A Case–Control Study of Non-Hodgkin Lymphoma and Exposure to Pesticides

Lennart Hardell, M.D., PhD.[1]
Mikael Eriksson, M.D., Ph.D.[2]

[1] Department of Oncology, Örebro Medical Center, Örebro, Sweden.

[2] Department of Oncology, University Hospital, Lund, Sweden.

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Address for reprints: Dr. Lennart Hardell, Department of Oncology, Örebro Medical Center, S-701 85 Örebro, Sweden.

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BACKGROUND. The incidence of non-Hodgkin lymphoma (NHL) has increased in most Western countries during the last few decades. Immunodefective conditions are established risk factors. In 1981, the authors reported an increased risk for NHL following exposure to certain pesticides. The current study was designed to further elucidate the importance of phenoxyacetic acids and other pesticides in the etiology of NHL.

METHODS. A population-based case–control study in northern and middle Sweden encompassing 442 cases and twice as many controls was performed. Exposure data were ascertained by comprehensive questionnaires, and the questionnaires were supplemented by telephone interviews. In total, 404 cases and 741 controls answered the questionnaire. Univariate and multivariate analyses were performed with the SAS statistical data program.

RESULTS. Increased risk for NHL was found for subjects exposed to herbicides (odds ratio [OR], 1.6; 95% confidence interval [CI], 1.0–2.5) and fungicides (OR, 3.7; 95% CI, 1.1–13.0). Among herbicides, the phenoxyacetic acids dominated (OR, 1.5; 95% CI, 0.9–2.4); and, when subclassified, one of these, 4-chloro-2-methyl phenoxyacetic acid (MCPA), turned out to be significantly associated with NHL (OR, 2.7; 95% CI, 1.0–6.9). For several categories of herbicides, it was noted that only exposure during the most recent decades before diagnosis of NHL was associated with an increased risk of NHL. Exposure to impregnating agents and insecticides was, at most, only weakly related to NHL.

CONCLUSIONS. Exposure to herbicides in total, including phenoxyacetic acids, during the decades before NHL diagnosis resulted in increased risk for NHL. Thus, the risk following exposure was related to the latency period. Fungicides also increased the risk for NHL when combined, but this group consisted of several different agents, and few subjects were exposed to each type of fungicide. ***Cancer* 1999;85:1353–60.** © *1999 American Cancer Society.*

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The mean age-adjusted incidence of non-Hodgkin lymphoma (NHL) increased in Sweden yearly by 3.6% in men and by 2.9% in women during the time period from 1958 to 1992.[1] Similarly, NHL also is one of the malignant diseases with the most rapidly increasing incidence in many other countries.[2] Many different environmental exposures have been proposed as etiologic factors.

Certain immunodefective conditions are established risk factors. Thus, immunosuppressive medication after organ transplantation,[3,4] human immunodeficient virus (HIV) infection,[5] and some autoimmune disorders, e.g., Sjögren's syndrome,[6,7] all have been associated with an increased incidence of NHL.

Some indications point to a viral genesis, especially regarding

Epstein–Barr virus (EBV) and endemic African Burkitt lymphoma.[8] A correlation between malignant lymphoma and elevated EBV antibody titers has been reported in a prospective cohort of healthy adults in Finland.[9] In parts of the world, the retrovirus human T-cell lymphotropic virus I (HTLV-I) is endemic and has been associated with adult T-cell leukemia/lymphoma.[10] However, no known risk factors explain the rapid rise of incidence in many countries, although different theories are debated with more or less support from various investigations.

Some investigators have noticed a covariation between NHL and skin malignancies.[11,12] Ultraviolet (UV) radiation, which has been demonstrated to have immunosuppressive effects in experimental animals,[13,14] has been proposed to be the common etiologic factor for both types of malignancies.[15] However, recent studies do not support these allegations.[16–19] Other theories involve chemical substances, both occupational and environmental, in a broader sense, that have been reviewed by us.[20]

Exposure to phenoxyacetic acids and the impregnating agents chlorophenols was first reported in 1979 as a possible risk factor for NHL.[21] This clinical observation was followed by a case–control study on malignant lymphoma, including both NHL and Hodgkin's disease (HD).[22] Increased risks for exposure to phenoxyacetic acids, chlorophenols, and organic solvents were found. Exposure to phenoxyacetic acids, particularly 2,4-dichlorophenoxyacetic acid (2,4-D), was associated with an increased risk for NHL in subsequent studies in the United States.[23,24]

Increased incidence and mortality of NHL were reported in the Seveso area after an accident in 1976 with trichlorophenol and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) contamination.[25] Cohorts of workers exposed to phenoxy herbicides, chlorophenols, and dioxins have shown an excess of NHL.[26,27] Increased risk of NHL has been found also in cohort studies of workers exposed to wood preservatives of the chlorophenol type.[28,29]

The levels of some dioxin and dibenzofuran congeners were significantly higher in the adipose tissue of 7 patients with B-cell malignancies (6 cases with NHL and 1 case with myeloma) compared with 12 surgical controls without malignant disease in a Swedish study.[30] Also, the TCDD toxic equivalent factor (TEF) was significantly higher in the cases. Several studies have reported an association between NHL and exposure to organic solvents including benzene.[22,31–33]

The aim of the present study was to further elucidate exposure to especially pesticides and organic solvents as risk factors for NHL. Moreover, there is a lack of knowledge about the risk, if any, of pesticides presently in use.

MATERIALS AND METHODS

Cases

The study encompassed male cases age $\geq$ 25 years with NHL diagnosed during 1987–1990. They were living in the four most northern counties of Sweden (Norrbotten, Västerbotten, Västernorrland, and Jämtland) and in three counties in mid-Sweden (Örebro, Värmland, and Sörmland). All cases who were reported to the regional cancer registries with a histopathologic diagnosis of NHL were included. No case had been included in our previous study on NHL.[22] The pathologic reports were scrutinized for all cases to confirm the diagnosis. Of the initial sample, 29 cases were thereby excluded, 14 due to wrong or uncertain diagnosis and 15 due to wrong year of diagnosis. Finally, 442 cases were included, 210 from the northern part of Sweden and 232 from the middle part of Sweden. Of these cases, 192 were deceased.

Controls

For each living case, two male controls matched for age and county were recruited from the National Population Registry. Thereby, the controls closest in age to the case were selected. For each deceased case, two deceased male controls were identified from the National Registry for Causes of Death. They were matched for age and year of death. For ethical reasons, subjects who had committed suicide were excluded. For deceased subjects, interviews were performed with the next of kin in the order of spouse, child, or other relative, who was identified through local parishes.

Assessment of Exposure

An 18-page questionnaire was mailed to the study subjects or to the next of kin for deceased individuals with an enclosed letter informing them that participation was voluntary. A complete working history was requested as well as information about exposure to different chemicals. For example, regarding the use of pesticides, subjects were asked for use within different occupations, such as forestry, farming, gardening, etc.; wet contact if not handling the sprayer; brand names of the different pesticides; and so on. In-depth knowledge of concentrations of active ingredients usually was lacking. Information also was assessed on years of exposure and cumulative exposure in days. Also, smoking habits, previous diseases, and certain food habits were assessed, the results of which will be presented in another paper. The rather comprehensive

questionnaire was used for two reasons. We wanted to cover most of the theories that have been presented regarding the etiology of NHL, but we wished to avoid a focus on exposure to pesticides and organic solvents, i.e., an a priori hypotheses. The questionnaire was somewhat modified and extended compared with earlier questionnaires that we have used and have been evaluated in our studies with findings verified by other research groups.

According to written instructions, a trained interviewer supplemented the answers over the telephone if the information was unclear regarding specified exposures. Most subjects, both cases and controls, were interviewed in this way. The questionnaires were blinded with regard to case or control status, i.e., it was not disclosed during the interviews or coding of the answers whether the subject was a case or a control. Exposure within 1 year prior to diagnosis (corresponding year for the matched control) was disregarded. All interviews were performed during 1993–1995.

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 95% confidence intervals (95% CI) were obtained. All 95% CIs were rounded outward, e.g., a 95% CI of 1.07–4.52 is written 1.0–4.6. Both univariate and multivariate analyses were performed. When exposure to different pesticides was analyzed, subjects with no pesticide exposure were taken as unexposed (cf. Table 1).

RESULTS

The questionnaire was answered by 404 cases (91%) and 741 controls (84%). Of the living cases, 91% participated compared with 83% of the living controls. The corresponding frequencies for next of kin were 92% of cases and 85% of controls. The mean age of both cases and controls was 65 years (range, 27–84 years for cases and 28–84 years for controls).

The case material was divided into different groups according to histopathology, i.e., B-cell lymphoma of aggressive (n = 157) or indolent (n = 185) types, respectively; T-cell lymphoma (n = 18); and other (n = 6) or unspecified types (n = 38). Exposure to herbicides resulted in an increased risk for NHL that, for specific agents, was highest for exposure to 4-chloro-2-methyl phenoxyacetic acid (MCPA; Table 1).

Exposure to each herbicide (MCPA, 2,4-D/2,4,5-trichlorophenoxyacetic acid [2,4,5-T], glyphosate, and others) was analyzed separately (Table 2). Dose response calculations also were performed by comparing high and low dose exposures divided by the median exposure time given in days (Table 2).

TABLE 1
Number of Exposed Cases and Controls, Odds Ratios, and 95% Confidence Intervals for Exposure to Pesticides

Agent	Number of exposed cases/controls	OR	CI
Herbicides	61/81	1.6	1.0–2.5
Phenoxyacetic acids	51/71	1.5	0.9–2.4
MCPA	12/11	2.7	1.0–7.0
2,4-D+2,4,5-T	43/62	1.3	0.7–2.3
Glyphosate	4/3	2.3	0.4–13
Other	12/7	3.4	1.1–9.9
Insecticides	90/139	1.2	0.8–1.7
DDT	66/107	1.1	0.7–1.7
mercurial seed dressing	17/25	1.6	0.7–3.4
pyrethrins	10/21	1.3	0.5–3.4
Fungicides	10/8	3.7	1.1–13
Impregnating agents	86/131	1.2	0.8–1.7
Chlorophenols	57/92	1.1	0.7–1.8
Pentachlorophenol	55/87	1.2	0.7–1.8
Arsenic	7/8	1.2	0.3–4.5
Creosote	15/26	1.2	0.5–2.8
Other	38/41	1.7	0.9–3.2

OR: odds ratio; CI: confidence interval; MCPA: 4-chloro-2-methyl phenoxyacetic acid.

TABLE 2
Exposure to Different Types of Herbicides with Dose Response Calculations[a]

Agent	Total OR (CI)	Median no. (days)	Low OR (CI)	High OR (CI)
Herbicides	1.6 (1.0–2.5)	32	1.5 (0.8–2.7)	1.8 (0.9–3.2)
Phenoxyacetic acids	1.5 (0.9–2.4)	30	1.6 (0.8–3.0)	1.3 (0.6–2.5)
MCPA	2.7 (1.0–7.0)	26	1.7 (0.4–6.5)	4.1 (1.0–17)
2,4-D+2,4,5-T	1.3 (0.7–2.3)	30	1.7 (0.8–3.3)	1.0 (0.4–2.2)
Other	3.0 (1.1–7.9)	8	2.0 (0.5–7.4)	6.8 (1.4–33)

OR: odds ratio; CI: confidence interval; MCPA: 4-chloro-2-methyl phenoxyacetic acid.
[a] High exposure is defined as > median number of days for exposed subjects.

ORs with regard to different latency (induction) periods, i.e., time from first exposure to diagnosis, were calculated (Table 3). For herbicides in total and for phenoxyacetic acids, the highest risks were seen when first exposure occurred 10–20 years before diagnosis, although a somewhat different pattern was seen for exposure to MCPA.

Time to diagnosis from last exposure to phenoxyacetic acids also was used in the calculation of the risk for NHL (Table 4). The OR was highest for exposure 1–10 years prior to diagnosis, whereas no increased risk was seen for those with the most recent exposure >20 years from the time of diagnosis.

Furthermore, an analysis of the importance of

TABLE 3
Exposure to Phenoxyacetic Acids, Impregnating Agents, and Organic Solvents[a]

	Latency period (yrs)			
Agent	**1–10 OR (CI)**	**>10–20 OR (CI)**	**>20–30 OR (CI)**	**>30 OR (CI)**
Phenoxyacetic acids	—[b]	3.7 (0.9–15)	1.6 (0.7–3.6)	1.2 (0.6–2.1)
MCPA	—[b]	3.6 (0.3–36)	0.5 (0.1–4.6)	4.8 (1.3–19)
2,4-D+2,4,5-T	—[c]	2.7 (0.7–12)	2.1 (0.9–5.1)	0.9 (0.4–1.7)
Impregnating agents	0.6 (0.1–3.7)	2.2 (0.9–5.2)	1.1 (0.5–2.3)	1.1 (0.7–1.7)
Chlorophenols	—[c]	0.9 (0.3–2.9)	1.8 (0.7–4.3)	1.1 (0.6–1.8)
Pentachlorophenol	—[c]	1.0 (0.3–2.9)	2.0 (0.7–5.3)	1.1 (0.7–1.8)
Creosote	—[b]	2.0 (0.1–32)	2.0 (0.1–32)	1.3 (0.5–3.0)

OR: odds ratio; CI: confidence interval; MCPA: 4-chloro-2-methyl phenoxyacetic acid.
[a] Calculations are made with exposure divided according to time from first exposure to diagnosis (latency period).
[b] No exposed cases, one exposed control.
[c] No exposed subjects.

TABLE 4
Exposure to Phenoxyacetic Acids, Impregnating Agents, and Organic Solvents[a]

	Time from last exposure to diagnosis			
Agent	**1–10 yrs OR (CI)**	**>10–20 yrs OR (CI)**	**>20–30 yrs OR (CI)**	**>30 yrs OR (CI)**
Phenoxyacetic acids	3.7 (1.2–11)	2.1 (0.9–4.8)	1.0 (0.4–2.1)	0.7 (0.2–2.1)
MCPA	3.0 (0.7–13)	5.2 (0.5–51)	1.2 (0.1–7.1)	—[b]
2,4-D+2,4,5-T	3.3 (0.6–18)	1.9 (0.8–4.4)	1.0 (0.4–2.3)	0.9 (0.3–2.5)
Impregnating agents	1.6 (0.9–2.6)	0.8 (0.3–1.9)	1.2 (0.5–2.4)	0.9 (0.4–1.9)
Chlorophenols	—[b]	1.3 (0.8–2.3)	1.1 (0.4–2.8)	0.6 (0.2–1.7)
Pentachlorophenol	—[b]	1.4 (0.8–2.4)	1.1 (0.4–2.6)	0.6 (0.1–1.9)
Creosote	2.3 (0.4–15)	—[c]	0.9 (0.2–3.2)	1.5 (0.4–5.4)

OR: odds ratio; CI: confidence interval; MCPA: 4-chloro-2-methyl phenoxyacetic acid.
[a] Calculations were made with exposure divided according to time from last exposure to diagnosis.
[b] One exposed case, no exposed controls.
[c] No exposed cases, four exposed controls.

TABLE 5
Exposure to Phenoxyacetic Acids During Different Decades[a]

Decade	Cases/controls	OR	CI
1940s	2/6	0.9	0.1–4.9
1950s	29/45	1.0	0.5–1.8
1960s	35/47	1.6	0.9–2.8
1970s	25/21	2.8	1.3–5.6
1980s	10/7	4.0	1.2–13

OR: odds ratio; CI: confidence interval.
[a] Note that one subject may be included in several decades.

exposure to phenoxyacetic acids during different decades showed increased risk for subjects during recent decades (Table 5). Similar calculations were performed for exposure to chlorophenols and organic solvents without any obvious pattern (data not shown).

Both exposure to glyphosate and other herbicides (Table 1) yielded increased risks for NHL. Among the different agents mentioned it is noted that 3 cases but no control were exposed to chlorosulphuron, and 4 cases and 3 controls were exposed to glyphosate.

Exposure to insecticides did not increase the risk for NHL (Table 1). Conversely, exposure in agriculture to fungicides resulted in an increased risk with a dose response effect. Thus, exposure $\leq$10 days (median number of exposure days) resulted in an OR of 1.4 (95% CI, 0.3–7.2) versus exposure >10 days, which resulted in an OR of 8.0 (95% CI, 0.9–72.0). In total, nine different fungicides were specified, however, there were few exposed subjects for each fungicide. It might be mentioned that four cases versus no controls reported exposure to dinocap. Neither chlorophenols nor other impregnating agents yielded an increased risk for NHL (Table 1).

TABLE 6
Number of Exposed Cases Controls with Odds Ratios and 95% Confidence Intervals for Other Exposures with at Least Ten Exposed Subjects

Agent	Number of exposed cases/controls	OR	CI
Ammonia	4/7	1.1	0.3–3.7
Asbestos	105/185	1.0	0.7–1.4
Chlorine	7/13	1.0	0.3–2.5
Cleaner	10/13	1.2	0.4–3.0
Cutting oils	30/44	1.2	0.7–2.1
Diesel	17/15	2.1	0.9–4.5
Glass wool	63/76	1.5	1.0–2.3
Insect repellents	188/346	1.0	0.7–1.3
Lead compounds	5/14	0.8	0.3–2.7
Lye	6/11	1.0	0.3–2.7
Mineral wool	53/87	1.1	0.7–1.6
Oil	33/60	1.0	0.6–1.7
Organic solvents	199/349	1.1	0.8–1.4
Plastics	14/25	1.1	0.5–2.2
Sulfur compounds	14/17	1.6	0.7–3.4
Wood glue	41/71	1.1	0.7–1.7

OR: odds ratio; CI: confidence interval.

Exposure to organic solvents did not increase the risk for NHL (Table 6). An increased risk was seen only when exposure with a latency period $>$ 20–30 years was considered (OR, 1.6; 95% CI, 0.9–2.6), but not with other latency criteria. When organic solvents were subclassified, no significantly increased ORs were found, but it may be noteworthy that exposure to air fuel (e.g., the MC77 type) was mentioned by four cases but by only one control.

Exposure to a number of other agents also was assessed (Table 6). Diesel increased the risk for NHL, and this risk was restricted to exposure $>$ 30 days (median number of exposure days; OR, 3.5; 95% CI, 1.2–10.4). Glass wool increased the risk, but produced no dose response effect.

Multivariate analysis of exposure to phenoxyacetic acids, other herbicides, and fungicides is presented in Table 7. The highest risk was found for exposure to herbicides other than phenoxyacetic acids. Increased risk also was found for exposure to fungicides, whereas the risk for MCPA was lower than in the univariate analysis. Exposure to glyphosate and phenoxy herbicides was considered in a separate multivariate analysis. For glyphosate, an OR of 5.8 (95% CI, 0.6–54) was found. For phenoyxacetic acids, an OR of 1.4 (95% CI, 0.8–2.2) was found.

TABLE 7
Multivariate Analysis of Different Exposures

	Univariate		Multivariate	
Agent	OR	CI	OR	CI
MCPA	2.7	1.0–7.0	1.3	0.4–3.9
2,4-D+2,4,5-T	1.3	0.7–2.3	1.2	0.6–2.0
Other herbicides	3.0	1.1–7.9	2.1	1.0–8.0
Fungicides	3.7	1.1–13	2.6	0.7–9.1

OR: odds ratio; CI: confidence interval; MCPA: 4-chloro-2-methyl phenoxyacetic acid.

DISCUSSION

This study was population based, using the Swedish Cancer Registry to identify the cases. The Swedish compulsory reporting system for malignant diseases makes it likely that almost all incident cases in the study area during the 4 years of inclusion were used. To avoid any selection of cases associated with prognosis, both living and deceased cases with NHL were included in this case–control study. To assess exposure in an equal manner for both cases and controls and to minimize recall bias, deceased controls were used for deceased cases. All interviews and coding of data were performed blinded with regard to case or control status to minimize observational bias. For the same reason, the interviews followed detailed, written instructions, asking for specific information on various occupations, including type of work, name of chemical used, number of working days, exposure conditions, etc. All answers were scrutinized by us according to the written criteria and, if necessary, supplemented further over the telephone. Thereby, exposure information was assessed in a similar manner for both cases and controls.

Regarding farmers and lumberjacks, the questionnaire data had to be supplemented over the telephone for all subjects due to the detailed, written instructions for the interviews. Thereby, exposure data were qualified regarding type of chemical used, years and number of days for exposure, methods of use, etc. Regarding the questions on exposure to pesticides, one case had answered “do not know,” and another did not answer these questions at all. Both turned out to be exposed during the supplementary telephone interviews. Three controls had answered the questions on pesticide use with “no.” All of them were classified as exposed after the telephone interviews. For the rest of the cases and controls who had stated pesticide exposure in the questionnaires, the telephone interviews verified such exposure. Thus, it is unlikely that observational bias was introduced during the telephone interviews. Excluding these additional two cases and three controls with pesticide exposure did not significantly change the results.

In this study, exposure to both herbicides and

fungicides resulted in significantly increased risks for NHL. Among herbicides, the phenoxyacetic acids constituted the main exposure category. These have been shown to increase the risk for NHL in several earlier studies.[16,22–24,26,27] In this study, however, the risk of increase was restricted to exposure during the last two decades preceding the diagnosis. In fact, a decreasing risk was found with increasing time since last exposure.

The combination of 2,4-D and 2,4,5-T, which constituted Agent Orange in U.S. warfare in Vietnam, was the most predominantly used herbicides in Swedish forestry. Since 2,4,5-T was banned in Sweden in 1977 because of its toxic properties, including the contamination with TCDD, no subjects in this study had their first exposure to this substance during the 10-year period preceding NHL diagnosis. Thus, it seems to be difficult to demonstrate any lymphomagenic effect from 2,4,5-T in subjects with lymphoma diagnosis during later years.

The phenoxyacetic acid MCPA, which is still much in use in agriculture as a weed killer, turned out to be a risk factor for NHL in this study based on the univariate analysis and the dose response calculations, although the multivariate analysis was less convincing. However, time from last exposure to diagnosis was not considered in the multivariate analysis. Thus, regarding lymphomagenesis, the univariate analysis may be more informative than the multivariate analysis (cf. Table 4). It is interesting to note that MCPA is not contaminated with dioxins. MCPA has not been debated much previously as carcinogenic; however, in our earlier study on NHL, four cases versus no controls were exposed to MCPA only.[16] Thus, the increased risk for NHL from exposure to phenoxyacetic acids may not depend on dioxins, even though some studies have associated exposure to TCDD with an increased risk for NHL.[25–27] This seems to be in contrast with the situation for soft tissue sarcoma, which has been associated mainly with TCDD and phenoxyacetic acids contaminated with that substance.[20]

In a multivariate analysis, exposure to both fungicides and herbicides was still a risk factor for NHL, although not exposure specifically to phenoxyacetic acids. It is important to note that the multivariate analysis included all exposure regardless of time period, and, in the univariate analysis, no statistically significant increased risk was found for exposure to phenoxyacetic acids, with the exception of MCPA. The interesting finding of an increased risk for exposure to phenoxyacetic acids during only the two decades prior to diagnosis of NHL (see Table 4), for technical reasons, was not investigated by multivariate methods. Furthermore, due to low numbers of exposed subjects in some of the categories, definite conclusions cannot be drawn for separate chemicals, such as MCPA and glyphosate, from the multivariate analysis.

Chlorophenols, which are chemically related to phenoxyacetic acids and have been used as, e.g., wood preservatives, were banned in Sweden in 1977. In the current study, exposure to these agents did not produce any significantly increased risk for NHL, in contrast to previous findings.[22] The possibility that this difference depends on a lack of late exposure cannot be ruled out.

Although they constitute a diversity of agents with few subjects exposed to each of them, fungicides, when combined, resulted in an increased risk for NHL in this study. Because such an association has not been described previously, further studies are necessary.

Regarding organic solvents, this investigation did not confirm previous results of an association.[22,31–33] The result of an increased risk found for the latency period of 20–30 years might be a chance result. Another possibility might be that most of the solvents that have been in use during more recent years are chemically different from previously used and are handled under better hygienic conditions.[34]

Furthermore, glass wool turned out to be a risk factor for NHL in this study, an association that has not been reported previously. It may be a random finding, which is supported by the lack of dose response effect.

The findings in this study support the role for chemical agents in the etiology of NHL. Exposure to pesticides and organic solvents as risk factors for NHL were a priori hypotheses. Thus, it is less likely that the results may be explained by multiple comparisons in the analysis, although that possibility cannot be ruled out completely. Many of the pesticides used during more recent years (e.g., the phenoxyacetic acids) were introduced after World War II, which could explain in part the increase in incidence during the same time period noted in many countries. Bearing in mind that immunosuppression is an established risk factor for NHL, it is interesting to note the immunotoxic effect reported for some pesticides, e.g., phenoxyacetic acids[35] and chlorophenols.[36,37]

Viruses have been associated with lymphomas in animals.[38,39] Burkitt lymphoma in East Africa is strongly correlated with EBV,[8] and HTLV-I seems to cause T-cell lymphoma in some parts of the world.[10]

Virus proliferation is held back by the immune system, and immunologic impairment may have been followed by development of B-cell lymphoma[40] and T-cell lymphoma[41] in animal studies. It should be noted that, in renal transplant patients, NHL is most

common in the first year after transplantation.[42] The incidence then falls to a fairly constant level. It has been suggested that development of NHL in these patients depends on factors present at the time of exposure to immunosuppressants, i.e., almost always EBV infection. These observations are of potential interest in relation to our finding of highest risk for herbicide exposure 1–10 year prior to diagnosis and decreasing risk for longer time spans (see Table 4).

Some of the chemicals with obvious hazardous effects, as shown by this and other studies, are banned in several countries. It is important to stress the finding of MCPA as a lympomagenic substance found in this investigation, because this chemical is still used widely in agriculture as a weed killer.

Other much used pesticides, e.g., glyphosate, also might be of concern. In fact, in this study, four cases and three controls were exposed to this herbicide (OR, 2.3; 95% CI, 0.4–13). Since the time period for diagnosis in this study, the use of glyphosate has increased dramatically, especially during the 1990s, and it is now the most common herbicide used in Sweden.[43] Gene mutations[44–46] and chromosomal aberrations[47] have been reported in mouse lymphoma cells exposed for glyphosate. Furthermore, the incidence of hepatocellular carcinoma, leukemia, and lymphoma was somewhat increased in one study on mice.[48] In culture of human lymphocytes, glyphosate increased the number of sister chromatid exchanges.[49] Recently, we published an increased risk for hairy cell leukemia, a rare type of NHL, for subjects exposed to glyphosate as well as for subjects exposed to other pesticides.[50] For these reasons, glyphosate deserves further epidemiologic studies.

Other environmental chemicals also might be of concern in lymphomagenesis. Thus, increased concentrations of PCBs[51,52] and chlordanes[53] have been reported in NHL patients. These substances are immunotoxic as well.[54,55] In conclusion, this study supports the role of certain chemicals for the development of NHL. On the basis of this study, the risk seems to decrease with time after last exposure.

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