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

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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 32 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) = 10.3; 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 populations exposed to phenoxy herbicides, chlorinated phenols, and dioxins during manufacture, while spraying, or after accidents.[1–15] 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.[2,6–9] 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.[16] 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.[1,6–8,17]

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

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slightly elevated risk was observed for non-Hodgkin's lymphoma (SMR = 129).[2,18] 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 or 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 21,183 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 died from a disease other than the two index neoplasms, or had died with a sarcoma but, similar to other studies,[19] were coded in the death certificate under a site code other than the specific rubric "Sarcomas of connective and other soft tissue" (*International Classification of Diseases*, 9th revision, code 171).[20]

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.[21] 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 overmatching 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.[22]

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.[23] Exposure of workers was reconstructed through the use of individual job records and of 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[1,17,24] or on the prevalence of the compounds in the occupational environment.[25] 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 was used as the conceptual framework in deriving levels of exposure included variables related to department/job, emission 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).[23] 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, dichlorodiphenyltrichloroethane (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.[26] 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.[27] 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 = 11.3; 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 = 0.9–309; *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 8.5 (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). Regression 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

	Soft Tissue Sarcoma†			Non-Hodgkin's Lymphoma‡		
Chemical*	Exposed Cases/Controls	OR	95% CI	Exposed Cases/Controls	OR	95% CI
Phenoxy herbicides						
Any phenoxy herbicide	10/30	10.32	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-TCP	0/3	—§		2/15	0.65	0.12–3.41
2,4-DCP	2/8	1.29	0.24–6.91	5/24	1.03	0.34–3.09
2,4,6-TCP	1/1	5.0	0.31–79.94	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	0.85–31.86	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
o-Cresol	2/11	0.88	0.15–5.07	5/38	0.53	0.18–1.59
PCOC	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	1.28	0.13–12.78	6/28	1.17	0.36–3.79
Chlorine	2/11	0.88	0.15–5.07	8/53	0.61	0.24–1.59
Gamma-butyrolactone	1/1	5.00	0.31–79.94	2/3	3.00	0.50–18.12
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	0.23–7.39	8/34	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-methyl-phenoxyacetic acid; MCPP: 4-chloro-2-methyl-phenoxypropionic acid; MCPB: 4-chloro-2-methyl-phenoxybutyric acid; 2,4-DCP: 2,4-dichlorophenol; 2,4,5-TCP: 2,4,5-trichlorophenol; 2,4,6-TCP: 2,4,6-trichlorophenol; 2,3,4,6-TeCP: 2,3,4,6-tetrachlorophenol; PCP: pentachlorophenol; MCA: monochloroacetic acid; PCOC: *p*-chloro-*o*-cresol; TeCB: tetrachlorobenzene; TCDD: 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.

† Total number of cases = 11; total number of controls = 55.

‡ 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 fibrous histiocytoma of the lower limb, a neurilemoma, a hemangiopericytoma of the back, a spindle cell neurilemoma, 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 gamma-butyrolactone 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 (nonexposed, low, medium, high exposure). We observed a three- to fourfold 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	0.61–53.41
Medium	2/7	6.13	0.33–129.7
High	3/5	13.71	0.90–309.0
2,4,5-T/TP			
Nonexposed	6/41	1.0	Referent
Low	1/5	1.91	0.03–40.29
Medium	1/3	7.50	0.09–637.1
High	3/6	7.65	0.46–476.8
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	9/47	1.0	Referent
Low	1/3		
Medium	1/4	1.0	0.02–10.53
High	0/1		
Any dioxin or furan	2/31	1.0	Referent
Nonexposed	4/12	4.49	0.59–53.41
Low	1/6	3.18	0.04–85.83
Medium	4/6	18.95	1.26–1236.0
High			
TCDD	6/42	1.0	Referent
Nonexposed	1/4	2.82	0.05–54.8
Low	1/4	6.60	0.08–539.9
Medium	3/5	10.55	0.60–671.4
High			

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

(OR = 1.0; 95% CI = 0.4–2.8), or dinoseb (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 of each plant. In comparison with the previous cohort mortality analysis,[2,18] 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	1.06	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	6/13	2.14	0.73–6.23
High	2/14	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	0.75–17.12
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	5/17	1.32	0.42–4.16
Any‡ chlorophenol			
Nonexposed	23/119	1.0	Referent
Low	0/13		
Medium	3/10	1.93	0.50–7.41
High	6/15	2.68	0.89–8.03
Pentachlorophenol			
Nonexposed	29/149	1.0	Referent
Low	0/2		
Medium	0/2	4.19	0.59–29.59
High	3/5		
Any dioxin or furan†	12/78	1.0	Referent
Nonexposed	7/34	1.44	0.50–4.13
Low	5/17	2.18	0.68–7.00
Medium	8/27	2.54	0.83–7.81
High			
TCDD	21/119	1.0	Referent
Nonexposed	4/18	1.42	0.44–4.64
Low	3/8	3.63	0.71–18.67
Medium	4/13	3.56	0.66–19.20
High			

* For abbreviations of chemical names, see footnote to Table 1.
† Two controls with unknown exposure.
‡ 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.[16] The semiquantitative type of analysis (due to the use of relative scores of exposure) did not justify a more exten-

sive application of time lagging or of a time-windows approach. A fully quantitative approach would be preferable and would have led to more valid estimates of risk, but few environmental measurements of past exposures and biological monitoring data were available.[25]

In this nested case-control study, as in other cohort and case-control studies,[3,5,10,15] exposures to phenoxy herbicides and their contaminants (dioxins) were associated with excess risk of soft tissue sarcoma. Risk was not specifically associated with those herbicides contaminated with TCDD, although we observed a dose-response relation for exposure to any polychlorinated dioxin or furan, to TCDD, and to 2,4,5-T, a herbicide contaminated with TCDD. An evaluation of the independent effect of each herbicide or contaminant on cancer risk is complicated, since few subjects in this study were exposed to only a single herbicide or chlorophenol, and exposures to many of the chemicals examined were highly correlated.[23] Furthermore, substantial exposure to TCDD has been shown to occur even among workers with a relatively short time of exposure[3] and also in workers producing only low volumes of 2,4,5-T, as in the Swedish cohort of this international study.[25,31]

None of the exposures examined in this study was strongly associated with excess risk of non-Hodgkin's lymphoma, although we observed a threefold increased risk in subjects with medium or high exposure to 2,4,5-T and TCDD. A high risk of non-Hodgkin's lymphoma has been found in studies of farmers and other agricultural workers.[32] Frequent use of phenoxy herbicides, in particular 2,4-D, has been associated with increased risk for non-Hodgkin's lymphoma in case-control studies conducted in Sweden,[13,14] Kansas,[11] Nebraska,[7] and Saskatchewan, Canada,[12] and in a U.S. cohort of 2,4-D manufacturing workers.[33] Low or no excess risks have been found in other cohort studies of workers manufacturing phenoxy herbicides,[3] including cohorts in the international register,[2,9] and in case-control studies in New Zealand,[8] Washington State,[34] and Iowa and Minnesota.[35] These contrasting findings may partially be due to the concomitant exposure of farmers to other potential risk factors for non-Hodgkin's lymphoma, such as other agricultural chemicals, zoonotic viruses, and solvents.[8,32] In this study, we observed a threefold risk, based on very small numbers, for exposure to a fungicide, pentachlorophenol, and for gamma-butyrolactone, a chemical used as a raw material. The excess risk for exposure to pentachlorophenol was confined to workers in one British cohort, originally constructed to evaluate the report of a cluster of lymphoma cases in the plant. Little information is available about these chemicals from studies on humans. Both chemicals have been tested in chronic bioassays,[17,24] and pentachlorophenol has been identified as an animal carcinogen.

It has been suggested that the excess cancer risks observed in sprayer and production cohorts exposed to phenoxy herbicides may be due to concomitant exposures to other chemicals, such as 4-aminobiphenyl and beta-naphthylamine in production cohorts,[36] or to a variety of pesticides in sprayer cohorts. Typical of most large manufacturing plants and of pesticide sprayer cohorts, workers in this cohort had been exposed to a large variety of chemicals.[25] It could therefore be argued that, in each of these cohorts, a chemical(s) other than the herbicides and their contaminants might be the cause of the increased risk of soft tissue sarcoma. This is unlikely. First, the cases occurred in six cohorts from four countries, and exposure to the herbicides and their contaminants was the only common chemical exposure. Exposure to 4-aminobiphenyl and beta-naphthylamine was not recorded in any of the manufacturing or spraying cohorts where sarcoma cases were diagnosed.[25] Second, the excess risk was associated with the herbicides and their contaminants rather than with other chemicals used in the production of the herbicides. Third, in the study on soft tissue sarcoma, increased risks were found both for production workers and sprayers (the latter being exposed to a wider variety of pesticides than the former). This indicates that exposures to pesticides other than phenoxy herbicides are not the most likely cause of the excess risk observed in the cohort analysis[2] and in this nested case-control study. We observed excess risk of soft tissue sarcoma for exposure to dinoseb (a contact herbicide) and to DDT, but these risks were partly (dinoseb) or totally (DDT) confounded by exposure to phenoxy herbicides. Evaluation, however, of exposure to these two chemicals was done on the basis of less accurate information than that available for the phenoxy herbicides and their contaminants, and this approach may have led to misclassification of exposure to them and consequently to only partial evaluation of their potential confounding effect.

In conclusion, results of these nested case-control studies indicate that workers with substantial exposure to phenoxy herbicides and their contaminants were at a higher risk of soft tissue sarcoma. Risk was not specifically associated with those herbicides contaminated with TCDD. This study provides, overall, relatively weak evidence that these workers were at increased risk of non-Hodgkin's lymphoma, although a small excess risk was observed in subjects with medium or high exposure to 2,4,5-trichlorophenoxyacetic acid, any polychlorinated dibenzodioxin or furan, and TCDD. Exposures to many of the compounds examined were highly correlated, complicating the identification of the effect of individual compounds.

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