Hodgkin Lymphoma, Multiple Myeloma, Soft Tissue Sarcomas, Insect Repellents, and Phenoxyherbicides

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Objective: *The objective of this study was to determine if there is an additional risk of developing Hodgkin lymphoma, multiple myeloma, or soft tissue sarcoma as a consequence of exposure to a combination of phenoxyherbicides, rubber gloves, DEET (N, N-diethyl-m-toluamide), and sunlight compared with each of the individual chemicals.* ***Methods:*** *This was a population-based study of men with specific cancers and age, province-matched control subjects.* ***Results:*** *No additional risk from these combinations of exposures of developing these three types of tumor was found in contrast to non-Hodgkin lymphoma.* ***Conclusions:*** *The mechanisms by which phenoxyherbicides contribute to the risk of multiple myeloma and non-Hodgkin lymphoma may be different.* (J Occup Environ Med. *2006;48:264–274*)

The safety and efficacy of insect repellents containing DEET (N, N-diethyl-m-toluamide) as the active ingredient have been investigated extensively in recent years, although these products have been in widespread use for decades.[1–3] Their effectiveness in preventing mosquitoes from landing on exposed skin and their safety for the general public when properly applied has been confirmed by extensive reviews[4] and evaluations of compilations of evidence.[5] The use of insect repellents is being promoted by public health professionals as a result of the relatively recent emergence of Lyme disease and illness caused by the West Nile virus.[6–8] Research interest in these compounds has been sparked by the emergence of illnesses among Gulf War veterans who were issued insect repellents containing DEET but who were also exposed to several other chemicals.[9–11] As a result, the evaluation of simultaneous exposure to a variety of chemicals, including DEET, has been the focus of animal[12] and epidemiologic studies.[13–17]

There is suggestive evidence in the literature that individuals who farm[18–29] who are exposed to certain types of animals,[30–34] to herbicides,[30,35–43] or to insecticides[31,44,45] are at increased risk of developing Hodgkin lymphoma (HL), multiple myeloma (MM), and soft tissue sarcomas (STS). The evidence from other studies has contradicted those putative associations.[45,46–64] One scientific puzzle that occurs repeatedly in epidemiologic studies of po-

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tential cancer associations with exposure to pesticides is the ubiquity of the exposure and the uncommon disease outcome. Therefore, there is an assumption that other factors must be involved that either increase or decrease the effect of the exposure in some individuals. The International Agency for Research on Cancer[65] has declared several phenoxyherbicides as a group to be probable human carcinogens. The widely used phenoxyacetic herbicides included are 2,4-D (2,4-dichlorophenoxyacetic acid), 2,4,5-T (2,4,5-trichloroacetic acid), and MCPA (4-chloro-2-methylphenoxyacetic acid).

As part of epidemiologic research designed to study the putative associations between exposure to selected pesticides and four types of cancer (MM, STS, HL, and non-Hodgkin lymphoma [NHL]),[66] we collected data on the use of insect repellents, which are the only class of pesticide that are repeatedly and routinely applied to human skin or clothing.[5,67] The current analysis was undertaken for three reasons. Moody and Nadeau,[68] in an in vitro study, found that the permeability to 2,4-D of the type of rubber gloves commonly recommended for use by farmers when mixing or applying pesticides was increased after the gloves were exposed to DEET and to ultraviolet rays (UVA) mimicking sunlight. This finding suggested a mechanism by which an increase in exposure to 2,4-D or other phenoxyherbicides might occur as dermal penetration of pesticides is increased by higher temperatures and by higher humidity.[69] Second, the finding by Moody and Nadeau[68] prompted us to evaluate the association between NHL and exposure to phenoxyherbicides incorporating exposure to DEET and use of rubber gloves into the statistical models.[70] We found that reported exposure to mecoprop, along with DEET and the use of rubber gloves, produced higher odds ratios (OR, 3.86; 95% confidence interval [CI], 1.57–9.49) compared with strata with other combinations: DEET and/or rubber gloves but no mecoprop (1.03; 95% CI, 0.72–1.47); mecoprop (yes), DEET, and/or rubber gloves (1.41; 95% CI, 0.71–2.80) (reference: no exposure to any of the three variables). We inferred exposure to sunlight by conducting the analysis using data from farm residents/workers. Parallel statistical analyses conducted with 2,4-D (or dicamba) did not produce higher odds ratios in the stratum with reported exposure to the herbicide, DEET, and rubber gloves. Third, we had data on HL, MM, and STS, which were collected simultaneously and using the same protocol as the NHL study. The current report investigates the putative association between phenoxyherbicide exposure and HL, MM, and STS, incorporating use of rubber gloves when mixing or applying pesticides and application of DEET into the statistical models.

Subjects and Methods

A summary of the methodology is presented as details have been previously published.[47,66] The cases were men, aged 19 years or older, resident in one of six Canadian provinces who had a first diagnosis of HL (International Classification of Diseases, 9th Revision [ICD-9] 201), MM (ICD-9 203), or STS (ICD-9 171 and selected morphology codes) between September 1, 1991, and December 31, 1994. Cases were ascertained from population-based provincial cancer registries, except in Quebec, where hospital ascertainment was used. The controls were men, aged 19 years or older, resident in the same province as the appropriate case, free of the cancers of interest, and selected at random within age constraints from the provincial health insurance records (four provinces), computerized telephone listings (one province), or voters' list (one province). The selection of controls was stratified by age ± 2 years to be comparable with the age distribution of the entire case group. Deceased subjects were ineligible as either cases or controls. All participating control subjects were used in the statistical analyses of each cancer site. A structured postal questionnaire was completed by each of the cases and controls. Based on the findings of a pilot study of 68 cases and 103 controls (unpublished data), structured pesticide exposure telephone interviews were conducted with individuals who indicated exposure to 10 hours or more per year of pesticide exposure on the postal questionnaire because this cutoff appeared to distinguish among incidental, bystander, and environmental exposures compared with more intensive exposure. A 15% random sample of cases (HL, $n = 33$; MM, $n = 46$; STS, $n = 42$; and controls, $n = 155$) who reported less than 10 hours per year of pesticide exposure were also interviewed by telephone.

With permission, we modified a pesticide exposure questionnaire developed by Hoar et al[59] to create the postal and telephone interview questionnaires used. Among other variables, the postal questionnaire captured demographic data, detailed lifetime occupation and occupational exposure history, indoor pesticide application, and pattern of use of insect repellents on skin or clothing. The trade names of repellent products used were requested and used to determine the names of the active ingredients. The telephone interview characterized exposure to individual pesticides by home/garden or occupational use, by days per year of use, and by average acres sprayed per year if applicable. During the telephone interview, details of occupational hygiene practices, including the uses of gloves and protective clothing during pesticide handling, were asked of only those subjects who indicated that they had occupational exposure. Members of subgroups who had lived or worked on farms were asked a general question concerning use of gloves or protective clothing while mixing/applying pesticides. Data were entered into a custom-designed SPSS data entry[71] program. Data from the postal survey

and telephone interview were merged by using the identification numbers. Statistical analysis followed the procedures recommended in Breslow and Day[72] using SAS software (1999–2001).[73]

We conducted descriptive analyses of each variable that included, when applicable, frequencies, ranges, means ± standard deviations (SD), and median values for cases and controls separately. Conditional logistic regression was used to compute odds ratios and 95% confidence intervals (with strata for age and province of residence). Adjusted odds ratios were calculated for "any" phenoxyherbicide exposure and for the commonly used phenoxyherbicides; 2,4-D, mecoprop, and MCPA; and for insect repellents containing DEET among the total study population and among subjects who had ever lived or worked on a farm. "Any" phenoxyherbicide exposure referred to exposure to combinations of chemicals classified as phenoxyherbicides, including the phenoxyacetic compounds (2,4-D, MCPA, 2,4,5-T); the phenoxy-2-propionics (dichlorprop, fenoprop, mecropop); the phenoxybutanoics (2,4-dichlorophenoxy butyric acid [2,4-DB]); and other phenoxyalkanoics (diclofop methyl, fenoxaprop). In addition, conditional logistic regression subanalyses of farm residents were conducted using the variables related to phenoxyherbicides exposure, insect repellents containing DEET, and use of rubber gloves included in the models. We did not include the use of rubber gloves in statistical models related to the total population because we could not infer exposure to sunlight while exposed to pesticides among nonfarmers. Similar analyses were repeated with dicamba-containing herbicides because our preliminary analysis showed that this herbicide met our criterion for inclusion in statistical models ($P < 0.20$) for MM and STS. The phrase "dicamba-containing herbicides" refers to products containing dicamba (3,6-dichloro-2-methoxybenzoic acid) as the primary active ingredient and to mixtures containing dicamba plus 2,4-D and mecoprop or glyphosate or mecoprop and MCPA amine or 2,4-D amine and mecoprop.

This study was approved by the appropriate ethics committees in each participating institution.

Results

Table 1 summarizes the frequency of exposure to the variables of interest (DEET, "any phenoxyherbicides," 2,4-D, mecoprop, MCPA, dicamba-containing herbicides, rubber gloves and other protective clothing and equipment) and the univariate odds ratios for each variable adjusted for age and province of residence. There were 1506 population-based controls, 316 cases of HL, 342 cases of MM, and 357 cases of STS. Exposure to mecoprop resulted in a statistically significant increase in risk for MM cases (OR_{adj}, 1.66; 95% CI = 1.02–2.71). Exposure to any of the other herbicides of interest produced statistically nonsignificant results for each case group. Exposure to DEET resulted in a statistically significant decrease in risk of HL (OR_{adj}, 0.74; 95% CI = 0.55–0.99). Unexpectedly, the use of protective devices

TABLE 1
Exposures of Interest Among Cases of HL, MM, STS, and Population Controls (n, %, age- and province-adjusted odds ratios and 95% confidence intervals)

	HL (Cases = 316)	MM (Cases = 342)	STS (Cases = 357)	Controls (1506)
Exposure to insect repellents containing DEET	190 (60.1%)	143 (41.8%)	199 (55.7%)	801 (53.2%)
	0.74 (055–0.99)	0.80 (0.62–1.04)	1.03 (0.80–1.34)	
Exposure to "any phenoxyherbicide" as defined in text	65 (20.6%)	87 (25.4%)	80 (22.4%)	321 (21.3)
	0.99 (0.70–1.38)	1.25 (0.93–1.68)	1.07 (0.80–1.44)	
Exposure to 2,4-D	57 (18.0%)	80 (23.4%)	69 (19.3%)	293 (19.5%)
	0.96 (0.67–1.37)	1.21 (0.89–1.65)	0.97 (0.71–1.32)	
Exposure to mecoprop	20 (6.3%)	27 (7.9%)	26 (7.3%)	81 (5.4%)
	1.26 (0.72–2.21)	**1.66 (1.02–2.71)**	1.40 (0.86–2.25)	
Exposure to MCPA	11 (3.5%)	8 (2.3%)	13 (3.6%)	46 (3.1%)
	1.24 (0.60–2.60)	0.71 (0.32–1.58)	1.05 (0.54–2.02)	
Exposure to "any dicamba-containing herbicides"	32 (10.1%)	38 (11.1%)	40 (11.2%)	131 (8.7%)
	1.30 (0.82–2.04)	1.32 (0.87–2.00)	1.30 (0.87–1.92)	
Reported use of protective measures while handling pesticides at work				
Rubber gloves	27 (8.5%)	21 (6.1%)	18 (5.0%)	118 (7.8%)
	1.0 (0.61–1.66)	0.71 (0.42–1.19)	**0.56 (0.33–0.95)**	
Rubber boots	12 (3.8%)	15 (4.4%)	12 (3.4%)	44 (2.9%)
	0.93 (0.45–1.90)	1.96 (1.00–3.85)	1.24 (0.63–2.44)	
Masks	10 (3.2%)	15 (4.4%)	14 (3.9%)	76 (5.0%)
	0.71 (0.36–1.42)	0.77 (0.42–1.42)	0.70 (0.38–1.28)	

HL indicates Hodgkin lymphoma; MM, multiple myeloma; STS, soft tissue sarcoma.

(rubber gloves, rubber boots, masks) while mixing/applying pesticides only produced odds ratios significantly lower than one for the total population of STS cases versus controls but not for farm dwellers/workers and not for the other two types of cancer.

The characterization of exposure to "any phenoxyherbicide," to individual phenoxyherbicides, and to dicamba in the presence/absence of exposure to DEET among cases of HL and MM are shown in Tables 2 and 3, respectively. The three dummy variables were: 1) no exposure to herbicide, yes to DEET; 2) yes to exposure to herbicide, no exposure to DEET; and 3) yes to both exposures. The reference category was no exposure to either the herbicide or DEET. Exposure to DEET without exposure to 2,4-D (Table 2) resulted in a lower risk of HL (0.71; 95% CI = 0.51–0.98), similar to that shown in Table 1 for DEET. Exposure to mecoprop (Table 3) without exposure to DEET resulted in a higher odds ratio (OR_{adj}, 2.30; 95% CI = 1.03–5.14) for MM than exposure to both DEET and mecoprop (OR_{adj}, 1.20; 95% CI, 0.64–2.22). There was a lower odds ratio for exposure to DEET without exposure to phenoxyherbicides for MM (0.72; 95% CI = 0.53–0.97). There were no statistically significant results for STS (data not shown). Table 4 shows the univariate analyses of the exposures of interest among those who had resided or worked on a farm. All of the results for each case group are consistent with no effect on risk of developing these specific types of tumors. Table 5 displays the results of similar analyses conducted on the subpopulaton of HL farm residents/workers with the use of rubber gloves while mixing or applying pesticides added to the models. Among this subpopulation, with the exception of the lowered estimates for DEET, each estimate of the odds ratios was statistically nonsignificant, indicating no measurable effect of exposure to any of the herbicides or herbicides/DEET/rubber gloves combinations of interest. The categories without exposure to the herbicides of interest but exposure to DEET with or without rubber gloves were all statistically significantly decreased. Among farm dwellers/workers, there were no statistically significant results for MM or STS cases (data not shown).

Discussion

Farmers may be exposed to herbicides through oral, dermal, inhalation, and ocular routes while handling, mixing, and spraying the chemicals as well as while cleaning equipment. Grover et al[74,75] measured exposure to 2,4-D amine among farmers who were conducting normal herbicide applications on their own farms. The researchers provided standard cotton clothing to each participant for each day of spraying, and also placed nine dermal patches under the clothing and four on the outside of the clothing to provide estimates of dermal and inhalation exposure. Twenty-four-hour urine samples were collected for each spray day and for 4 to

TABLE 2
Characterization of Exposure to 'Any Phenoxyherbicide,' to Individual Phenoxyherbicides of Interest, to Dicamba-Containing Herbicides and DEET Among 316 Cases of HL and 1506 Controls; Conditional Logistic Regression Models of Exposure to DEET and the Phenoxyherbicide of Interest

	HL		Control		
	N	Percent	n	Percent	OR_{adj} (95% CI)†
A. No DEET and no phenoxyherbicide exposure (reference)*	108	34.2	601	39.9	
DEET exposure; no phenoxyherbicide exposure	143	45.2	584	38.8	0.72 (0.52–1.01)
"Any phenoxyherbicide" exposure; no DEET exposure	18	5.7	104	6.9	0.95 (0.53–1.71)
Exposure to both DEET and "any phenoxyherbicide"	47	14.9	217	14.4	0.75 (0.48–1.17)
B. Individual phenoxyherbicides and DEET					
No DEET and no 2,4-D exposure (reference)	112	35.4	612	40.6	
Exposure to DEET; no 2,4-D	147	46.5	601	39.9	**0.71 (0.51–0.98)**
Exposure to 2,4-D; no DEET	14	4.4	93	6.2	0.84 (0.44–1.60)
Exposure to both DEET and 2,4-D	43	13.6	200	13.3	0.75 (0.47–1.18)
No DEET and no mecoprop exposure (reference)	120	38.0	685	45.5	
Exposure to DEET; no mecoprop	176	55.7	740	49.1	0.74 (0.55–1.01)
Exposure to mecoprop; no DEET	6	1.90	20	1.3	1.62 (0.57–4.57)
Exposure to both DEET and mecoprop	14	4.4	61	4.0	0.88 (0.44–1.76)
No DEET and no dicamba exposure (reference)	117	37.0	667	44.3	
DEET exposure, no dicamba exposure	167	52.8	708	47.0	0.73 (0.54–1.00)
Dicamba exposure, no DEET exposure	9	2.8	38	2.5	1.30 (0.56–2.98)
Exposure to both DEET and dicamba	23	7.3	93	6.2	0.96 (0.54–1.71)

*No reported exposure to the indicated substance constitutes the reference category in each model.
†All models include adjustment for the variables age and province of residence.
HL indicates Hodgkin lymphoma; OR, odds ratio; CI, confidence interval.

TABLE 3
Characterization of Exposure to 'Any Phenoxyherbicide,' to Individual Phenoxyherbicides of Interest, to Dicamba-Containing Herbicides and DEET Among 342 cases of MM and 1506 Controls; Conditional Logistic Regression Models of Exposure to DEET and the Phenoxyherbicide of Interest

	MM		Control		
	n	Percent	n	Percent	OR_{adj} (95% CI)†
A. No DEET and no phenoxyherbicide exposure (reference)*	165	48.2	601	39.9	
DEET exposure; no phenoxyherbicide exposure	90	26.3	584	38.8	**0.72 (0.53–0.97)**
"Any phenoxyherbicide" exposure; no DEET exposure	34	9.9	104	6.9	1.08 (0.69–1.70)
Exposure to both DEET and "any phenoxyherbicide"	53	15.5	217	14.4	1.08 (0.74–1.59)
B. Individual phenoxyherbicides and DEET					
No DEET and no 2,4-D exposure (reference)	170	49.7	612	40.6	
Exposure to DEET; no 2,4-D	92	26.9	601	39.9	**0.71 (0.52–0.96)**
Exposure to 2,4-D; no DEET	29	8.5	93	6.2	1.00 (0.62–1.61)
Exposure to both DEET and 2,4-D	51	14.9	200	13.3	1.08 (0.73–1.59)
No DEET and no mecoprop exposure (reference)	188	45.5	685	45.5	
Exposure to DEET; no mecoprop	127	37.1	740	49.1	0.80 (0.61–1.06)
Exposure to mecoprop; no DEET	11	3.2	20	1.3	**2.30 (1.03–5.14)**
Exposure to both DEET and mecoprop	16	4.7	61	4.0	1.20 (0.64–2.22)
No DEET and no dicamba exposure (reference)	185	54.1	667	44.3	
DEET exposure, no dicamba exposure	119	34.8	708	47.0	0.79 (0.60–1.04)
Dicamba exposure, no DEET exposure	14	4.1	38	2.5	1.45 (0.74–2.85)
Exposure to both DEET and dicamba	24	7.0	93	6.2	1.06 (0.63–1.79)

*No reported exposure to the indicated substance constitutes the reference category in each model.
†All models include adjustment for the variables age and province of residence.
MM indicates multiple myeloma; OR, odds ratio; CI, confidence interval.

TABLE 4
Exposures of Interest Among Farm Dwelling/Working Cases of HL, MM, STS, and Population Controls (n, %, age- and province-adjusted odds ratios, and 95% confidence intervals)

	HL 117 (37.0%)	MM 176 (51.5%)	STS 156 (43.7%)	Controls 673 (44.7%)
Exposure to insect repellents containing DEET	74 (63.2%)	87 (49.4%)	91 (58.3%)	381 (57.0%)
	0.86 (0.59–1.24)	0.83 (0.57–1.21)	1.14 (0.77–1.68)	
Exposure to "any phenoxyherbicide" as defined in text	40 (34.2%)	62 (35.2%)	46 (29.5%)	207 (30.8%)
	1.17 (0.71–1.94)	1.23 (0.84–1.80)	1.01 (0.67–1.51)	
Exposure to 2,4-D	35 (29.9%)	59 (33.5%)	41 (26.3%)	186 (27.6%)
	1.17 (0.70–1.96)	1.31 (0.89–1.93)	0.96 (0.63–1.47)	
Exposure to mecoprop	11 (9.4%)	16 (9.1%)	12 (7.7%)	51 (7.6%)
	1.27 (0.56–2.87)	1.21 (0.65–2.27)	0.98 (0.50–1.92)	
Exposure to MCPA	10 (8.6%)	7 (4.0%)	12 (7.7%)	44 (6.6%)
	1.15 (0.49–2.70)	0.53 (0.22–1.23)	1.08 (0.53–2.22)	
Exposure to "dicamba-containing herbicides"	21 (17.9%)	27 (15.3%)	23 (14.7%)	97 (14.4%)
	1.28 (0.68–2.39)	1.00 (0.61–1.65)	0.99 (0.58–1.67)	
Reported usage of protective measures while handling pesticides at work				
Rubber gloves	21 (18.0%)	17 (9.7%)	15 (9.2%)	96 (14.3%)
	1.12 (0.59–2.13)	0.56 (0.31–1.01)	0.57 (0.31–1.06)	
Rubber boots	9 (7.7%)	11 (6.2%)	10 (6.4%)	38 (5.6%)
	0.96 (0.41–2.28)	1.36 (0.63–2.93)	1.13 (0.52–2.44)	
	9 (7.7%)	12 (6.8%)	10 (6.4%)	66 (9.8%)
Masks	0.86 (0.39–1.88)	0.61 (0.31–1.21)	0.52 (0.25–1.07)	

HL indicates Hodgkin lymphoma; MM, multiple myeloma; STS, soft tissue sarcoma.

7 days after each spray day to measure 2,4-D amine and metabolites. The authors reported variation in excreted amounts in urine dependent on 1) the amount of parent compound sprayed, 2) the frequency of spray days, 3) the interval between spray days, 4) the same subject on different days, and 5) between subjects. Some of the variation was the result of the different types of equipment used and by the practices of the

TABLE 5

Characterization of Exposure to 'Any Phenoxyherbicide,' to Individual Phenoxyherbicides of Interest and to Dicamba-Containing Herbicides, to DEET, and Use of Rubber Gloves Among Farm Residents/Workers (HL 117, Controls 673); Model Using Stratified Analyses of Exposure to DEET, the Phenoxyherbicides of Interest, and Use of Rubber Gloves While Mixing or Applying Pesticides Among Farm Residents/Workers

				HL		Control		
Model Type II	**Any Phenoxyherbicides**	**DEET**	**Rubber Gloves**	**n**	**Percent**	**n**	**Percent**	**OR_{adj} (95% CI)†**
Reference*	No	No	No	34	29.1	214	31.8	
Group 1	No	Yes	No	43	36.8	252	37.4	**0.36 (0.19–0.68)**
	No	Yes	Yes					
Group 2	Yes	No	Yes	24	20.5	149	22.1	0.58 (0.28–1.17)
	Yes	Yes	No					
	Yes	No	No					
Group 3	Yes	Yes	Yes	16	13.7	58	8.6	0.62 (0.26–1.49)
	2,4-D	**DEET**	**Rubber gloves**	**n**	**%**	**n**	**%**	
Reference	No	No	No	36	30.8	220	32.7	
Group 1	No	Yes	No	46	39.3	267	39.7	**0.36 (0.19, 0.67)**
	No	Yes	Yes					
Group 2	Yes	No	Yes	20	17.1	136	20.2	0.57 (0.28, 1.17)
	Yes	Yes	No					
	Yes	No	No					
Group 3	Yes	Yes	Yes	15	12.8	50	7.4	0.65 (0.26, 1.58)
	Mecoprop	**DEET**	**Rubber gloves**					
Reference	No	No	No	39	33.3	248	36.9	
Group 1	No	Yes	No	67	57.3	374	55.6	**0.42 (0.24, 0.74)**
	No	Yes	Yes					
Group 2	Yes	No	Yes	7	6.0	36	5.4	0.72 (0.25, 2.12)
	Yes	Yes	No					
	Yes	No	No					
Group 3	Yes	Yes	Yes	4	3.4	15	2.2	0.58 (0.14, 2.33)
	Dicambra	**DEET**	**Rubber gloves**					
Reference*	No	No	No	38	32.5	243	36.1	
Group 1	No	Yes	No	58	49.6	333	49.5	**0.38 (0.21–0.70)**
	No	Yes	Yes					
Group 2	Yes	No	Yes	10	8.6	57	8.5	0.61 (0.24–1.52)
	Yes	Yes	No					
	Yes	No	No					
Group 3	Yes	Yes	Yes	11	9.4	40	5.9	0.67 (0.25–1.78)

*No reported exposures to the indicated substances constitutes the reference category in each model. The words no and yes indicate no exposure and exposure, respectively.

Reference: no exposure to DEET, nor to herbicide of interest or use of rubber gloves.

Group 1: exposure to DEET and/or rubber gloves, no exposure to herbicides of interest.

Group 2: exposure to herbicides and to DEET or use of rubber gloves or neither DEET nor rubber gloves.

Group 3: exposure to herbicides and to DEET and use of rubber gloves.

†All models include adjustment for the variables age and province of residence.

HL indicates Hodgkin lymphoma; OR, odds ratio; CI, confidence interval.

farmers. Smaller equipment may lead to the necessity to refill the tank with herbicide more frequently. There were instances in which the measured amount on the dermal patch samples on clothing were higher by several magnitudes than measurements obtained from hand washes with sodium bicarbonate and vice versa. The baseline measurements of 2,4-D acid equivalents in urine were not zero micrograms per liter in these actively farming subjects. Semchuk et al[76] found detectable levels of 2,4-D, MCPA and dicamba in plasma samples of rural Saskatchewan residents in midwinter, months after herbicide application season in that climate. Application of DEET to the forearm skin of six male volunteers showed that DEET tagged with carbon 14 was detectable within plasma after 2 hours and that skin is not a reservoir for DEET.[77] Clearly, the fate of phenoxyherbicides and/or their metabolites within the human body can be modified by many factors. Interestingly, a laboratory study[13] on hairless mouse skin showed that the

presence of the active ingredients in sunscreens and sunscreen/bug repellent combinations enhanced the penetration of 2,4-D as well as decreased the lag time between application and detection of the herbicide. Another study[78] using hairless mouse skin showed that coapplication of DEET and each of 14 different drugs, enhanced the absorption of the drugs to varying degrees. In a study of three pesticides tested individually, Tisch et al[79] found dose-dependent similar increases in genotoxicity of permethrin, DEET, and the organophosphate diazinon using primary human nasal mucosal cells as substrate. The finding of a potential protective effect of the insect repellent DEET was an incidental finding for which we did not have an a priori epidemiologic or biologic hypothesis at the initiation of the statistical analyses. In a recent review of the literature related to epidemiologic studies of DEET and cancer, we found one case–control study of testicular cancer[80] and occupational exposures that reported a statistically significant increase in risk in a dose–response fashion with exposure to DEET. We did not find any studies reporting a protective effect of DEET in relationship to cancer.

Our objective was to determine whether there was an addition to the risk of developing cancer resulting from combined exposure to DEET, rubber gloves, phenoxyherbicides, and inferred sunlight compared with exposure to these substances individually. We tested this idea using case–control data accumulated on three types of tumors for which there is evidence of etiologic associations with agriculture, agricultural practices, and exposures to chemicals, including herbicides, insecticides, and fungicides statistically adjusted for other known risk factors but for which there is very limited, no, or contradictory evidence of increased risk resulting from exposure to phenoxyherbicides.

Hodgkin Lymphoma

Mortality studies that used death certificates to determine occupation found farmers to be at elevated risk of developing HL.[24] Early case–control studies conducted in Sweden reported statistically elevated odds ratios for developing HL among men occupationally exposed to phenoxyherbicides, chlorophenols, and organic solvents,[16] whereas a large (N = 354,620) retrospective cohort study,[32] which identified 355 men who developed HL, found associations with mink farmers and forestry workers but not crop farmers, an occupation likely to be exposed to herbicides. A smaller cohort[81] of Swedish pesticide applicators (n = 20,245) did not find an elevated risk of HL. A case–control linkage (occupational census to either mortality or incidence data) study conducted in Italy and Denmark[53] found contradictory results in the two countries. Farmers in Denmark were at statistically significant lower risk of HL, whereas Italian farmers were at significantly higher risk of death from HL. The authors[53] explained the discrepancy as resulting from the use of professional pesticide applicators in Denmark, whereas Italian farmers applied these chemicals themselves. Another Italian study[31] questioned hospitalized cases and controls about their occupations and occupational exposures, and the authors reported that exposure to livestock and meat processing as well as exposure to herbicides and pesticides for more than 10 years, without further definition, to be independent risk factors for developing HL. A study in Kansas[45] found no association among men between HL and use of insecticides on crops or on animals. A mortality cohort study[82] conducted among workers at a phenoxyherbicide-manufacturing plant in Germany found significantly elevated risks for NHL but not HL. A larger international cohort[83] that included both men and women and in which exposure was estimated from company records did not find associations between occupational exposure to phenoxyherbicides and HL. In our univariate analyses, none of the classes of herbicides or individual herbicides increased risk of HL, whereas exposure to the insecticides diazinon, chlorpyrifos, and carbaryl, certain prediagnostic medical conditions, and a positive family history of leukemia, lymphoma, or multiple myeloma increased risk (data not shown). Furthermore, any potential enhancement of exposure to phenoxyherbicide caused by increased permeability of work gloves to these herbicides induced by DEET had no effect on the risk estimates supporting the idea of specificity of risk to specific tumor types in response to a given exposure.

Multiple Myeloma

Using death certificates to define occupation and ecologic surrogate measures of exposure at the county level, Cantor et al[21] found excess mortality from MM among farmers, especially in counties that had higher numbers of acres treated with insecticides. An earlier similar study by Burmeister et al[22] reported positive associations with both herbicides and insecticides for MM. Death from MM in a large cohort of farmers in Alberta,[51] Saskatchewan, and Manitoba whose agricultural census data were linked to population census data was not associated with exposure to herbicides.

Case–control studies have also produced contradictory results. Farming as an occupation was associated with MM in studies from Canada,[29] New Zealand,[20,33] England,[23] the United States,[25,27] and Italy[44] (cultivation of apples and pears only). Brown et al[84] and Brownson and Reif[19] found no association between MM and farming in Iowa and Missouri, respectively. The same result was found for both men and women in Denmark[54,55] and in Italy.[50] Some of these studies included questions related to herbicides and insecticides.

Pearce et al[33] and Erikson and Karlsson[30] reported associations with phenoxyherbicides but only at the 90% confidence level. An Iowa study[84] included questions related to a large number of individual insecticides and herbicides, including phenoxyherbicides and dicamba, and found no statistically significant associations. In contrast, based on data from four geographically dispersed regions of the United States, Demers et al[25] reported that workers in agriculture who reported "high" exposure to pesticides, not further defined, were at increased risk of MM. The same group reported significant associations between "high" exposure to pesticides and both IgA and IgG lymphoma.[27] In an Italian study,[44] herbicides were not associated with MM but chlorinated insecticides and DDT were. A nested case–control mortality study[28] found that herbicide or insecticide exposures were not independent predictors but increased the statistically significant odds ratio related to farming. Swedish agricultural workers[34] were found to be at a small but statistically significant increased risk compared with other gainfully employed men in a large cohort study with 19 years of follow up. Lee et al[35] adjusted for the use of 2,4-D and four other herbicides whose use was highly correlated with the use of alachlor, the principal herbicide of interest to them, and found that alachlor exposure was not related to MM. Two reports on the same cohort[40,46] in The Netherlands produced contradictory evidence, the first reporting a statistically significant higher standardized mortality rate resulting from MM for licensed herbicide applicators compared with the general population and the follow-up study reporting nonsignificant results after an additional 13 years. A meta-analysis[26] based on studies published between 1981 and 1996 concluded that a 23% to 38% increase in risk of MM could be attributed to the occupation of farming but did not provide information on which aspect of agricultural practices or exposures might be involved. Aerial pesticide applicators are known to be exposed to a variety of chemicals and, in a retrospective cohort study,[48] were found to be at lower risk of death from MM than flight instructors. In both univariate and stratified analysis, using the total population but not when using the farm resident/worker subgroup, we found that exposure to mecoprop increased risk of MM without adjustment for other potential risk factors, ie, previous health conditions, family history of selected cancers, exposure to DDT, lindane, or carbaryl. We did not find reports of associations between MM and mecoprop in the literature. Because the statistically significant association was found in the total population but not in the more heavily exposed farm population, chance may be an explanation. Combination of exposure to phenoxyherbicides, to DEET, rubber gloves, and inferred sunlight did not increase risk of MM.

Soft Tissue Sarcoma

Beginning more than 25 years ago, reports of case–control studies[34,42,43] conducted in Sweden concluded that exposure to phenoxyherbicides raised risk of STS by three- to sixfold compared with the general population risk among men. Similar studies conducted in New Zealand,[62–64] the United States,[45,58] Sweden,[85] Italy,[52] and a meta-analysis[56] of published case–control and cohort studies contradicted the earlier Swedish studies. Researchers have speculated that the formulations of phenoxyherbicides sold in Sweden may have had higher concentrations of carcinogenic contaminants compared to other countries. Several of the case–control studies were plagued by small sample sizes and by the usual difficulties encountered in defining exposure in the distant past using questionnaire-based study designs. Three studies that used record linkage techniques and that had large sample sizes also produced contradictory results. Balarajan and Acheson[18] found an odds ratio of 1.7 (95% CI, 1.00–2.88) for farmers, farm managers, and market gardeners as a group compared with other workers, whereas Wiklund et al[57,60] reported no association of agricultural occupations and STS. A Danish cohort study[38] of employed gardeners, both men and women, reported statistically significant increased risks of developing STS among men but not among women based on three cases among the men. Another cohort study[36] of workers involved in either the production or spraying of phenoxyherbicides also reported statistically significant increased risks among those with "high exposure to phenoxyherbicides" as defined by three industrial hygienists. A Danish cohort[37] of workers engaged in the manufacture of phenoxyherbicides found an indication that risk of STS was increased, specifically after a 10-year latency period was included in the model. All three of the cohort studies had small numbers of cases. Soft tissue sarcoma was not associated with exposure to phenoxyherbicides as a group, to 2,4-D, to mecoprop, to MCPA, or to dicamba in this study.

In summary, there is clear evidence of internal exposure to phenoxyherbicides, among individuals who apply them, that transdermal penetration of phenoxyherbicides will be enhanced by exposure to DEET, to heat, and to moisture, and that individuals differ in the rate at which phenoxyherbicides are metabolized and excreted. The finding of a potential protective effect of the insect repellent DEET was an incidental finding for which we did not have an a priori, epidemiologic, or biologic hypothesis at the initiation of the statistical analysis. Therefore, we considered it inappropriate to speculate. Among the four types of tumors studied simultaneously and using identical methodology, the risk of NHL was enhanced among farming men exposed to mecoprop and to DEET who reported using rubber gloves when mixing or applying herbicides. The same results were not

found for HL, MM, or STS tumors for which the epidemiologic evidence of associations with phenoxyherbicides is not as compelling as for NHL. The findings in this report in relationship to phenoxyherbicides and HL, MM, and STS do not have implications for associations with exposure to other chemical classes of herbicides, for insecticides, or for fungicides as risk factors for HL, MM, and STS.

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