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Soft Tissue Sarcoma and Non-Hodgkin's Lymphoma in Relation to Phenoxyherbicide and Chlorinated Phenol Exposure in Western Washington^{1,2}

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ABSTRACT—A population-based case-control study was conducted in western Washington State to evaluate the relationship between occupational exposure of men aged 20-79 to phenoxyacetic acid herbicides and chlorinated phenols and the risks of developing soft tissue sarcoma (STS) and non-Hodgkin's lymphoma (NHL). Occupational histories and other data were obtained by personal interviews for 128 STS cases and 578 NHL cases, diagnosed between 1981 and 1984, and for 694 randomly selected controls without cancer. Among the study subjects with any past occupational exposure to phenoxyherbicides, the estimated relative risk and 95% confidence interval of developing STS was 0.80 (0.5-1.2), and of developing NHL, 1.07 (0.8-1.4). Risk estimates of developing STS and NHL associated with past chlorophenol exposure were 0.99 (0.7-1.5) and 0.99 (0.8-1.2), respectively. No increasing risk of either cancer was associated with overall duration or intensity of chemical exposure or with exposure to any specific phenoxyherbicide per se. However, estimated risks of NHL were elevated among men who had been farmers, 1.33 (1.03-1.7), forestry herbicide applicators, 4.80 (1.2-19.4), and for those potentially exposed to phenoxyherbicides in any occupation for 15 years or more during the period prior to 15 years before cancer diagnosis, 1.71 (1.04-2.8). Increased risks of NHL were also observed among those with occupational exposure to organochlorine insecticides, such as DDT [1.82 (1.04-3.2)] and organic solvents [1.35 (1.06-1.7)], and to other chemicals typically encountered in the agricultural, forestry, or wood products industries. These results demonstrate small but significantly increased risks of developing NHL in association with some occupational activities where phenoxyherbicides have been used in combination with other types of chemicals, particularly for prolonged periods. They do not demonstrate a positive association between increased cancer risks and exposure to any specific phenoxyherbicide product alone. Moreover, these findings provide no evidence of increased risks of developing NHL associated with chlorinated phenol exposure or of developing STS associated with exposure to either class of chemical.—*JNCI* 1987; 78:899-910.

Recent studies from Sweden (1-5) and elsewhere (6-10) have reported an increased risk of STSs or NHLs in association with occupational exposures to phenoxyacetic acid herbicides and/or chlorinated phenols. Negative studies of this association have also appeared (11-15). Implicated as the putative carcinogen in most of these studies is TCDD (CAS: 1746-01-6), a trace contaminant formed during the manufacture of chemicals that are derived from alkaline hydrolysis of 1,2,4,5-tetrachlorobenzene. Of particular concern in this respect are 2,4,5-trichlorophenol and the phenoxyherbicides 2,4,5-T (CAS: 93-76-5) and 2-(2,4,5-trichlorophenoxy)-

propionic acid (Silvex), which have been reported to be contaminated with TCDD as high as 30 ppm (16). Moreover, TCDD is the prototype of a larger series of halogenated aromatic hydrocarbons including other PCDDs, dibenzofurans, and biphenyls, all of which share similar biochemical properties and which may also contaminate phenoxyherbicide or chlorophenol products in commercial use. Hence concern exists regarding the possible health risks from exposure to chemical products in which any such contaminants may be present.

The present study was conducted to investigate the relationship between the incidence of STSs and NHLs and past exposure to phenoxyherbicides and chlorinated phenols with the use of population-based case-control approach. Subjects were drawn from the male population of western Washington State, where phenoxyacetic acid herbicides and chlorophenols have been widely utilized during the past 40 years by agricultural, forestry, and wood products industries. Specific emphasis was placed on identification of intervening factors or conditions that may influence human susceptibility to the risk of cancer in association with exposure to phenoxyacetic acids, chlorophenols, or PCDDs.

ABBREVIATIONS USED: CSS=Cancer Surveillance System; 2,4-D=2,4-dichlorophenoxyacetic acid; DDT=1,1'-(2,2,2-trichloroethylidene)bis[4-chlorobenzene]; ICD-O=International Classification of Diseases for Oncology, First Revision; NHL=non-Hodgkin's lymphoma; PCDD=polychlorinated dibenzo-p-dioxin; STS=soft tissue sarcoma; 2,4,5-T=(2,4,5-trichlorophenoxy)acetic acid; TCDD=2,3,7,8-tetrachlorodibenzo-p-dioxin.

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SUBJECTS AND METHODS

Acquisition of cases and controls.—From 1983 through 1985 men with either STS or NHL were identified through the CSS, a population-based tumor registry that has covered 13 counties of western Washington State since 1974. Men eligible to participate in the study were between the ages of 20 and 79 at diagnosis and had been diagnosed during the years 1981-84 as having either STS or NHL, as classified histologically by the World Health Organization ICD-O (17). Case definitions of eligibility for STS by ICD-O codes are 8800-8804, 8810-8813, 8830-8832, 8840, 8850-8860, 8890-8920, 8990-8991, 9040-9044, 9120, 9130, 9150, 9170, 9251, 9260, 9503, 9540-9560, and 9580-9581. Case definitions of eligibility for NHL by ICD-O codes are 9590-9642, 9690-9701, and 9750. The CSS obtains data from all hospitals throughout a 13-county region, and essentially complete population coverage is attained.

During 1983-85 a control group without STS or NHL was also selected. Live control subjects aged 20-64 were chosen by means of a random-digit-dialing procedure as described by Waksberg (18). Because the elderly are relatively sparse in the general population, it was not economical to locate all older controls by random digit dialing. Thus additional live control subjects aged 65-79 were chosen at random from data supplied by the Health Care Financing Administration covering Social Security recipients in the study area. Controls were group matched to NHL cases by vital status and 5-year age group with a ratio of 1.2 controls per case. Deceased controls exclusive of homicides and suicides were identified from noncancer death certificates for persons aged 20-79 with a date of death occurring during the study period and with a residence within the 13-county study area. The disposition of case and control subjects according to vital status, interview outcome, and pathologic review of STS is presented in table 1.

Interview procedure.—All study subjects, including proxies, were interviewed in person by experienced interviewers at a time and location of their choice. The interview lasted approximately 1 hour and covered the

participant's residential, military, and medical histories with a detailed section on occupational exposures to herbicides, chlorophenols, and other chemicals prior to diagnosis or interview. Detailed information on known or suspected risk factors for STS and NHL, including past history of immunosuppressive disorders, use of immunosuppressant medication, or family history of cancer or immune disease, was also obtained. Additional information, including pathology, stage, extent of disease, and date of diagnosis, was collected for each case from data supplied by the CSS. "Exposure" for all variables refers to that occurring prior to the date of diagnosis for the cases and prior to the date of interview for controls. The effect of recall differences on cancer risk owing to the difference in lapse time between diagnosis and interview for the cases (≈ 1 yr) versus initial contact and interview for controls (≈ 1 mo) was evaluated and found to be negligible. Risk estimates among living and deceased cohorts were comparable for essentially all associations; hence living and deceased groups were combined in all analyses.

The questionnaire utilized in the interview was designed after identifying the principal occupations and activities undertaken within the study area that have involved the manufacture or use of phenoxyherbicides and/or chlorophenols. Such occupations and activities were identified in consultation with local industrial and university representatives who had had long-term experience with forestry, wood products, and agricultural industries in the Pacific Northwest. This consultation resulted in identification of 34 specific job titles (e.g., wood products worker; herbicide applicator) and 17 specific job activities (e.g., spray weeds with phenoxyherbicides; manufacture chlorophenols) involving potential exposure to either phenoxyherbicides or chlorophenols. In addition, 14 specific phenoxyherbicide or chlorophenol preparations in common commercial use in the study area were identified. Each job title or activity was then assigned to a "high," "medium," "low," or "no" exposure category for both phenoxyherbicides and chlorophenols, reflecting the consensus of the consultant group of the likely intensity of exposure to each

TABLE 1.—A case-control study of STS and NHL in relation to phenoxyherbicide and chlorophenol exposure in western Washington State: Subject disposition

Subject disposition	STS				NHL				Controls			
	Living		Dead		Living		Dead		Living		Dead	
	No.	Percent	No.	Percent	No.	Percent	No.	Percent	No.	Percent	No.	Percent
Total identified as eligible	150	—	56	—	527	—	219	—	622	—	288	—
Physician refusal	20	13	7	13	80	15	23	11	—	—	—	—
Respondent refusal	4	3	2	4	15	3	8	4	95	15	29	10
Other reasons for noninterview	6	4	4	7	24	5	10	5	51	8	40	14
Total interviewed	120	80	43	77	408	77	178	81	476	77	219	76
Excluded by pathologic review	21	18 ^a	12	28 ^a	—	—	—	—	—	—	—	—
Excluded as noneligible post interview ^b	2	—	0	—	6	—	4	—	1	—	0	—
Total subjects for analysis	97	—	31	—	402	—	174	—	475	—	219	—

^a Percent of total interviewed.

^b Based on diagnosis, age, residence, or date of diagnosis.

chemical received in that occupation. Examples of occupational activities in each exposure category are given in the tables.

In the interview, cue questions referring to each specific job title, activity, or chemical preparation were asked to determine whether a subject had worked in an occupation involving probable exposure to phenoxyherbicides or chlorophenols. If an affirmative response to any cue question was elicited, a series of additional inquiries was made to acquire detailed information regarding the extent of exposure to specific chemicals of interest and the precise time intervals during which each exposure episode had occurred. Among the additional questions asked was an inquiry regarding the name and address of the supervisor or a close co-worker in each job episode where possible chemical exposure had occurred. This information was used with subject's permission to corroborate self-reported exposure to specific chemicals and to verify exposure histories in instances where the subject or his proxy was uncertain regarding the actual exposure circumstances in that job. Additional measures taken to reduce the likelihood of recall bias with respect to the reporting of phenoxyherbicide or chlorophenol exposure included avoiding a deliberate focus on these specific chemicals in the interview and conducting the interview during a period (1983-85) of relatively low local or national media attention to the herbicide-cancer issue. The study was not advertised locally, and subjects were not made aware of the focus of the investigation except that it had broad implications with respect to environmental factors related to cancer etiology.

In coding occupational exposure to phenoxyherbicides or chlorophenols based on job descriptions, the inclusive dates during which a person was employed in any specific occupation or activity were recorded in the questionnaire. In the analysis, however, occupational exposure to phenoxyherbicides and chlorophenols was considered to have begun no earlier than 1946 and 1937, respectively, the years when these chemicals first came into widespread commercial use in the study area. The coding of each job episode held by a study subject according to intensity and duration of exposure permitted evaluation of the exposure history of each subject in terms of duration of continuous or cumulative exposure at each dose level. Thus a complete exposure profile on each subject for each class of chemical under evaluation was obtained.

Quality control procedures.—Several quality control procedures were employed to verify the accuracy of the data collected by interview. First, 145 respondents from a total of 1,444 who completed interviews were randomly selected and were recontacted by telephone approximately 1 month after the interview date. Interview and reinterview responses to seven questions were compared. Five of the seven questions reflected an 88% or higher agreement with the original interview, and one item had an 81% agreement rate. The remaining item, cups of coffee consumed per week, had a 34% agreement rate, although 55% of the discrepancies involved minor disagreements regarding the precise number of cups consumed.

A second quality control procedure consisted of independent recoding of a random sample of 238 coded interviews. The overall agreement rate between codes and recodes was 99%. The agreement rate was 98.9% for codes pertaining to phenoxyherbicides and 98.3% for codes pertaining to chlorophenols.

Pathologic review of soft tissue sarcoma case materials.—Pathologic review of histologic slides and/or sections prepared from tissue blocks of STS cases was conducted to verify the initial diagnosis of STS. Reviews were performed by a pathologist (B.K.) with expertise in soft tissue tumors. For the review of STS, specimen materials were acquired from each participating hospital where the initial diagnosis of STS was made and were then coded and sent "blind" to the project pathologist. In all, histologic material from 155 cases was obtained for review. Twenty percent of the slides or sections were resubmitted to the pathologist as an internal check of his first diagnosis. In a few circumstances the project pathologist disagreed with either the CSS or himself regarding the diagnosis of either STS per se or the specific histologic classification of STS. In these instances a sample of the disparate slides was sent to the Armed Forces Institute of Pathology in Washington, DC, for resolution of STS and/or histologic-type classification. This three-tier STS evaluation procedure resulted in retention of 45% of the STS cases in the study with histologic diagnosis as originally determined, and an additional 34% of cases retained with STS were confirmed although they were of a different histologic classification than originally made. Of the original cases 21% were determined either not likely to be STS, or of indeterminate pathology, and, consequently, were excluded from the study. Many of these were primary bone tumors. In light of the widely accepted high level of reliability associated with the accurate identification of NHL according to broad histologic classifications, pathologic materials from NHL cases were not reviewed for verification in this study.

Statistical methods.—The data analysis includes estimates of relative risks as odds ratios and their 95% confidence intervals for a number of variables of interest. The most common confounding variable was age; thus all relationships were age adjusted by 5- or 10-year age groups, where possible. Pooled odds ratios were calculated by means of the Mantel-Haenszel method (19). Test-based confidence intervals were calculated by means of the method of Miettinen (20). In addition, logistic regression analysis (21) was used to evaluate the joint effect of several variables and possible interactions between chemical exposure and other potential risk factors on cancer risks. The total number of subjects represented in each analysis varies according to the rate of unknown responses; for occupational assessments unknowns were omitted from the analyses. In all other analyses unknowns were included in the "none" or "no exposure" category. The percentage of the total study population responding affirmatively with respect to specific job titles, exposures, or other characteristic is presented in the tables. "Significance" in all analyses was determined at the 5% level.

TABLE 2.—Selected characteristics of 128 STS case men, 576 NHL case men (diagnosed 1981-84), and 694 interviewed population control men (1983-85)

Specification	STS, %	NHL, %	Controls, %
Age, yr			
20-39	28.1	10.9	10.2
40-59	29.7	34.4	34.0
60-79	42.2	54.7	55.8
Education			
Less than high school	21.1	26.3	26.4
High school graduate	76.6	72.0	70.6
Unknown	2.3	1.7	3.0
Race			
White	89.8	94.4	95.1
Black	2.3	2.1	2.3
Other	7.0	3.4	2.6
Unknown	0.8	0.0	0.0
Annual income level			
<\$15,000/yr	25.8	28.0	24.1
\$15,000-\$30,000/yr	32.8	37.3	39.2
>\$30,000/yr	33.6	33.6	34.3
Refused	3.9	0.5	0.7
Unkown	3.9	0.7	1.7

RESULTS

Characteristics of the Study Population

Table 2 presents a comparison of NHL and STS cases and controls for selected demographic attributes. The 3 groups were similar in most respects. Notable differences included a higher proportion of STS cases than controls among subjects in the 20-39 age group and a higher percentage of STS cases in the "other" race category. Asians account principally for this difference.

Risks Related to Intensity of Chemical Exposure

When estimates of relative risks of both STS and NHL were determined for various levels of phenoxyherbicide or chlorophenol exposure among the entire study population, no increasing trend or risk estimates significantly different from unity for any exposure level were seen (table 3). However, elevations in risk were observed for several specific occupations involving chemical exposure. Estimates of relative risks of STS and NHL for various occupations involving exposure principally to phenoxyherbicides are shown in table 4. When viewed across job categories involving increasing levels of exposure, no clear indication of increasing risk is observed. No significantly increased risks of either cancer were seen among those in occupations involving low exposure to phenoxyherbicides, although a nearly significant 1.70 (0.9-3.1) odds ratio for NHL was observed among landscapers.

Among those in medium-exposure occupations, no significantly elevated risks of STS were seen. A small but significantly increased risk of NHL [1.33 (1.03-1.7)] was observed among farmers, an occupation traditionally associated with regular use of weed killers. This observation is consistent with reports from other studies that have identified agricultural occupational groups at increased NHL risk (22-25). Further evaluation of this

observation with regard to duration of exposure and to use of specific substances indicated that the risk of NHL increased from 1.02 (0.7-1.5) among those working as farmers from 1 to 9 years to 1.62 (0.9-2.9) among farmers with 10-19 years in that occupation. However, no increased risks of developing NHL were observed among those with more than 20 years as farmers, 0.92 (0.5-1.6). Additionally, there were no increased risks of NHL among farmers who reported having "regularly worked with" 2,4-D [0.68 (0.3-1.4); CAS: 94-75-7], 2,4,5-T [0.74 (0.3-2.1)], or phenoxyherbicides per se [0.71 (0.3-1.5)] when compared with study subjects reporting no phenoxyherbicide exposure. The estimated risk of developing NHL among farmers who reported having regularly sprayed weed killers by backpack, tractor, or aircraft was 1.13 (0.7-1.9). A risk of developing NHL equal to 1.46 (0.8-2.8) was observed among farmers who reported having worked with the specific organochlorine insecticides DDT and chlordane.

In occupations associated with high herbicide exposure, none was associated with a statistically significant increased risk of developing STS. A substantially increased risk of developing NHL [4.80 (1.2-19.4)] was noted for persons who claimed to have worked regularly in jobs involving the spraying of weed killers in national, state, or commercial forests. However, increased risks of this magnitude were not observed among those engaged in other herbicide spraying activities or among those who worked as herbicide formulators or applicators per se. Further evaluation of the risk of NHL observed among forestry herbicide sprayers with respect to specific chemicals used and duration of exposures indicated that all forestry sprayers reported the combined use of 2,4-D and 2,4,5-T as well as various commercial herbicide preparations containing these and other chemicals. An infinite risk estimate was attained for developing NHL among forestry herbicide applicators specifically in association with phenoxyherbicide

TABLE 3.—Risk (pooled odds ratio) of developing STS or NHL in men aged 20-79 by estimated intensity of past occupational exposure to phenoxyherbicides or chlorophenols: 128 STS cases and 576 NHL cases (diagnosed 1981-84) and 694 population control men (interviewed 1983-85) in western Washington State*

Exposure category	STS	NHL	Percent study population
	OR (95% CI)	OR (95% CI)	
Phenoxyherbicides			
None	1.0	1.0	63.3
Low	0.56 (0.3-1.1)	0.90 (0.6-1.3)	12.0
Medium	0.99 (0.6-1.7)	0.95 (0.7-1.3)	16.5
High	0.89 (0.4-1.9)	1.24 (0.8-1.9)	8.2
Chlorophenols			
None	1.0	1.0	41.5
Low	0.90 (0.5-1.6)	0.97 (0.7-1.3)	16.5
Medium	0.93 (0.6-1.5)	0.92 (0.7-1.2)	31.8
High	0.93 (0.5-1.8)	0.92 (0.9-1.4)	10.2

*The percentage of the total study population in each exposure category is also presented.

TABLE 4.—Risk (pooled odds ratio) of developing STS or NHL in men aged 20-79 for specific occupations and activities involving potential phenoxyherbicide exposure: 128 men with STS and 576 men with NHL in western Washington State (diagnosed 1981-84) and 694 population control men (interviewed 1983-85)^a

Occupation or activity	Phenoxyherbicides		Percent study population
	STS	NHL	
	OR (95% CI)	OR (95% CI)	
Low exposure			
Landscaper	0.92 (0.3-2.8)	1.70 (0.9-3.1)	3.6
Railway worker	1.14 (0.6-2.2)	1.06 (0.7-1.5)	10.7
Telephone lineman	0.73 (0.1-3.6)	1.28 (0.6-2.6)	2.4
Medium exposure			
Gardener-groundskeeper	1.07 (0.5-2.2)	0.83 (0.5-1.4)	6.1
Farmer	1.25 (0.8-1.9)	1.33 ^b (1.03-1.7)	30.0
Working in sprayed area	1.34 (0.7-2.6)	1.33 (0.9-2.0)	8.4
High exposure			
Herbicide formulator-mixer	1.24 (0.3-5.3)	1.53 (0.7-3.3)	2.1
Herbicide applicator	1.77 (0.5-6.6)	1.33 (0.8-3.9)	2.2
Spraying herbicides from backpack	0.80 (0.3-2.4)	0.82 (0.4-1.5)	3.3
Spraying herbicides from tractor or aircraft	1.27 (0.5-3.1)	1.51 (0.9-2.5)	4.9
Spraying farmlands with herbicides	1.35 (0.5-3.3)	1.35 (0.8-2.4)	4.3
Spraying forests with herbicides	—	4.80 ^b (1.2-19.4)	1.0
Spraying near utility lines or railroad tracks	—	1.03 (0.3-3.1)	0.9

^a The percentage of the total study population in each occupation or activity is also presented.

^b P<.05.

exposure, inasmuch as there were no control subjects who served as forestry herbicide sprayers and did not use phenoxyherbicides. This association was statistically significant with P=.004. However, only a very small number of exposed subjects (7) were involved. The risks of STS and NHL associated with all occupations involving potential exposure to phenoxyherbicides considered together were 0.80 (0.5-1.2) and 1.07 (0.8-1.4), respectively. The risks of developing NHL associated with exposure specifically to 2,4-D and 2,4,5-T and to phenoxyherbicides in general among the entire study population were 0.73 (0.4-1.3), 0.98 (0.5-2.0), and 0.87 (0.5-1.5), respectively.

Table 5 presents risk estimates of STS and NHL for various occupations and activities involving chlorophenol exposure. As in the case of phenoxyherbicides, no clear indication of increasing risks of either STS or NHL is apparent when viewed across job categories involving increasing levels of exposure to chlorophenols. Somewhat elevated risks of developing STS are suggested for lumber graders [2.66 (1.1-6.4)] and log-lumber inspectors [4.83 (0.6-38.2)], although other jobs involving comparable chlorophenol exposure offer no suggestion of substantially increased STS risks. No specific jobs involving chlorophenol exposure were associated with increased risks of developing NHL. When all

TABLE 5.—Risk (pooled odds ratio) of developing STS or NHL in men aged 20-79 for specific occupations and activities involving potential chlorophenol exposure: 128 men with STS and 576 men with NHL in western Washington State (diagnosed 1981-84) and 694 population control men (interviewed 1983-85)^a

Occupation or activity	Chlorophenol		Percent study population
	STS	NHL	
	OR (95% CI)	OR (95% CI)	
Low exposure			
Planer mill worker	1.55 (0.5-4.7)	1.39 (0.7-2.7)	3.1
Feeder man	1.31 (0.4-4.7)	1.44 (0.7-2.31)	2.9
Bander man	0.90 (0.2-4.4)	1.45 (0.6-3.4)	1.8
Medium exposure:			
Log-lumber inspector	4.83 (0.6-38.2)	0.40 (0.0-3.6)	0.4
Sawmill worker	0.97 (0.5-1.8)	1.03 (0.7-1.4)	15.0
Wood products worker	1.27 (0.7-2.3)	0.88 (0.6-1.3)	13.0
Fork lift driver in mill	1.52 (0.6-3.6)	1.44 (0.8-2.6)	4.2
High exposure			
Lumber grader	2.66 ^b (1.1-6.4)	0.94 (0.5-1.9)	3.1
Wood preserver	0.79 (0.1-5.9)	1.64 (0.6-4.2)	1.4
Manufacturer of chlorophenols	1.37 (0.4-4.3)	1.72 (0.9-3.4)	3.0

^a The percentage of the total study population in each occupation or activity is also presented.

^b P<.05.

occupations involving potential exposure to chlorophenols were considered together, the risks of developing STS and NHL were 0.99 (0.7-1.5) and 0.99 (0.8-1.2), respectively.

Results of Supervisor-Co-worker Survey

Corroboration of self-reported occupational exposure to phenoxyherbicides, chlorophenols, and other chemicals was sought through telephone contact with employer supervisors or co-workers of subjects who had been employed in jobs involving potential exposure to such substances. Confirmation of subjects' responses regarding exposure was provided in essentially all instances where employers or co-workers could be reached. There were no significant differences between agreement rates for cases or controls. The ability to acquire corroborative evidence of exposure ($\approx 80\%$ of contacts attempted) was greatest for most recent occupations held.

Risks Related to Duration of Chemical Exposure

Inasmuch as cancer risks may vary with length of exposure to specific carcinogens or tumor-promoting agents, it was of interest to estimate the relative risks of STS and NHL for various lengths of cumulative exposure to either phenoxyherbicides or chlorophenols. Hence risk estimates of both cancer types for 10-year durations (1-10, 11-20, >20) of exposure to phenoxyherbicides or chlorophenols were calculated. In this context, exposure refers to any level of occupational phenoxyherbicide or chlorophenol exposure during any portion of the time period since 1946 or 1937, respectively, up to the date of diagnosis (cases) or interview (controls). "Duration" refers to the total length of cumulative exposure during this time period. From these calculations, it was determined that the risk of neither STS nor NHL increased with the duration of phenoxyherbicide or chlorophenol exposure for periods of 20 years or more when all levels of exposure are considered concomitantly. Moreover, no increased risks of either cancer were seen when increasing lengths of exposure to

only high levels of phenoxyherbicides or chlorophenols were considered.

Evaluation of a Latent Period for Cancer Development

The average latent period for a carcinogenic effect of aromatic hydrocarbons in humans has been postulated to be on the order of 15-30 years (26). It was, therefore, of interest to determine if exposure to either phenoxyherbicides or chlorophenols prior to an assumed latent period of 15 years before cancer diagnosis was associated with an increased risk of STS or NHL. For these determinations, the risk of each cancer type were calculated for two durations of cumulative exposure (1-14 and >15 yr) during the period between 1946 or 1937 for phenoxyherbicides and chlorophenols, respectively, and 15 years prior to diagnosis or interview. The results revealed a significant increase in the risk of NHL [1.71 (1.04-2.8)] among those with cumulative exposures to phenoxyherbicides of more than 15 years during the period preceding 15 years before diagnosis. When a 5-year latent period for cancer development was assumed, the risk of NHL among those with 15 years or more of prelatency phenoxyherbicide exposure dropped to 1.29 (0.9-2.0). In contrast, the risk of developing NHL was 2.51 (0.5-13.0) among subjects with more than 15 years of herbicide exposure prior to a 25-year assumed latent period. No increased risks of STS for either chemical or of NHL for chlorophenols were observed in relation to chemical exposure for any latent period or cumulative exposure assumption.

Evaluation of Other Risk Factors for STS and NHL

Since autoimmune diseases, primary immunodeficiency syndromes, and other conditions that compromise immune competence may act as independent risk factors of STS or NHL, it was of interest to determine the risks of either type of cancer associated with such conditions existing prior to the year of cancer diagnosis (or interview). Table 6 presents risk estimates of STS

TABLE 6.—Risk (pooled odds ratio) of developing STS or NHL among men aged 20-79 with factors or conditions associated with compromise of immune competence: 128 men with STS and 576 men with NHL (diagnosed 1981-84) and 694 population controls (interviewed 1983-85) in western Washington State^a

Risk factor	STS	NHL	Percent study population
	OR (95% CI)	OR (95% CI)	
Malaria	1.14 (0.4-3.1)	1.47 (0.9-2.5)	4.7
Preexisting cancer			
Nonskin	0.88 (0.3-2.5)	1.24 (0.7-2.1)	4.8
Skin	1.47 (0.7-3.1)	1.57 ^c (1.03-2.4)	7.5
Corticosteroids	0.70 (0.4-1.1)	0.91 (0.7-1.2)	27.5
Rheumatoid arthritis		1.38 (0.9-2.2)	5.9
Low gamma or immunoglobulin		1.59 (0.5-4.6)	1.0
Immunosuppressant drug therapy ^b		10.97 ^c (2.1-57.3)	0.7
Immune deficiency in a blood relative		1.51 (0.4-5.6)	0.6

^aThe percentage of the total study population with each risk factor is also presented.

^bAzathioprine, cyclophosphamide, chlorambucil, and/or mercaptopurine.

^c $P < .05$.

TABLE 7.—Risk (pooled odds ratio) of developing STS or NHL among men aged 20–79 associated with miscellaneous occupational factors or conditions among 128 men with STS and 576 men with NHL (diagnosed 1981–84) and 694 population controls (interviewed 1983–85) in western Washington State^a

Condition	STS	NHL	Percent study population
	OR (95% CI)	OR (95% CI)	
Insecticides			
Chlordane	0.96 (0.2–4.8)	1.61 (0.7–3.8)	1.6
DDT	1.10 (0.4–3.2)	1.82 ^b (1.04–3.2)	4.0
Industrial chemicals			
Organic solvents	1.10 (0.7–1.7)	1.35 ^b (1.06–1.7)	29.8
Lead-lead arsenate	1.51 (0.9–2.6)	1.60 ^b (1.1–2.3)	12.0
Welding-metal fumes	1.30 (0.9–2.0)	1.31 ^b (1.03–1.7)	31.1
Chloracne	3.32 (0.8–14.0)	2.12 (0.6–7.0)	1.0
Skin blisters from chemicals	1.72 (0.9–3.2)	1.06 (0.7–1.6)	7.8
Cigarette smoking	0.93 (0.6–1.4)	0.85 (0.8–1.1)	73.5
Coffee drinking	0.49 (0.4–1.2)	1.28 (0.9–1.9)	89.8

^a The percentage of the total study population with each condition or factor is also presented.

^b $P < .05$.

and NHL for a number of such conditions or factors. All assessments were made from subject interviews, not from medical records. Immunosuppressant drug therapy received for any reason prior to the year of diagnosis of NHL was the greatest risk factor for either cancer. Immune deficiency in a blood relative was also associated with an increased (although nonsignificant) risk of NHL. In contrast, the use of corticosteroids for observed periods of use up to 29 years was not associated with an increased risk of either cancer type.

Of specific note is the 1.38-fold increased risk of NHL observed in relation to a history of rheumatoid arthritis. Although not statistically significant, this observation is interesting in light of the current controversy surrounding the question of increased risks of NHL among persons afflicted with autoimmune diseases (27). Preexisting skin cancer was also associated with a slightly increased risk of both STS and NHL. Although the type of skin cancer was not ascertained in this study, several histologic types of STS and NHL can have dermal manifestations that could have been misreported as "skin cancer." Among these are the soft tissue tumors, dermatofibrosarcoma (8832/3) and Kaposi's sarcoma (9140/3), and the non-Hodgkin's lymphoma, mycosis fungoides (9700–9701/3). Kaposi's sarcoma was excluded from evaluation in this study, and none of those reporting skin cancer was found to have this form of STS. Among those 12 STS cases reporting a prior history of skin cancer, none was found to have dermatofibrosarcoma; among 53 NHL cases, none had confirmed mycosis fungoides.

Malaria was evaluated as a potential risk factor for STS and NHL in light of studies suggesting an etiologic association between malarial infection and the risks of developing sarcomas or lymphomas through mechanisms involving plasmodial suppression of immune defenses against malignant diseases (28, 29). The risk of developing neither STS nor NHL was significantly elevated in association with a self-reported prior history of malaria alone.

Finally, table 7 presents risk estimates associated with

various occupational and/or lifestyle factors that were observed in the present study to independently alter the risk of STS or NHL and that might, therefore, be considered as potential modifiers of the effect of chemical exposure on cancer risks. Of particular note is the significantly increased risk of NHL seen among men with previous exposure to organic solvents, lead or lead arsenate pesticides, and welding and metal fumes. The risk of NHL was also elevated among men reporting previous exposure to the organochlorine insecticides chlordane and DDT. Also of note is the increased risk of both STS and NHL observed among those reporting a prior incidence of chloracne. Although this condition was not clinically confirmed in this study, this observation is of considerable interest inasmuch as chloracne is an important clinical manifestation of exposure to high levels of chlorinated dibenzodioxins and furans in humans (30). The statistical association of reported chloracne with phenoxyherbicide exposure was of borderline significance ($P < .075$) in this study. Neither cigarette smoking nor coffee drinking was a risk factor for either cancer.

Not shown in table 7 are a number of other factors or conditions that were also evaluated as potential risks factors, but for which no significant or suggestive associations with either STS or NHL were found. These include: exposure to radiation, x-rays, or radioactive materials; exhaust fumes from motorized equipment; home use of phenoxyherbicides; residency near areas sprayed with weed killers; tuberculosis vaccination; consumption of multiple vitamins; eating fish caught in Puget Sound; and use of alcohol.

Logistic regression analysis was used to estimate the potential interaction between phenoxyherbicides or chlorophenols and various other single variables appearing in table 6 or 7 as well as others of interest. Intervening variables for which the interaction with phenoxyherbicides or chlorophenols were determined included: organochlorine pesticides (DDT+chlordane), lead-lead arsenate, welding or metal fumes, inherited or acquired diseases of the immune system, any prior cancer, prior skin cancer, home use of phenoxyherbicides, family his-

tory of cancer, and family history of diseases of the immune system. All analyses were controlled for age. Results of the logistic regression analysis for these variables confirmed the magnitude of the risks shown in tables 6 and 7. None of the interactions between chlorinated phenol or phenoxyherbicide exposure and these variables was statistically significant, with the exception of that between phenoxyherbicides and organic solvents as a risk factor for NHL. The odds ratio for joint exposure compared with exposure to neither substance was 1.50 with a 95% confidence interval of 1.03-2.18. The odds ratio estimates from the model for exposure solely to organic solvents or phenoxyherbicides were nonsignificantly 1.12 and 0.85, respectively. The significance of the joint exposure in this case may be a result of the large number of comparisons made in this study or, possibly, due to a genuine synergistic effect.

Positive although nonsignificant interactions were also observed between exposure to either phenoxyherbicides or chlorophenols and coexisting or preexisting autoimmune diseases or immune deficiency syndromes when those listed on table 6 and others (mononucleosis, celiac sprue, and Sjögren's syndrome) were considered jointly. This interaction was most notable with chlorophenols where the odds ratio for joint exposure (compared with neither) was 1.40 (0.95-2.07) as compared with 0.91 (0.72-1.14) and 1.32 (0.99-1.78), respectively, for chlorophenol or immune deficiency alone. These observations are worthy of note in light of the widely held theory (31) that the etiology of malignant lymphomas involves failure of immunoregulation in the face of a persistent stimulus for lymphocyte proliferation. In autoimmune diseases, chronic antigenic stimulation is provided by the constant exposure to self-antigens, whereas in primary immunodeficiency syndromes, recurrent infections are the likely source for antigenic stimulation. In contrast, TCDD is well recognized as a suppressant of both humoral and cell-mediated immunity in animals (32-34) and has been recently characterized as a depressant of cell-mediated immunity in humans during prolonged, low-level exposure (35). Immunosuppression by other PCDDs has also been described (36). Therefore, further consideration should be given to the possibility that the statistical interactions, however slight, observed in this study between phenoxyherbicides or chlorophenols and immunosuppressive disorders have biologic relevance with respect to the etiology of NHL in humans.

DISCUSSION

The results of the present study demonstrate significantly increased risks of developing NHL among men in occupations involving farming and forestry herbicide spraying and for occupations involving prolonged phenoxyacetic acid herbicide exposure when a latent period of 15 or more years before cancer diagnosis is considered. However, neither phenoxyherbicides nor chlorophenols alone appear to constitute a sufficient cause of either NHL or STS when evaluated within a popula-

tion residing in western Washington State, since increased cancer risks were not observed for numerous other occupations or activities involving comparable opportunity for exposure to these substances. In this regard, the present findings are not consistent with results of studies conducted in Swedish and other populations, which report consistent and substantially increased risks of both types of cancer in association with occupational exposure to specific chlorophenols or phenoxyacetic acids or to combinations of these chemicals.

In consideration of possible reasons underlying the apparent lack of consistency between the results of Swedish studies and those conducted here and elsewhere, three issues that have not received major attention with regard to this question include: *a*) differences in the intensities or dosages of chemicals received by workers in comparable occupational activities, *b*) differences in the extent of environmental (nonoccupational) exposure to the chemicals received by the respective study populations, and *c*) differences between study populations with respect to the proportional distribution of other risk factors that in combination with phenoxyherbicides or chlorophenols contribute causally to the cancers putatively associated with chemical exposure alone.

In addressing the question of differences in dosages of chemicals received by workers engaged in comparable job activities, it is likely that, should the chemicals under investigation independently increase cancer risks in humans, this effect should be more apparent among persons receiving higher dosages. In considering this possibility as it pertains specifically to application of phenoxyherbicides, it is known that spraying activities, as well as work in sprayed areas, extend over substantially shorter periods of the year in Sweden than occur in western Washington State, owing largely to climatic differences in the length of the growing season. Thus Swedish workers participate in activities in which phenoxyherbicide exposure is typically consolidated within a 2- to 3-month period annually, during which spraying activities involving intensive herbicide exposures that extend over several consecutive weeks at a time are not uncommon (1, 37). In contrast, the annual spraying season in the Pacific Northwest extends over 6-7 months, during which individual spraying episodes usually span only a few days at a time and may be separated by weeks or even months during which no spraying is performed. Such differences in herbicide use patterns could conceivably lead to Swedish applicators receiving appreciably higher cumulative exposures to biologically active substances than occurs among workers engaged in less intensive use patterns, as supported by several studies of this question (38, 39).

To analyze this possibility quantitatively, we have employed the pharmacokinetic model developed by Gehring et al. (40) from the oral study of 2,4,5-T in humans to calculate maximum absorbed daily dosages of herbicide received by Swedish and American workers. The workers in question engaged in activities with comparable job description, namely, herbicide applica-

tor with the use of tractor-drawn equipment. Calculations, based on urinary herbicide concentrations with the use of data derived from studies of applicators under actual field conditions (37, 41), indicate that the maximum daily dose of 2,4,5-T absorbed by American workers in an application operation involving two sprayings, 2 weeks apart, is in the range of 12-86 $\mu\text{g}/\text{kg}$ body weight, with a mean maximum daily dose of 45 $\mu\text{g}/\text{kg}$. In contrast, calculated maximum daily dosages received by Swedish workers, doing the same type of work but involving spraying for 3-4 hours/day over a consecutive 2-week period, ranged from 11 to 315 $\mu\text{g}/\text{kg}$, with a mean maximum daily dosage of 90 $\mu\text{g}/\text{kg}$. Maximum daily dosages received by American workers involved in other modes of herbicide application were backpack crew, 19-104 $\mu\text{g}/\text{kg}$; helicopter crew, 17-23 $\mu\text{g}/\text{kg}$; and mixers, 12-138 $\mu\text{g}/\text{kg}$. These results suggest that maximum daily dosages of herbicides received by Swedish applicators could substantially exceed those received by American counterparts as well as those engaged in other modes of spraying operations. From the pharmacokinetic studies in humans (40), it is known that 2,4,5-T is absorbed and excreted in the urine with a half-life of about 1 day following a single oral exposure. Moreover, from measurements of urinary 2,4,5-T, the maximum dose that can be absorbed on repeated exposures is estimated to be about 100 $\mu\text{g}/\text{kg}/\text{day}$, with the expected maximum concentration in plasma of individuals receiving repeated daily doses reaching a plateau after 3 days of such exposure. Based on these considerations, the calculated mean maximum daily dose of 2,4,5-T received by Swedish workers under the occupational circumstances described above (90 $\mu\text{g}/\text{kg}$) would approximate that required to produce the maximum plasma concentration of 2,4,5-T that could be sustained during spraying operations. Thus Swedish applicators would experience higher sustained tissue levels during repeated frequent exposure episodes, as well as higher tissue concentrations of any PCDDs or other contaminants that would be concomitantly absorbed than would be experienced by American counterparts, who receive lower exposures on a more sporadic basis.

Although the implications of these calculations with respect to human cancer risks are difficult to estimate, they are nevertheless of interest in light of findings from recent studies of Swedish subjects (42) involving analysis of PCDDs in abdominal fat from both cases of STS and NHL as well as control subjects. These studies reported that cancer cases exposed to phenoxyherbicides 16-31 years previously had levels of highly chlorinated PCDDs significantly higher than control subjects unexposed to phenoxyherbicides. Interestingly, no differences in case or control TCDD levels were seen. These findings are consistent with the observations from both Swedish (2) and Danish (7) studies of increased cancer risks among persons exposed to phenoxyherbicides and chlorophenols that do not contain detectable levels of TCDD per se but that are most likely contaminated with a variety of other chlorinated dibenzodioxins and furans (43, 44), some of which have been shown to have carcinogenic potential

(45, 46). Moreover, the capacity of TCDD, and presumably its approximate isostereoisomers, to act as a cocarcinogen (47) and a tumor promoter (48, 49) have been well characterized. These properties are highly dose dependent. Thus the exposure of Swedish workers to potentially higher concentrations of biologically active substances associated with the use or manufacture of phenoxyherbicides or chlorinated phenols is a consideration possibly consistent with the higher cancer risks observed in studies on such subjects. A recent study by Hoar et al. (25) showing that the relative risk of NHL dramatically increased with the number of days of phenoxyherbicide use per year among agricultural workers in the United States supports this view.

Differences in risk estimates observed between this and the Swedish studies might also be accounted for on the basis of variation in the extent of nonoccupational exposure received by the general populations in areas where the studies were conducted. Several investigators (50, 51) have recently reported widespread contamination of the general population in the United States and Canada with PCDDs and PCDFs, based on analysis of human fat samples. The findings indicate that, although higher levels of total dioxins and other contaminants may be seen in some exposed persons, there is considerable overlap in actual tissue concentrations of such substances between some persons with confirmed occupational exposures and others who are not previously known to have been exposed through job-related activities. These observations suggest that epidemiologic studies conducted in areas where the extensive use of phenoxyherbicides and chlorophenols has occurred may have inadvertently included subjects who have experienced significant exposure to the chemicals of concern outside of the occupational setting. Should this be the case, it is possible that estimates of actual risk based on recall of occupational exposures alone may be underestimated, owing to nondifferential misclassification of subjects according to exposure status (52).

To estimate the extent to which nonoccupational exposure to phenoxyherbicides may have occurred in the present investigation, we have evaluated data from several air-monitoring studies (53, 54) conducted during the spraying season in the Pacific Northwest. These data indicate that phenoxyacetic acids as well as PCDDs can be transported in the atmosphere, either as vapor or adsorbed on particles, for distances ranging from several hundred feet up to a mile from the application area (54), depending on weather conditions and mode of dispersion. The maximum concentration of 2,4,5-T, for example, found in 24-hour collections from sampling stations in one study (55) was 3.4 $\mu\text{g}/\text{m}^3$. Concentrations of up to 10 $\mu\text{g}/\text{m}^3$ of other phenoxyherbicides have been detected at sampling sites in agricultural regions of Washington State (56). If it is assumed that a 70-kg person inhales 30 m^3 of air per day, a person residing in the proximity of a sprayed area could conceivably receive a dose of 2,4,5-T equal to 1.5 $\mu\text{g}/\text{kg}/\text{day}$ during the spraying operation solely from atmospheric sources. These levels are on the order of 10-50 times less than those

received from occupational sources, as described above, and moreover are received via a different route of exposure (inhalation versus dermal), which could alter absorption rates appreciably. However, 24% of STS cases, 23% of NHL cases, and 21% of control subjects in the present study responded positively to the question "Have you ever lived in an area where weed spraying was routinely done by truck or airplane?" This response suggests that considerable population exposure to phenoxyherbicides and their contaminants from environmental sources could have occurred over the 40-year exposure-assessment period. Eliminating subjects who reported residential or home use exposures to phenoxyherbicides or chlorophenols in the present study did not alter the estimated risks of developing STS or NHL. Hence it is unlikely that bias due to such exposures could account for the large differences in risk estimates observed between these and the Swedish studies. Nevertheless, should phenoxyherbicides and/or their contaminants increase the risk of cancer at environmental exposure levels, or, as recently suggested, produce subclinical immune system alterations that may predispose to such risks (35), it is possible that risk estimates based solely on assessment of occupational exposures could be attenuated as a result of exposure misclassification. Confirmation of this possibility awaits further investigations based on direct analysis of tissue chemical content or the development of a reliable surrogate measure of past chemical exposure.

A third possible reason for a lack of consistency between the results of this and the Swedish studies may be differences between the study populations with respect to the proportional distribution of factors or conditions other than chemical exposure that contribute to the cancers under evaluation. If, for example, a specific inherited, lifestyle, or environmental condition that independently predisposes to increased risks of the cancer(s) associated with chemical exposure is more prevalent among Scandinavians than among other populations, increased cancer risks could be observed in the former group, even if the prevalence of phenoxyherbicide or chlorophenol exposure were the same or even less than that occurring elsewhere. In this regard it is interesting to note in the present study that exposure to the insecticides DDT and lead arsenate as well as to agricultural and industrial chemicals, such as organic solvents and welding-metal fumes, are associated with significantly increased risks of developing NHL (table 7). Compromise of the immune system (31), exposure to zoonotic viruses (24, 57), and chronic mitogenic stimuli (24, 31) have also been suggested as etiologic factors for NHL.

The extent to which differences in the proportional distribution of such factors between Swedish and the local study populations might account for the inconsistencies observed between the results of this and the Swedish studies cannot be currently estimated, since neither the specific conditions that modify the effects of chemical exposure on cancer risks nor their prevalence among the respective populations have as yet been iden-

tified. However, information based on interview responses from existing studies (4) indicates that Swedish populations may have had as much as twice the frequency of exposure to DDT (5.8-7.8 vs. 3.8% locally) as well as to total insecticides (14.6 vs. 7.9%), and this higher exposure may underlie some increased risk of developing cancer, particularly NHL, independently of or in combination with the chemicals currently under study. On the other hand, the frequency of exposure to organic solvents, for which a small but significant interaction with phenoxyherbicides was observed in this study, was approximately equal (28.2 vs. 29.9%) between Swedish and local study populations. Similarly, the frequency of cigarette smoking, now or ever, among Swedish and local study populations was comparable (71 vs. 73%). Little or no data are available regarding population differences in nutritional, medical, or other lifestyle factors that might serve as component causes of STS or NHL or that modify the effect of chemical exposures on cancer risks.

The prospect that inherited factors or conditions among Scandinavians might contribute to increased risks of developing cancer in that population when exposed to the chemicals under investigation is another possibility that might account for differences in risk estimates observed. Although specific studies of this question have as yet to be accomplished, laboratory investigations have shown that the binding affinity of the TCDD receptor in biological tissues, as well as subsequent receptor-mediated events, are genetically determined and may vary considerably even among different strains of the same animal species (58). That such variations are also a characteristic of human genealogy is suggested by recent studies (59) that demonstrate both the presence of the Ah (TCDD) receptor in human lung as well as considerable heterogeneity in the human population in regard to lung Ah receptor concentrations. Moreover, evidence of heritable differences in aryl hydrocarbon hydroxylase induction among humans (60) has been presented. Recently, a hereditary predisposition for the development of STS has been described in the study of Danish phenoxyherbicide manufacturers (7). However, no attempt has been made to determine the frequency of this condition among Scandinavian or other populations or to investigate the extent to which the presence of such a condition could modify the effect of chemical exposure on cancer risks.

In the present investigation, we have taken advantage of the fact that approximately 6% of the population of the study area is of Scandinavian heritage (61) to make a crude evaluation as to the extent to which this factor (Scandinavian heritage) might constitute an increased risk of STS or NHL in association with phenoxyherbicide or chlorophenol exposure. For this assessment, the surnames of all study subjects were segregated into Scandinavian or "other" categories by a member of the University of Washington Department of Scandinavian Languages and Literature who had expertise in Scandinavian genealogy. Through this effort 169 subjects with Scandinavian surnames were identified including

15 STS cases, 66 NHL cases, and 88 controls. No increased cancer risks were associated with having Scandinavian as compared with non-Scandinavian names. However, when the analysis was restricted to Scandinavians only, the risk estimates for STS in relation to past occupational chemical exposures were substantially greater than those observed among the study population as a whole both for high-level phenoxyherbicide [2.8 (0.5-15.6)] and high-level chlorophenol [7.2 (2.1-24.7)] exposures. These estimates are comparable in magnitude to those reported among subjects in Swedish (1-5) and Danish (7) studies. Moreover, the distribution of predominant histologic types of STS was comparable to that reported from the Swedish studies (2). No increased risks of NHL in relation to chemical exposures were observed among persons with Scandinavian surnames. Although the assignment of Scandinavian ancestry in these studies remains unconfirmed, the results are interesting inasmuch as they suggest that factors specific to Scandinavian descent, as opposed to residency or occupation in Scandinavian countries, may contribute to increased risks of STS when exposed to the chemicals under evaluation in this study. Further investigation of this issue may be warranted to help resolve the inconsistency between Swedish studies and those conducted elsewhere.

In conclusion, the results of the present investigation demonstrate increased risks of NHL in several specific occupations in which phenoxyacetic acid herbicides are used, as well as for prolonged occupational exposure to these substances. However, they are not consistent with results from Swedish and other studies reporting substantially increased risks of either STS or NHL associated with phenoxyherbicides or chlorophenols as sole or major component causes of these diseases. Since methods of study design and analysis in this and the Swedish studies were similar in most respects, it is possible that factors specific to the populations under evaluation account for the inconsistencies observed. Concerns that bear further consideration in this regard include possible differences in the intensity or distribution of chemical exposures between the study populations and variations in the proportional distribution of specific inherited, life-style, and/or environmental factors that modify the effect of chemical exposure on the risks of cancer development.

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