Supplement

Scand J Work Environ Health 2005;31(1):18-25

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This article in PubMed: www.ncbi.nlm.nih.gov/pubmed/16190145

Review

Scand J Work Environ Health 2005;31 suppl 1:18–25

Agricultural exposures and non-Hodgkin's lymphoma

by Neil Pearce, PhD,[1] Dave McLean, PhD[1]

Pearce N, McLean D. Agricultural exposures and non-Hodgkin's lymphoma. *Scand J Work Environ Health* 2005;31 suppl 1:18–25.

Farmers have an increased risk of non-Hodgkin's lymphoma (NHL), several studies have found increased risks of NHL among producers or sprayers of pesticides. The findings are markedly inconsistent across countries and studies, but overall there is evidence of an increased risk among production workers and professional pesticide sprayers with heavy exposures. However, this increased risk does not appear to be confined to workers exposed to phenoxy herbicides containing 2,3,7,8-tetrachlorodibenzo-p-dioxin, and it may be due to phenoxy herbicide exposure itself rather than to the dioxin contaminants. Other pesticide exposures, including organochlorine and organophosphorous insecticides, have also been associated with NHL in some studies, as have nitrates in drinking water. Farmers may also have exposure to oncogenic viruses carried by farm animals, and studies of slaughterhouse workers and meat inspectors have found increased risks of NHL.

Key terms cancer; herbicide; insecticide; meat worker; occupation; pesticide; review.

The incidence of non-Hodgkin's lymphoma (NHL) has been increasing for the last 40 years in the United States and other industrialized countries (1). Some of this increase has occurred among patients with HIV or AIDS (human immunodeficiency virus or acquired immunodeficiency syndrome), but this portion does not appear to account for the majority of the increase. (1). Some studies have found small increased risks of non-Hodgkin's lymphoma (NHL) among farmers and other agricultural workers, despite their low overall cancer risk (2–5). The increased risk appears to be higher among farmers in the central part of the United States (6), and it is these farming states that appear to have experienced the greatest increase in NHL incidence (7). Since the association of NHL with agricultural occupations is well-established, we focus on studies that have more-detailed information on specific exposures. Particular attention has been given to the possible role of phenoxy herbicides (5), but we also consider other pesticides and other agricultural exposures (particularly oncogenic viruses). In addition, we briefly consider other occupational and environmental exposures that may be relevant to agriculture.

Pesticides

Some studies have found associations between general pesticide exposure and NHL, although there are some exceptions (8, 9). They not only include studies of adults, but also some of exposures among children due to parental use of pesticides (10–13).

Herbicides

Attention has particularly been focused on the phenoxy herbicides, which include 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), and 2,4-dichlorophenoxyacetic acid (2,4-D). 2,4,5-T has been of particular interest because it is contaminated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). 2,4-D and other commonly used phenoxy herbicides are not contaminated by TCDD, but they are contaminated by other dioxins and dibenzofurans (14). A series of case–control studies in Sweden found increased risks of soft-tissue sarcoma (15, 16) and malignant lymphoma (17) among agricultural workers who

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had been exposed to phenoxy herbicides (table 1). The findings for NHL were further investigated in case–control studies in New Zealand (18, 19), the United States (20–23), Canada (24), Italy (25), Sweden (26–28), and Australia (29), as well as in 36 cohorts in 12 countries that were part of an international collaborative study organized by the International Agency for Research on Cancer (IARC) (30–32). The latter studies are of particular interest because the exposures among production workers and professional sprayers are likely to be much higher than the exposures of the general population that have been investigated in the population-based case–control studies.

The findings of these studies are summarized in table 1. The principal feature of the table is the considerable variation in relative risk estimates. Hardell et al (17) found a sixfold risk in Sweden in the first study of phenoxy herbicides and NHL. Another Swedish study (26) also found an elevated odds ratio (OR 4.9), although this study also found elevated risks for other exposures. Olsson & Brandt (27) found little evidence of an increased risk (OR 1.3), whereas, in a more recent Swedish study, Hardell & Eriksson (28) found a modestly increased risk [OR 1.5, 95% confidence interval (95% CI) 0.9–2.4].

Studies conducted in other countries have generally not confirmed the high risks found in the Swedish studies, although some have found modestly increased risks in association with high levels of exposure. Hoar et al (21) found a twofold risk in Kansas in the United States, but the risk was more than sevenfold for persons who reported using herbicides for >20 days a year. A similar study in Nebraska in the United States found a nonsignificant odds ratio of 1.5 (95% CI 0.9–2.5), but, once again, the odds ratio increased with increasing exposure (22). McDuffie et al (24) found an association between occupational phenoxy herbicide exposure and NHL in a Canadian case–control study. The predominant exposure was 2,4-D, but the odds ratio was higher for exposure to mecoprop. On the other hand, Pearce et al (19), Woods et al (20), and Cantor et al (23) found little evidence of elevated risks for NHL among persons exposed to phenoxy herbicides, and Pearce (33) found no association with days per year of exposure. La Vecchia et al (25) found a twofold elevated risk of NHL for agricultural workers, but the association was weaker for the specific question on herbicide use.

A series of cohort studies in Sweden (not shown in table 1) has also yielded findings at variance with those of the Swedish case–control studies. A study of 354 620 Swedish men classified as farmers or forestry workers in the 1960 census found no evidence of an increased risk of NHL or Hodgkin's disease (34), and a similar

Table 1. Relative risk estimates from studies of non-Hodgkin's lymphoma in persons exposed to phenoxy herbicides. (RR = risk ratio; 95% CI = 95% confidence interval; 2,4-D = 2,4-dichlorophenoxyacetic acid; 2,4,5-T = 2,4,5-trichlorophenoxyacetic acid; MCPA = 4-chloro-2-methylphenoxyacetic acid; TCDD = 2,3,7,8-tetrachlorodibenzo-p-dioxin)

Type of study	Country or state	Predominant phenoxy exposure	Exposed cases (N)	RR	95% CI
Case–control studies					
Hardell et al, 1981 (17)	Sweden	Any	27	4.7	2.6–8.3
Hoar et al, 1986 (21)	Kansas	2,4-D	24	2.2	1.2–4.1
Pearce et al, 1987 (19)	New Zealand	Any	44	1.0	0.6–1.7
Woods et al, 1987 (20)	Washington	Any		1.2	0.8–1.9
Olsson & Brandt, 1988 (27)	Sweden	Any herbicide		1.3	0.8–2.1
Persson et al, 1989 (26)	Sweden	Any	6	4.9	1.0–27.0
Zahm et al, 1990 (22)	Nebraska	2,4-D	43	1.5	0.9–2.5
Cantor et al, 1992 (23)	Iowa and Minnesota	Any	118	1.2	0.9–1.6
Smith & Christophers, 1992 (29)	Australia	Any	7	2.7	0.7–9.6
Bertazzi & di Domenico, 1994 (37) [a]	Italy	TCDD	4	1.6	0.6–4.3
Kogevinas et al, 1995 (31) [b]	Multiple	Any	19	1.3	0.5–2.9
		2,4-D	12	1.1	0.5–2.7
		2,4,5-T	10	1.9	0.7–4.8
		MCPA	15	0.9	0.4–2.2
Hardell & Eriksson, 1999 (28)	Sweden	Any	51	1.5	0.9–2.4
		2,4-D/2,4,5-T	43	1.3	0.7–2.3
		MCPA	12	2.7	1.0–7.0
McDuffie et al, 2001 (24)	Canada	Any	131	1.4	1.1–1.8
Cohort studies					
Kogevinas et al, 1997 (32)	Multiple	Any	34	1.3	0.9–1.8
		TCDD	24	1.4	0.9–2.1
		Other	9	1.0	0.5–1.9
Bertazzi et al, 2001 (38)	Italy	TCDD	7	1.5	0.7–3.2

[a] Nested case–control study based on a cohort study by Saracci et al (30), which was updated in Kogevinas et al (32).
[b] Nested case–control study based on the same population as Bertazzi et al (36) and Bertazzi et al (38).

study of pesticide applicators found a relative risk of 1.0 for NHL (95% CI 0.6–1.5), whereas a relative risk of approximately 4.5 was expected on the basis of the previous Swedish case–control study findings (35). Other cohort studies of occupational and environmental exposures have found modestly increased risks. In particular, the international collaborative study organized by the International Agency for Research on Cancer has brought together data for 21 863 workers in 36 cohorts in 12 countries (30, 32). This study found an increased risk for soft-tissue sarcoma [6 deaths, standardized mortality ratio (SMR) 2.0, 95% CI 0.8–4.4] and a small increased risk for NHL (24 deaths, SMR 1.4, 95% CI 0.9–2.1) for workers exposed to phenoxy herbicides contaminated with TCDD or higher chlorinated dioxins. There was also a small increased risk for overall cancer when these workers were compared with those in the same cohorts with minimal or no exposure to TCDD [relative risk (RR) 1.3, 95% CI 0.9–1.8)].

Table 1 also shows the findings from the cohort study of the population exposed to dioxin after the 1976 accident in Seveso, Italy (36–38). The findings are of particular interest because this population was exposed to TCDD itself, rather than to phenoxy herbicides. The 20-year follow-up found a small nonsignificant overall increase in NHL deaths and a larger increased risk after 15 years of follow-up (5 cases, RR 2.8, 95% CI 1.1–7.0).

Some studies have also been conducted among Vietnam veterans possibly exposed to Agent Orange, a mixture of 2,4,5-T and 2,4-D with high levels of TCDD contamination. These studies generally had little specific exposure data (apart from service in Vietnam) and therefore have not been included in the table. The Selected Cancer Study (39) found an odds ratio of 1.5 for NHL (99 cases, 95% CI 1.1–2.0) for male veterans who served in Vietnam when compared with male veterans who did not. A similar Australian study (40) found a relative risk of 1.8 (4 cases, 95% CI 0.4–8.0) for NHL for service in Vietnam. Some other studies from the United States Department of Veterans Affairs and various studies of state veterans have also, but not consistently, found small nonsignificant increased risks of NHL (41).

Finally, a study of lymphoma in dogs (42) found an increased risk of lymphoma in association with the dog owners' use of 2,4-D on their lawns or the treatment of yards by commercial lawn care companies.

Thus some studies have found increased risks of NHL from exposure to phenoxy herbicides or TCDD, but the findings are strikingly inconsistent. The Swedish studies have been criticized with regard to the possibility of recall bias or interviewer bias when the exposure histories of cancer cases was compared with those of healthy controls drawn from the general population. Such tendencies could have been fostered by suggestions made in previous interviews in the hospital and by newspaper publicity (43). However, Axelson (44, 45) carried out a simple check for recall bias and concluded that serious bias had not occurred. Swedish case–control studies of other cancer sites have used the same study design and have not found sixfold risks, although the relative risk estimates were slightly elevated. The New Zealand NHL study (18, 19) used both general population controls and other cancer controls at a time when there was considerable media publicity concerning possible health effects of 2,4,5-T and found similar reported exposure patterns in the two groups. Selection bias could occur using this study design if other cancers were also caused by phenoxy herbicide exposure, but any such bias is likely to be small (46).

Differences in the characteristics of the populations and exposures studied should also be considered. If the TCDD contaminant of 2,4,5-T is involved, then it is possible that the levels of contaminants have been different in Sweden, New Zealand, the United States, and Italy. However, available evidence does not suggest major differences between Sweden and New Zealand (47). Furthermore, the Kansas study predominantly involved exposure to 2,4-D, and the Swedish studies also do not necessarily implicate TCDD since an elevated risk for NHL was also observed among persons exposed to 2,4-D and other phenoxy herbicides that do not contain TCDD.

Differences in spraying practices could also be important. Due to the climate, spraying in Sweden is usually carried out intensively during a 2- to 3-month period, whereas spraying in New Zealand and Washington State occurs intermittently over a longer period (20). These differences could result in Swedish herbicide sprayers receiving a relatively high absorbed dose. This conjecture is consistent with the finding of Hoar et al (21) of markedly increased risks of NHL (but not soft-tissue sarcoma or Hodgkin's disease) among persons spraying herbicides for >20 days a year. However, a reanalysis of the New Zealand NHL data found a relative risk of 1.1 (95% CI 0.3–4.1) for persons spraying ≥20 days a year (33).

In general, the studies with more sophisticated exposure assessment (eg, review by industrial hygienists) show smaller risks than those based on self-reports. Nevertheless, some studies have found small increased risks from high levels of exposure, including the cohort studies of production workers and sprayers (32) and the United States studies of sprayers with frequent exposure (21). Thus the Swedish studies have, to some extent, been confirmed qualitatively even if they have not been confirmed quantitatively, though even this "confirmation" occurs in some studies and not in others. Furthermore, many of the more-positive studies involved

phenoxy herbicides that are not contaminated with TCDD. The original Swedish study found no difference in risk between phenoxy herbicides contaminated, and those not contaminated, with TCDD, several of the positive studies in the United States involved 2,4-D, and in the most recent Swedish study the relative risk was highest for 4-chloro-2-methylphenoxyacetic acid (MCPA). This finding is not universal, and, in fact, the IARC cohort study suggests that an increased risk, if it exists, is associated with TCDD exposure (31, 32). Nevertheless, it is possible that the increased risk for NHL may not depend on dioxins (41), whereas the increased risk for soft-tissue sarcoma has mainly been associated with TCDD (28).

Insecticides

Arsenic is the insecticide that has been most clearly established as a human carcinogen. This is an established lung carcinogen and may also cause hematologic malignancies (48). Arsenic compounds have been used as pesticides for more than a century, particularly in sheep-dips and vineyards, although their use has declined in recent decades (49). They are still used for the preservation of farm fencing materials, and a New Zealand study found a small excess risk of NHL among fencing workers (18, 19). However, arsenic compounds would appear to be of limited importance for agricultural workers in general (50).

Various case–control studies of NHL that have collected information on insecticide exposure have reported weak but consistent excesses for some commonly used organochlorines. In particular, Hardell et al (17) found an association of NHL with DDT (dichloro-diphenyl-trichloroethane) use. Organophosphates have also been associated with NHL in studies in Nebraska (22) and Iowa and Minnesota (23). Zheng et al (51) conducted a pooled analysis of three population-based case–control studies carried out in four midwestern states in the United States (21–23) and found an association with carbamate pesticide use, particularly with Sevin. Baris et al (52) found only a weak association with DDT use (OR 1.2, 95% CI 1.0–1.6) in a pooled analysis of the same cohorts, although the risk increased to 1.5 times (95% CI 1.0–2.3) among farmers with ≥15 years of exposure. Waddell et al (53) conducted a further pooled analysis of the same cohorts and found an association with organophosphate exposure (OR 1.5, 95% CI 1.2–1.9), but direct interviews showed a significantly lower risk (OR 1.2) than proxy interviews (OR 3.0). Nanni et al (54) found a nonsignificant association of insecticide exposure (carbamates, phosphates, and DDT) in a highly agricultural area of Italy.

Finally, some studies have reported associations of insecticide with childhood cancer. Buckley et al (10) reported an association between childhood NHL and frequent household insecticide use by the mother (OR 7.3, 95% CI 0.8–63.9), use of garden sprays by the mother (OR 1.7, 95% CI 0.7–4.4), and extermination around the home (OR 3.0, 95% CI 1.4–6.2). Similarly, Leiss & Savitz (12) reported an excess of NHL among children whose homes had been exterminated or had pest strips. Kristensen et al (11) reported an increased risk of childhood NHL with the level of pesticide expenditures in a cohort of children of Norwegian farmers.

Other agricultural exposures

In addition to pesticide exposure, agricultural work comprises a wide variety of tasks, each involving potentially carcinogenic exposures. Farmers and farm laborers may come into contact with animal viruses, bacteria and fungi, pesticides, solvents, fuels and oils, and dusts (2). Other agricultural workers, such as fencing workers, slaughterhouse workers, meat inspectors, and veterinarians, experience some of the same exposures. As already noted, the factors responsible for the increased risks of NHL among farmers are not well understood, but most studies have focused on pesticides. However, farmers are also exposed to other agricultural chemicals, zoonotic viruses, and factors that increase chronic antigenic stimulation, and these other aspects of farming should also be briefly considered.

Other agricultural chemicals

In addition to being exposed to pesticides (insecticides or herbicides), farmers are exposed to other chemicals, including solvents, emulsifiers, fuels, and oils. Olsson & Brandt (27) found an association between occupational solvent exposure and NHL risk in a case–control study in Sweden. Agricultural chemicals may also be used in other situations, such as for wood treatment and preservation. Hardell et al (17) found increased risks in association with exposure to chlorophenols, used as fungicides and wood preservatives in the timber industry, although other studies (55) have not found any increase. A New Zealand study found a small excess risk for fencing workers (18, 19). Several studies have reported excess risks for wood workers (56, 57), and there is inconsistent evidence of an increased risk for sawmill workers (18, 19, 58). Some descriptive studies involving census tract data, which have noted associations between NHL and sales of pesticides, have also found associations with sales of fuel, oil, and other farm chemicals (59). One study (60) reported an association with nitrate levels in drinking water in community water supplies used in the Nebraska case–control study (22), but

this finding was not confirmed in a more recent study in Minnesota conducted by Freedman et al (61). Finally, exposure to ultraviolet (UV) light is an established cause of immunosuppression and may thereby increase the risk of NHL (62), although it is not clear to what extent it may explain the increased risk among farmers.

Zoonotic viruses

A possible role for exposure to zoonotic viruses has been suggested by studies of slaughterhouse workers. An elevated risk was first reported for a Baltimore meat cutters' union cohort (63) and subsequently in two New Zealand case–control studies (18, 19, 64). No elevation has been observed for butchers in any of the cohort studies conducted (65–68), but, in all instances, the numbers have been small. In a mortality odds ratio analysis after an additional 9 years of follow-up of the 10 841 Baltimore meat cutters' union members, using the non-meat workers as a reference group, an elevation in risk was observed for NHL (mortality odds ratio 5.2, P=0.14, 6 exposed cases) among slaughterhouse workers (69). A case–control study nested within the Baltimore union cohort investigated a range of risk factors for all lymphohematopoietic cancers (70). An increase in risk in association with ever having worked in the meat industry (OR 2.2), strongest for those with >5 years of exposure (OR 2.9) and for those who ever worked in a slaughterhouse (OR 2.8) or in the meat department of a supermarket (OR 2.7), was observed. The increased risk was largely confined to those with >5 years of exposure (OR 3.7) and to those who had ever worked slaughtering animals (OR 5.3). A higher risk was also observed for those who ever worked with raw meat (OR 2.5) and, in particular, for those who handled raw meat for >5 years (OR 3.1). For NHL, a spectacular increase in risk was observed among those who had ever worked in a slaughterhouse (OR 12.0).

Two recent case–control studies have again found significant associations between work as a butcher or in a related occupation and NHL (71) and work in meat packaging or processing and follicular lymphoma (72). A United States population-based case–control study of occupational exposures and NHL (72) found an association between work in the meat packaging and processing industry, and follicular lymphomas was found (OR 1.6, 95% CI 1.0–2.7). Some evidence of a dose–response relationship was also observed with the risk associated with exposure for ≤2 years (OR 1.2, 95% CI 0.6–2.2), increasing significantly for those with >2 years of exposure (OR 2.1, 95% CI 1.1–4.2). In a recent case–control study based on the Swiss cancer registry, which used other cancer registrants as controls, elevated risks were also observed for NHL (OR 1.7, 95% CI 1.0–3.0, 15 cases) in the occupational category "butchers and related occupations" (70).

Veterinarians are another occupational group with exposure to farm animals, and there is inconsistent evidence that veterinarians may be at increased risk of hematologic malignancies. Blair & Hayes (73) studied 5016 deaths among white male veterinarians and found elevated risks for Hodgkin's disease [prevalence mortality ratio (PMR) 1.9, 95% CI 1.1–3.0) and cancer of other lymphatic tissue (PMR 1.9, 95% CI 1.3–2.8). Interestingly, the prevalence mortality ratio for all hematologic malignancies was elevated for meat inspectors (PMR 3.4, 95% CI 1.4–6.6), a finding consistent with the increased risks among slaughterhouse workers.

Although the epidemiologic evidence for the role of oncogenic animal viruses in human cancer is currently weak, several potentially zoonotic viruses exist in the agricultural environment. These include the herpes virus that causes Marek's disease in poultry (74), the avian leukosis virus (75), papilloma viruses in cattle (76, 77), and perhaps other currently undetected viruses. The rapid proliferation of information concerning retroviruses suggests that other members of this family will be found in domestic animals as well as humans. Thus, although exposure to farm animal viruses could not directly account for the increase in NHL in the general population, it is of relevance to the more general issue of the causation of NHL by viruses in the general population.

Most interest has centered on the bovine leukemia virus, an exogenous C-type retrovirus that has been established as the etiologic agent of the adult form of bovine lymphosarcoma (78–83). However, human studies, including studies of NHL cases among children, have not shown evidence of infection (84), and it is becoming increasingly unlikely that this virus increases the risk of NHL among humans. Nevertheless, there are other oncogenic viruses carried by farm animals, and these viruses have not been adequately studied to date. Of special interest in this context are several retroviruses from the genera *Alpharetrovirus*, *Betaretrovirus Gammaretrovirus,* and *Deltaretrovirus* that have been identified as the cause of malignant diseases in animals. There are also members of the *Lentivirus* genus that are known to cause chronic immunodeficiency diseases, and immunosuppression may be associated with NHL. Other oncogenic retroviruses present in healthy animals that are processed in the meat industry include the sheep enzootic nasal tumor virus, which causes tumors of the upper respiratory tract in sheep, and the Jaagsiekte sheep retrovirus that causes bovine pulmonary adenomatosis, which is a transmissible lung cancer in infected sheep that resembles human bronchioalveolar carcinoma (85). Members of the *Lentivirus* genus include the bovine immunodeficiency virus, which, as its name suggests,

causes chronic immunodeficiencies in cattle, and the Maedi-Visna virus, which causes chronic interstitial pneumonia and demyelinating leukencephalomyelitis in sheep.

Several retroviruses infect lower primates, for example, the Mason-Pfitzer monkey retrovirus and the Simian retrovirus, both of which cause immunosuppression but not malignant diseases in infected animals, the Gibbon ape leukemia virus, which causes myeloproliferative disorders in Gibbons, and the simian T-cell lymphotropic viruses, which cause T-cell lymphoma in old-world monkeys. Serological testing has shown that infection in humans with a simian retrovirus does occur among people occupationally exposed to nonhuman primates (86). There is, however, little epidemiologic or experimental evidence of zoonotic viral causes of human malignancies. Moreover, in a recent study, cell samples taken from 44 patients with various malignant hematological diseases were tested for evidence of putative human oncoretroviruses using consensus primers for polymerase chain reaction (PCR) developed from genome regions of known animal retroviruses (87). These PCR primers were capable of specifically amplifying type C and D exogenous animal retroviruses, without amplifying human endogenous retroviral elements, but no human homologues of nucleotide sequences of known animal oncoretroviruses (or related previously undetected human retroviruses) were found.

Concluding remarks

In summary, several studies have found increased risks of NHL among producers or sprayers of pesticides, particularly phenoxy herbicides, as well as people exposed environmentally in industrial accidents or in service in the Vietnam War, but the findings are markedly inconsistent across countries and studies. Other studies have not found the high levels of risk in association with "ever exposure" that were reported in the Swedish studies. Nevertheless, overall, there is evidence of a small increased risk, particularly among production workers and professional pesticide sprayers with heavy exposures. However, this increased risk does not appear to be confined to workers exposed to phenoxy herbicides containing TCDD and may be due to phenoxy herbicide exposure itself rather than to the dioxin contaminants. Other pesticide exposures, including organochlorine and organophosphorous insecticides, have also been associated with NHL in some studies. NHL has also been associated with some other occupational exposures, but these are generally rare, and the findings are inconsistent, although some studies have found an increased risk of NHL in work involving wood or exposure to solvents or related chemicals. Perhaps it would be more useful to group exposures according to the likely mechanism of action (eg, immunosuppression) rather than on the basis of use (eg, herbicides, insecticides). It is possible that such analyses may yield more consistent and meaningful patterns than the widely varying findings that have been observed to date. Finally, agricultural workers may also be exposed to oncogenic viruses carried by farm animals. Studies of slaughterhouse workers and meat inspectors have found increased risks of NHL, but the specific causal agent(s) has(have) not yet been identified.

Acknowledgments

The Centre for Public Health Research is supported by a Programme Grant from the Health Research Council of New Zealand.

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