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Exposure to Pesticides as Risk Factor for Non-Hodgkin's Lymphoma and Hairy Cell Leukemia: Pooled Analysis of Two Swedish Case-control Studies

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Increased risk for non-Hodgkin's lymphoma (NHL) following exposure to certain pesticides has previously been reported. To further elucidate the importance of phenoxyacetic acids and other pesticides in the etiology of NHL a pooled analysis was performed on two case-control studies, one on NHL and another on hairy cell leukemia (HCL), a rare subtype of NHL. The studies were population based with cases identified from cancer registry and controls from population registry. Data assessment was ascertained by questionnaires supplemented over the telephone by specially trained interviewers. The pooled analysis of NHL and HCL was based on 515 cases and 1141 controls. Increased risks in univariate analysis were found for subjects exposed to herbicides (OR 1.75, CI 95% 1.26–2.42), insecticides (OR 1.43, CI 95% 1.08–1.87), fungicides (OR 3.11, CI 95% 1.56–6.27) and impregnating agents (OR 1.48, CI 95% 1.11–1.96). Among herbicides, significant associations were found for glyphosate (OR 3.04, CI 95% 1.08–8.52) and 4-chloro-2-methyl phenoxyacetic acid (MCPA) (OR 2.62, CI 95% 1.40–4.88). For several categories of pesticides the highest risk was found for exposure during the latest decades before diagnosis. However, in multivariate analyses the only significantly increased risk was for a heterogeneous category of other herbicides than above.

Keywords: Non-Hodgkin's lymphoma; Hairy cell leukemia; Pesticides; Phenoxyacetic acids; Glyphosate; Impregnating agents

INTRODUCTION

Non-Hodgkin's lymphoma (NHL) is one of the malignant diseases with the most rapidly increasing incidence in the western world [1]. In Sweden, the mean age-adjusted incidence increased yearly by 3.6% in men and 2.9% in women during the time period 1958–1992 [2]. Hairy cell leukemia (HCL) was first described in 1958 and is regarded as a rare subgroup of NHL. HCL is more common in men with 23 male and 9 female patients reported to the Swedish Cancer Register in 1999 for the whole country [3].

The etiology of NHL is regarded to be multifactorial with different environmental exposures being part of it. Certain immunodefective conditions are established risk factors such as immunosuppressive medication after organ transplantation [4,5] and HIV-infection [6]. Also viral genesis, especially regarding Epstein–Barr virus (EBV) and endemic African Burkitt lymphoma has been indicated [7].

Regarding chemicals, exposure to phenoxyacetic acids, chlorophenols and organic solvents were associated with increased risk for NHL in Swedish studies [8–10]. In subsequent studies exposure to phenoxyacetic acids, particularly 2,4-dichlorophenoxyacetic acid (2,4-D), was associated with an increased risk for NHL [11,12]. These associations have been reviewed by us giving reference also to other studies [13].

We have now performed one case-control study on NHL, which did not include HCL [14], and another on HCL, specifically [15]. Both these studies focused interest especially on exposure to pesticides. In the NHL study, we found increased risks for subjects exposed to herbicides or fungicides. Among herbicides, phenoxyacetic acids

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TABLE I Number of exposed cases and controls, odds ratio (OR) and 95% confidence interval (CI) for exposure to pesticides and organic solvents

Agent	Number of exposed cases/controls	OR	CI
Herbicides	77/103	1.75	1.26–2.42
Phenoxyacetic acids	64/90	1.65	1.16–2.34
MCPA	21/23	2.62	1.40–4.88
2,4-D + 2,4,5-T	48/70	1.48	0.99–2.20
Glyphosate	8/8	3.04	1.08–8.52
Other	15/13	2.90	1.34–6.37
Insecticides	112/184	1.43	1.08–1.87
DDT	77/138	1.27	0.92–1.73
Mercurial seed dressing	20/33	1.40	0.77–2.47
Pyrethrins	13/27	1.16	0.57–2.25
Fungicides	18/17	3.11	1.56–6.27
Impregnating agents	104/162	1.48	1.11–1.96
Chlorophenols	66/106	1.37	0.98–1.92
Pentachlorophenol	64/101	1.40	0.99–1.98
Arsenic	8/10	1.75	0.66–4.54
Creosote	22/35	1.54	0.87–2.66
Other	40/67	1.35	0.88–2.04
Organic solvents	250/492	1.16	0.93–1.44

dominated. One subclass of these, 4-chloro-2-methyl phenoxyacetic acid (MCPA), turned out to be significantly associated with NHL. For several categories of herbicides, we observed that only exposure during the latest decades before diagnosis of NHL was associated with an increased risk for NHL. In the HCL study, we found increased risk for exposure to different categories of pesticides [15]. However, due to comparatively low number of study subjects, it was not meaningful to make further analyses of the tumor induction period.

Thus, the risk patterns for NHL and HCL in these studies, performed by the same methodology, showed similarities with respect to pesticides. Since the NHL study included patients with many different variants of NHL, it seemed motivated also to include HCL, as nowadays being regarded as a NHL subgroup, in a pooled analysis regarding risks in relation to pesticide exposure. The purpose was to enlarge the study size thereby allowing more precise risk estimates.

MATERIALS AND METHODS

Cases

The NHL study encompassed male cases aged ≥25 years with NHL diagnosed during 1987–1990 and living in the four most northern counties of Sweden and three counties in mid-Sweden [14]. They were recruited from the regional cancer registries and only cases with histopathologically verified NHL were included, in total 442 cases. Of these cases 192 were deceased.

From the national Swedish Cancer Registry, 121 male patients with HCL diagnosed during 1987–1992 were identified from the whole country [15]. One case later turned out to have been diagnosed in 1993, but was included in the study. Only living cases were included.

Controls

For living NHL cases two male controls matched for age and county were recruited from the National Population Registry.

For each deceased case two deceased controls matched also for year of death were identified from the National Registry for Causes of Death. For deceased subjects interviews were performed with the next-of-kin.

Similarly, four male controls matched for age and county were drawn to each case of HCL from the National Population Registry.

Assessment of Exposure

In both studies a similar questionnaire was mailed to the study subjects or next-of-kin for deceased individuals. A complete working history was asked for as well as exposure to different chemicals. If the information was unclear a trained interviewer supplemented the answers over the phone, thereby using written instructions. Years and total number of days for exposure to various agents were assessed. Also names of different agents were carefully asked for. If necessary, the Swedish Chemical Inspectorate was contacted to obtain information on the chemical composition of different brands of pesticides and other agents. A minimum exposure of one working day (8 h) and a tumor induction period of at least one year were used in the coding of chemicals. Thus, total exposure less than one day as well as exposure within one year prior to diagnosis (corresponding time for the matched control) were disregarded. The questionnaires were blinded as to case or control status during the interviews and coding of data.

Statistical Analysis

Conditional logistic regression analysis for matched studies was performed with the SAS statistical program (SAS Institute, Cary, NC). Thereby odds ratios (OR) and

TABLE II Exposure to different types of herbicides with dose-response calculations. High exposure is defined as > median number of days for exposed subjects. Range of exposure in days given within parenthesis

Agent	Total OR (CI)	Median number of days	OR (CI)	
			Low	High
Herbicides	1.75 (1.26–2.42)	33 (1–709)	1.74 (1.10–2.71)	1.79 (1.15–2.79)
Phenoxyacetic acids	1.65 (1.16–2.34)	33 (1–709)	1.65 (1.01–2.66)	1.67 (1.02–2.69)
MCPA	2.62 (1.40–4.88)	25 (1–491)	1.94 (0.79–4.55)	3.61 (1.49–9.05)
2,4-D + 2,4,5-T	1.48 (0.99–2.20)	30 (1–709)	1.87 (1.08–3.20)	1.20 (0.68–2.08)
Other	2.90 (1.34–6.37)	11 (1–220)	2.26 (0.76–6.77)	3.37 (1.08–11)

95% confidence intervals (CI) were obtained. Both univariate and multivariate analyses were done. In this pooled analysis adjustment was made for study, study area and vital status. When risk estimates for different pesticides were analyzed only subjects with no pesticide exposure were taken as unexposed, whereas subjects exposed to other pesticides were disregarded.

RESULTS

The questionnaire was answered by 404 cases (91%) and 741 controls (84%) in the NHL study. Regarding HCL 111 cases (91%) and 400 controls (83%) participated. In the following results are given for the pooled analysis containing 515 cases and 1141 controls.

An increased risk was found for exposure to herbicides, insecticides, fungicides and impregnating agents, Table I. Regarding specific agents OR was highest for glyphosate and MCPA.

For herbicides dose-response calculations were also performed by comparing high and low dose exposures divided by the median exposure time in days, Table II. Exposure to MCPA gave a dose-response effect. Also for the group constituting of other herbicides than phenoxyacetic acids the risk was highest in the group with high exposure.

For herbicides in total and phenoxyacetic acids as a group the highest risks were seen when first exposure occurred 10–20 years before diagnosis, Table III. This was also the case for insecticides and impregnating agents. Within the latter group, however, an induction period of 20–30 years gave the highest risk for both creosote and pentachlorophenol.

Time to diagnosis from last exposure to different agents was also used in the calculation of risk estimates, Table IV. For phenoxyacetic acids the OR was highest for exposure 1–10 years prior to diagnosis whereas no increased risk was seen for those with last exposure >20 years from the time of diagnosis.

TABLE III Exposure to phenoxyacetic acids, insecticides, impregnating agents and organic solvents. Calculations are made with exposure divided according to time span from first exposure to diagnosis (induction period)

Agent	Induction period, years			
	1–10 OR (CI)	>10–20 OR (CI)	>20–30 OR (CI)	>30 OR (CI)
Herbicides	1.00 (0.05–11)	2.32 (1.04–5.16)	1.63 (0.87–2.98)	1.70 (1.12–2.58)
Phenoxyacetic acids	–*	2.88 (1.11–7.72)	1.54 (0.85–2.76)	1.50 (0.94–2.37)
MCPA	–*	5.36 (1.57–21)	0.89 (0.20–3.03)	3.77 (1.49–9.99)
2,4-D + 2,4,5-T	–†	2.87 (0.81–11)	1.87 (0.98–3.53)	1.15 (0.67–1.93)
Insecticides	1.20 (0.25–4.70)	2.84 (0.95–8.54)	2.19 (1.14–4.17)	1.31 (0.96–1.77)
DDT	–†	2.64 (0.61–11)	1.63 (0.80–3.26)	1.17 (0.82–1.65)
Impregnating agents	1.20 (0.37–3.49)	2.27 (1.15–4.49)	1.89 (1.07–3.30)	1.23 (0.85–1.75)
Chlorophenols	–†	1.91 (0.82–4.44)	1.90 (0.98–3.65)	1.13 (0.73–1.71)
Pentachlorophenol	–†	1.91 (0.82–4.44)	2.13 (1.07–4.25)	1.13 (0.73–1.72)
Creosote	–*	0.88 (0.04–7.27)	5.33 (1.26–27)	1.34 (0.69–2.49)
Organic solvents	1.51 (0.65–3.37)	1.38 (0.84–2.24)	1.46 (1.00–2.12)	1.02 (0.79–1.30)

* No exposed cases, one exposed control.
† No exposed subjects.

TABLE IV Exposure to phenoxyacetic acids, impregnating agents and organic solvents. Calculations are made with exposure divided according to time span from last exposure to diagnosis

	Time span, last exposure-diagnosis, years			
Agent	1–10 OR (CI)	>10–20 OR (CI)	>20–30 OR (CI)	>30 OR (CI)
Herbicides	2.53 (1.38–4.64)	1.68 (0.88–3.14)	1.22 (0.66–2.19)	1.84 (0.95–3.51)
Phenoxyacetic acids	3.22 (1.59–6.65)	2.06 (1.03–4.09)	1.01 (0.54–1.81)	1.26 (0.57–2.62)
MCPA	3.52 (1.58–7.99)	2.33 (0.56–9.09)	0.92 (0.13–4.39)	–*
2,4-D + 2,4,5-T	4.31 (1.12–21)	1.85 (0.90–3.78)	1.04 (0.54–1.94)	1.41 (0.65–2.92)
Insecticides	2.37 (1.40–4.02)	0.87 (0.48–1.53)	1.45 (0.85–2.41)	1.46 (0.94–2.24)
DDT	1.45 (0.65–3.10)	1.13 (0.62–1.97)	1.46 (0.83–2.50)	1.20 (0.69–2.02)
Impregnating agents	1.92 (1.30–2.82)	0.79 (0.40–1.46)	1.67 (0.88–3.11)	1.19 (0.61–2.21)
Chlorophenols	–†	1.52 (1.02–2.25)	1.36 (0.61–2.86)	0.84 (0.32–1.96)
Pentachlorophenol	–†	1.59 (1.06–2.37)	1.28 (0.58–2.67)	0.81 (0.29–2.01)
Creosote	2.56 (0.85–7.67)	0.93 (0.13–4.17)	1.17 (0.36–3.43)	1.54 (0.60–3.75)
Organic solvents	1.17 (0.91–1.50)	1.00 (0.66–1.50)	1.39 (0.84–2.25)	0.99 (0.56–1.69)

* one exposed case, one exposed control.
† No exposed case or control.

Furthermore, exposure to phenoxyacetic acids during different decades from the 1940s was analyzed. Increased risk was found during recent decades, Table V.

No statistically significant increased risk was found for the whole group of organic solvents in this pooled analysis, but when the solvents were subgrouped according to specific substances there were increased risks for vanolen (OR = 1.91, CI = 1.03–3.49; $n = 20$ cases) and aviation fuel (OR = 3.56, CI = 1.03–12; $n = 6$ cases).

Multivariate analysis of exposure to phenoxyacetic acids, insecticides, fungicides and impregnating agents is presented in Table VI. An increased risk persisted for exposure to herbicides, fungicides and impregnating agents, however not statistically significant.

A separate multivariate analysis was performed on exposure to herbicides. Lower risk estimates were obtained although all herbicides still constituted risk factors for NHL, Table VII.

DISCUSSION

The cases in this study were identified by using the Swedish Cancer Registry, which is composed by six regional registries. In Sweden, the reporting of malignant diseases to the Cancer Registry is compulsory, which makes it likely that most incident cases in the study area were identified. Controls were selected from the National Population Registry and, in order to minimize recall bias, deceased controls were used for deceased cases in one of the studies [14] which were the basis for this analysis. In the other only living cases were included [15]. Recall bias is always a matter of concern in a case-control study with self-reported exposures. Farmer as occupation did not increase the risk in this pooled analysis (OR = 1.19, CI = 0.95–1.49) which indicates that the risk increase for pesticides was not explained merely by misclassification of exposure. All interviews and coding of data were performed blinded as to case or control status in order to minimize observational bias.

TABLE V Exposure to phenoxyacetic acids during different decades. Note that one subject may occur during several decades

Decade	Cases/controls	OR	CI
1940s	4/6	1.46	0.37–5.23
1950s	35/53	1.44	0.91–2.26
1960s	43/58	1.68	1.10–2.55
1970s	32/33	2.37	1.42–3.95
1980s	16/33	3.25	1.53–7.07

TABLE VI Multivariate analysis of exposure to pesticides

	Univariate		Multivariate	
Agent	OR	CI	OR	CI
Herbicides	1.75	1.26–2.42	1.39	0.96–2.02
Insecticides	1.43	1.08–1.87	1.07	0.78–1.45
Fungicides	3.11	1.56–6.27	2.02	0.97–4.23
Impregnating agents	1.48	1.11–1.96	1.30	0.98–1.72

TABLE VII Multivariate analysis of exposure to herbicides. Odds ratios (OR) and 95% confidence intervals (CI) are given

	Univariate		Multivariate	
Agent	OR	CI	OR	CI
MCPA	2.62	1.40–4.88	1.67	0.77–3.57
2,4-D + 2,4,5-T	1.48	0.99–2.20	1.32	0.88–1.96
Glyphosate	3.04	1.08–8.52	1.85	0.55–6.20
Other herbicides	2.90	1.34–6.37	2.28	1.02–5.15

This study was a pooled analysis of two case-control studies, one on NHL [14] and the other on HCL [15] to provide larger numbers, which would allow more detailed analyses regarding the timing of exposure and adjustment of multiple exposures. This method was justified since HCL is a type of NHL and similar methods and questionnaires were used in both studies. Also the findings regarding pesticide exposure were relatively homogenous for both studies. The smaller HCL study had a somewhat higher prevalence of exposure and therefore has in this pooled analysis more weight than one would expect.

Conditional logistic regression analysis was performed since both studies in this pooled analysis were matched. Heterogeneity in findings was averaged after stratification by study. Since the NHL study included also deceased cases and controls adjustment was made for vital status. Finally, in the HCL study the whole Sweden was included as study base whereas in the NHL study only parts of Sweden were included. Thus, adjustment was made for geographical area for cases and controls, i.e. county.

In the multivariate analysis exposure to herbicides, fungicides and impregnating agents increased the risk although OR was lower than in the univariate analysis. Significantly increased risk remained only for the heterogeneous group of "other herbicides". The results in multivariate analysis must be interpreted with caution since exposure to different types of pesticides correlate. Multivariate analysis is mainly useful to estimate the risk factors that seem to be most important.

Several previous studies have associated exposure to phenoxyacetic acids, primarily 2,4-D and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), with an increased risk for NHL [8–12,16–18]. Concerning MCPA data are sparse although in our first study on NHL, we found an increased risk [9,10].

In this pooled analysis, most subjects were regarding herbicides exposed to phenoxyacetic acids, mostly the combination of 2,4-D and 2,4,5-T. 2,4-D was withdrawn from the Swedish market in 1990 and 2,4,5-T was prohibited in 1977. Also MCPA, the phenoxy herbicide still commonly used in Sweden, increased the risk for NHL. Glyphosate is the herbicide now mostly used in Sweden. In this study, exposure to glyphosate was a risk factor for NHL. Thus, regarding herbicides lymphomagenesis seems not to be depending on contaminating dioxins, i.e. 2,3,7,8-TCDD in 2,4,5-T. A contributing effect of such exposure cannot be excluded, although not supported by mortality results in a cohort of workers exposed to 2,3,7,8-TCDD [19]. IARC classified recently 2,3,7,8-TCDD as a human carcinogen, Group I [20].

In the univariate analysis exposure to insecticides, mostly DDT, increased the risk for NHL. In the multivariate analysis no risk was found. This is in accordance with our previous results [9,10] and a pooled analysis of three case-control studies concluded that DDT is not a risk factor for NHL [21]. Furthermore, analysis of serum DDT/DDE has not given a clear association with NHL [22,24,25].

Regarding fungicides an increased risk for NHL has previously been reported from USA [11]. Our result with increased risk for NHL needs to be further studied since the finding was based on few subjects exposed to several types of fungicides.

Chlorophenols, which are chemically related to phenoxyacetic acids and have been used as e.g. wood preservatives, were banned in Sweden in 1978. An increased risk for NHL was found in this pooled analysis, but also for exposure to arsenic and creosote. Both chlorophenols and creosote have been associated with NHL [26,27].

An association between exposure to organic solvents and NHL has been described [9,10,28–30]. However, such an association was not confirmed now although an influence of tumor induction period can not be ruled out, *c.f.*, below. Another possibility might be that solvents used during later years are less toxic than previously, e.g. water based, and that they are more cautiously handled [31].

To further elucidate mechanisms in lymphomagenesis analysis of tumor-induction period (latency) and also time from last exposure to diagnosis was performed. Thereby the corresponding year for diagnosis was used for the matched control. For 2,4-D, 2,4,5-T and chlorophenols no subject had first exposure during 1–10 years prior to diagnosis due to restrictions in the use of these chemicals in Sweden during that time period. For fungicides such calculations were not meaningful due to low number of exposed subjects.

The highest risk for exposure to herbicides, insecticides and impregnating substances was found for last exposure 1–10 years prior to diagnosis. Correspondingly, in general the lowest risks were found for the longest tumor induction periods.

Do these results cast further light on the etiology of NHL? Certainly, exposure to some chemicals is of significance in lymphomagenesis. Furthermore, bearing in mind that several of these chemicals are immunotoxic, e.g. certain pesticides and chlorophenols [27,32,33] and immunosuppression is an established risk factor for NHL [34] such toxicity might be of importance for chemical agents.

Viruses have been associated with lymphomas in animals [35,36] and more specifically EBV for humans [7,37]. Virus proliferation in lymphocytes is held back by the immune system and immunosuppression may be followed by development of both B-cell and T-cell

lymphoma in animals [38–39]. For renal transplant patients treated with immunosuppressive drugs the risk for NHL is highest during the first years after transplantation and then declines [40].

Timing of exposure in relation to risk of NHL, particularly in regard to higher risk for recent exposures, seemed to be an interesting result regarding lymphomagenesis. Several interpretations are possible such as chance finding, late stage in lymphomagenesis, type of exposure or interaction with other factors. Certainly immunmodulation by pesticides [32,33] is one hypothesis which should be more elaborated on, possibly with interaction with latent virus infection such as EBV. This might explain the short tumor induction period. In fact, results from the included HCL-study showed interaction between EBV-infection and exposure to such chemicals [41,42]. Additionally, polychlorinated biphenyls [22,24,25] and chlordanes [23,24], chemicals that are immunotoxic [43,44], have been associated with an increased risk for NHL.

The etiology of NHL is multifactorial and further studies should consider immunotoxic effects by the studied chemicals as well as tumor induction period and interaction with virus infection, e.g. EBV.

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