0.33-129.7
High	3/5	13.71	0.90-209.0
2,4,5-T/TP			
Nonexposed	6/1	1.0	Referent
Low	1/5	1.91	0.03-40.29
Medium	1/3	7.50	0.09-637.1
High	3/6	1.65	0.46-476.3
MCPA/P/B			
Nonexposed	1/26	1.0	Referent
Low	2/6	13.17	0.55-961.3
Medium	4/12	10.28	0.90-541.7
High	4/11	10.87	0.84-644.7
Any chlorophenol			
Nonexposed	0/47	1.0	Referent
Low	1/3	1.0	
Medium	1/4	1.0	0.02-10.53
High	0/1		
Any dioxin in furan			
Nonexposed	2/31	1.0	Referent
Low	4/12	4.49	0.59-33.41
Medium	1/6	3.18	0.04-35.33
High	4/6	18.95	1.26-1236.0
TCDD			
Nonexposed	1/42	1.0	Referent
Low	1/4	2.82	0.05-34.8
Medium	1/4	6.60	0.08-539.9
High	3/5	10.55	0.60-671.4

* For abbreviations of chemical names, see footnote to Table 1.

(OR = 1.0; 95% CI = 0.4-2.8), or dioxin (OR = 1.1; 95% CI = 0.4-2.8). ORs for phenoxy herbicides, chlorophenols, and their contaminants were only minimally modified when adjustment was made for exposure to any of these six pesticides.

Discussion

The two case-control studies were conducted within an international cohort of workers exposed to phenoxy herbicides, chlorophenols, and dioxins. The study population includes workers with substantial exposure to these chemicals, as documented by measurements of serum levels of dioxins in workers^{4,28-31} and by information on the job histories of the workers and on the production history at each plant. In comparison with the previous cohort mortality analysis,^{1,2} the two case-control studies included two to three times more cases and used modeling to estimate individual exposure. Risk estimates in the nested case-control studies are higher

TABLE 3. Odds Ratios for Non-Hodgkin's Lymphoma by Level of Exposure to Selected Chemicals: Cumulative Exposure Has Been Lagged by 5 Years

Chemical* and Exposure	Number of Cases/Controls	OR	95% CI
Any† phenoxy herbicide			
Nonexposed	13/71	1.0	Referent
Low	6/22	1.54	0.52-4.52
Medium	6/33	1.26	0.36-3.19
High	7/30	1.36	0.46-4.03
2,4-D/DP/DB†			
Nonexposed	20/100	1.0	Referent
Low	4/29	0.73	0.22-2.43
Medium	1/13	0.14	0.03-0.73
High	1/14	0.69	0.11-4.55
2,4,5-T/TP			
Nonexposed	22/123	1.0	Referent
Low	4/19	1.32	0.41-4.25
Medium	3/7	3.58	0.18-17.12
High	3/9	3.65	0.61-21.71
MCPA/P/B†			
Nonexposed	17/80	1.0	Referent
Low	6/29	0.98	0.30-3.15
Medium	4/30	0.62	0.18-2.18
High	5/11	1.32	0.42-4.16
Any† chlorophenol			
Nonexposed	23/110		Referent
Low	0/13		
Medium	3/10	1.93	0.50-7.41
High	0/5		
Pentachlorophenol			
Nonexposed	29/149	1.0	Referent
Low	0/2		
Medium	0/2		
High	3/5	4.19	0.59-29.59
Any dioxin in furan†			
Nonexposed	11/73	1.0	Referent
Low	7/34	1.44	0.50-4.13
Medium	3/17	2.18	0.63-7.90
High	3/27	2.54	0.83-7.31
TCDD			
Nonexposed	21/119	1.0	Referent
Low	4/15	1.42	0.44-4.64
Medium	3/8	3.63	0.71-18.67
High	4/13	3.56	0.66-19.20

* For abbreviations of chemical names, see footnote to Table 1.

† For phenoxy herbicides, chlorophenols, and dioxins.

‡ One control with unknown exposure.

than those observed in the cohort analysis, but overall, they accord well with the results of that analysis.

A 5-year time-lagged analysis was applied, ignoring any chemical exposures in a matched set occurring less than 5 years before disease occurrence (cases) or selection into the study (controls). The underlying assumption is that exposures in a late stage of a carcinogenic process do not affect the timing of occurrence of the disease, although the selection specifically of a 5-year limit is arbitrary. A longer time limit would probably be less appropriate, since one of the major chemicals examined, TCDD, has been shown to be a complete carcinogen with a potent tumor-promoting action.³² The semiquantitative type of analysis (due to the use of relative scores of exposure) did not justify a more exten-

- Green LM, Kauppinen T, Lyng E, Mathew W, Neuburger M, Consonni D, Pearce N, Winkelmann R. Cancer mortality in workers exposed to phenoxy herbicides and chlorophenols. *Lancet* 1991;338:1027-1032.
- Engelhardt MA, Hiltunen KE, Markow DA, Pasarelli LA, Henschler CA, Swenberg ML, Gracie AL, Lutz TA, Steinmann K, Suttan M. Cancer mortality in workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *N Engl J Med* 1991;324:212-218.
- Mant A, Berger J, Dwyer JH, Flesch-Janis D, Nagel S, Walzsch H. Cancer mortality among workers in chemical plant contaminated with dioxin. *Lancet* 1991;338:959-964.
- Bertazzi PA, Pesatori AC, Consonni D, Tironi A, Landi MT, Zocchetti C. Cancer incidence in a population accidentally exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Epidemiology* 1993;4:398-406.
- Johnson ES. Important aspects of the evidence for TCDD carcinogenicity in man. *Environ Health Perspect* 1993;99:363-390.
- Hoar Zahm S, Weisenburger DD, Babbitt PA, Saal RC, Vaught JB, Cantor KP, Blair A. A case-control study of non-Hodgkin's lymphoma and the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) in Eastern Nebraska. *Epidemiology* 1993;4:149-156.
- Pearce N, Berthiaume P. Increasing incidence of non-Hodgkin's lymphoma: occupational and environmental factors. *Cancer Res (suppl)* 1992;52:544a-550b.
- Lyng E. Cancer in phenoxy herbicide manufacturing workers in Denmark, 1947-87: an update. *Cancer Causes Control* 1993;4:261-272.
- Hardell L, Eriksson M, Axelsson O, Fredriksson M. Dioxin and mortality from cancer (Letter). *N Engl J Med* 1991;324:1810-1811.
- Hoar SK, Blair A, Holmes FF, Bousen CD, Robel RJ, Hoover R, Fraumeni JF Jr. Agricultural herbicide use and risk of lymphoma and soft-tissue sarcoma. *JAMA* 1986;256:1141-1147.
- Wigle DT, Semenciw RM, Wilkins K, Riedel L, Morrison HI, Mao Y. Mortality study of Canadian male farm operators: non-Hodgkin's lymphoma mortality and agricultural practices in Saskatchewan. *J Natl Cancer Inst* 1990;82:575-582.
- Hardell L, Eriksson M, Lenner P, Lundgren E. Malignant lymphoma and exposure to chemicals, especially organic solvents, chlorophenols and phenoxy acids: a case-control study. *Br J Cancer* 1981;43:169-176.
- Persson B, Dahlander A, Fredriksson M, Brage HN, Ohlson CG, Axelsson O. Malignant lymphomas and occupational exposures. *Br J Ind Med* 1989;46:516-522.
- Xingren G, Fredriksson M, Norling Brage H, Nordenskjold B, Axelsson O. Soft tissue sarcoma and occupational exposures. *Cancer* 1990;66:806-811.
- Pitot HC, Goldworthy TL, Moran S, Kennan W, Clauert HP, Maronpot RR, Campbell HA. A method to quantitate the relative initiating and promoting potencies of hepatocarcinogenic agents in their dose-response relationships to altered hepatic foci carcinogenesis. *Carcinogenesis* 1987;8:1491-1499.
- International Agency for Research on Cancer (IARC) Monographs on the Evaluation of the Carcinogenic Risk of Chemicals: Evaluation of Carcinogenicity. An Update of IARC Monographs, vols. 1-42 (suppl 7). Lyon: International Agency for Research on Cancer, 1987.
- Kojevina M, Winkelmann R, Saracci R, Kauppinen T. Cancer Mortality in Workers Exposed to Chlorophenoxy Herbicides and Chlorophenols. IARC Internal Report 92/002. Lyon: International Agency for Research on Cancer, 1992.
- Suruda AJ, Ward EM, Fingerhut MA. Identification of soft tissue sarcoma deaths in cohorts exposed to dioxin and to chlorinated naphthalenes. *Epidemiology* 1993;4:147-153.
- World Health Organization. Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death (9th revision conference). Geneva: WHO Health Organization, 1977.
- Checkoway H, Pearce NE, Crawford-Brown DJ. Research Methods in Occupational Epidemiology. New York: Oxford University Press, 1989.
- Pearce N. Incidence density matching with a simple SAS computer program. *Int J Epidemiol* 1989;18:951-954.
- Kauppinen T, Pinneri B, Marow D, Kojevina M. Retrospective assessment of exposure by modelling in a collaborative study on cancer risks among workers exposed to phenoxy herbicides and chlorophenols. *Scand J Work Environ Health* 1994;20:260-269.
- International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, vol. 53. Occupational Exposures in Insecticide Application and Some Pesticides. Lyon: International Agency for Research on Cancer, 1992.
- Kauppinen T, Kojevina M, Johnson ES, Saracci R, Bertazzi PA, Bueno-de-Mesquita HB, Gagnon D, Green LM, Johnson ES, Linton M, Lyng E, Mathew W, Neuburger M, Osman J, Pearce NE, Winkelmann R. Chemical exposure in manufacture of chlorophenoxy herbicides and chlorophenols and in spraying of phenoxy herbicides. *Am J Ind Med* 1993;23:415-422.
- SAS Institute. SAS Version 6. Cary, NC: SAS Institute, 1990.
- Mehta C, Patel N. SAS User's Tutorials. Cambridge, MA: CYTEL Software Corp., 1993.
- Neuburger M, Landwog W, Demtl F. Blood levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin in chemical workers after chloracne and in comparison groups. *Int Arch Occup Environ Health* 1991;63:325-327.
- Johnson ES, Parsons W, Weinberg CR, Shore DL, Mathews J, Patterson DK Jr, Needham LL. Current serum levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin in phenoxy acid herbicide applicators and characterization of historical levels. *J Natl Cancer Inst* 1992;84:1648-1653.
- Smith AH, Patterson DG Jr, Warner ML, Mackenzie R, Needham LL. Serum 2,3,7,8-tetrachlorodibenzo-p-dioxin levels of New Zealand pesticide applicators and their implication for cancer hypotheses. *J Natl Cancer Inst* 1992;84:104-108.
- Linton M, Hansson M, Rappe C, Kojevina M. Dioxins in blood from Swedish phenoxy herbicide workers. *Lancet* 1994;344:611-612.
- Blair A, Hoar Zahm S, Pearce NE, Henschler CA, Fraumeni JF Jr. The cancer etiology from studies of farmers. *Scand J Work Environ Health* 1992;18:209-215.
- Bond GG, Wetterstrom 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* 1989;46:98-105.
- Arvidson J, Gustaf L, Svensson RK, Hensler LB, Knudsen PG. Soft tissue sarcoma and non-Hodgkin's lymphoma in relation to phenoxy herbicide and chlorinated phenoxy compounds in western Washington. *J Natl Cancer Inst* 1987;78:599-602.
- Cantor KP, Blair A, Everett G, Gibbon R, Burmeister LF, Brown LM, Schuman L, Dick FR. Pesticides and other agricultural risk factors for non-Hodgkin's lymphoma among men in Iowa and Minnesota. *Cancer Res* 1992;52:2447-2453.
- Collins JJ, Straub ME, Levinson GJ, Conner PR. The mortality experience of workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin in a trichlorophenol process accident. *Epidemiology* 1993;4:7-13.