Pesticides and non-Hodgkin Lymphoma: An Overview for the Clinician

David Berz, MD, PhD, Jorge J. Castillo, MD, Daniela N. Quilliam, MPH, REHS, Gerald Coelvin, DO

Non-Hodgkin Lymphoma (NHL) represents a heterogeneous group of malignant diseases arising from the lymphatic tissues. Grossly, those disease entities can be subdivided into T- and B-cell lymphomas. Several systems have been developed over the last decades in order to further subclassify NHL. The World Health Organization (WHO) recognizes greater than 40 pathological subtypes of NHL. As molecular techniques evolve, the heterogeneity of this group of diseases is expanding further.

There were an estimated 56,390 new cases and 19,200 deaths from NHL in 2005. It was the 6th most common cancer among men and the 5th most common cancer among women.1 The incidence of NHL increased at a rate of 3-4% per year during the 1970s and 1980s and stabilized in the 1990s.2 Initially, better diagnostic techniques, changes in the classification patterns of NHL and the AIDS epidemic were potential explanations for this rise. However, more recent data revealed that the changes in NHL incidence are not fully explained by those phenomena and suggest that increasing exposures to not fully defined environmental factors, like diet or occupational exposures seem to be of importance.

The incidence of NHL is not homogeneous throughout the United States (US). NHL-related mortality is higher in the central, more agricultural areas of the US. Hence, agricultural occupational exposures to pesticides have been investigated as causes for the development of NHL in numerous laboratory and epidemiological studies. Because of the large variety of potentially toxic substances, the corresponding wide spectrum of chemical structures and the sophisticated statistical techniques employed in the epidemiological investigations, the literature on the subject of the association of the development of NHL and use of pesticides is not straightforward.

What is a Pesticide?

The United States Environmental Protection Agency (US EPA) defines pesticides as any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating insects, roddents or other animals, unwanted plants or weeds, fungi or microorganisms like bacteria or viruses. Approximately 890 pesticide compounds are marketed in the US in the form of more than 20,000 different products.

Methodological Difficulties with the Available Studies

Many studies tried to link farm life with the increased incidence of NHL. This does not consider whether the individual diagnosed with NHL participated in farming or was exposed to any of the toxic substances in question. Other investigations focused on the association of pesticide use and the development of NHL. Those studies often did not sufficiently address the question of the intensity of the exposure, its tenure, which pesticide was used and which type of lymphomas were observed.

Along with those more principal problems, most of those studies were retrospective cohorts or had a cross-sectional case-control design, which are generally associated with various types of biases, including coverage, sampling, selection, and recall bias.

Pesticides Frequently Used in the USA

Phenoxyacetic acid herbicides

PAH

This group of pesticide compounds encompasses 2,4,5-T, which was found to contain a direct dioxin derivative that was banned in most European countries and the US in 1977, and 2,4-D, which is one of the most frequently used broadleaf pesticides in the US.

Early case control studies suggested an association between a professional PAH exposure and an increased incidence of NHL. Although most follow-up studies revealed a similar association, the findings have not always been statistically significant. An early interview-based Swedish case-control study from 1981 reported a 6-fold increase of NHL in individuals using PAH.3 Subsequent studies from Kansas, Nebraska and New Zealand demonstrated an elevated incidence among PAH-using farmers.4,5 Those studies also suggested that increased, unprotected and prolonged use of those pesticides seemed to increase the risk for NHL development. More recent studies showed a trend towards increased NHL incidence in the PAH using farming population without reaching statistical significance.6 A large-scale international retrospective cohort study (SMR = 1.39, 95% CI 0.89-2.06) and a large retrospective effort from the Netherlands (RR=1.7, 95% CI 0.2-16.5) on the increase of NHL risk in occupational PAH exposure both showed trends towards an increase in NHL incidence in those populations.7,8

In summary, the methodological difficulties of those large scale studies notwithstanding, PAH appears to increase the development of NHL and prolonged and more intense use seems to strengthen this association.

Agent Orange

Agent Orange, used mainly for warfare, is a dioxin-contaminated mixture of PAH. It has been extensively investigated as a cause of NHL.9,10 Although uncontrolled studies revealed an increase in NHL incidence in Vietnam veterans, ongoing large-scale Vietnam based studies are still examining the association of increased NHL incidence and exposure to Agent Orange.

Thus far, there is insufficient evidence to conclude whether there is an increased incidence of NHL in Vietnam veterans who were exposed to Agent Orange.

Chlorophenol herbicides (CPH)

The CPH are a group of nineteen compounds which are chemically related to the PAH and which have the potential for dioxin contamination. They are mainly used in wood preservation and have been banned in many European countries since the 1970s but large amounts may still exist in soil and sedi-
ments even after the discontinuation of their use. Chlorophenols are still in use in several industries in the US. Most studies did identify a trend for increased NHL incidence in CPH exposed individuals without statistical significance and often large confidence intervals for the proposed association odds ratio. Another international project identified a not statistically significant trend for the development of NHL with prolonged CPH exposure. In addition, a recently published German study suggested an increased incidence of CPH and indolent as well as aggressive lymphoma subtypes. Another recent study from the Netherlands suggested an association of glyphosate exposure and hairy cell leukemia. Other studies could not establish such a relationship. Further, the large scale prospective agricultural health study was not able to detect an association between NHL incidence and glyphosate exposure.

In summary, at this time we feel that there is no sufficient evidence that glyphosate induces NHL in farmers.

Organochlorine Insecticides (OCI)
The OCIs are a heterogenous group of insecticides that encompass DDT, DDD, DDE among others. The OCIs exert their toxic effect by virtue of opening sodium channels and hence generating steady action potentials. Due to their long half-lives the OCIs have a strong tendency for bioaccumulation in adipose tissues. Most of the OCI compounds are banned in the US because laboratory studies on rodents revealed carcinogenicity.

OCIs have been investigated for their potential to increase NHL incidence, with lindane and DDT being the most widely studied compounds. Although an early study from Kansas with few lindane exposed cases showed an increase of NHL with lindane use in the agricultural setting (OR=6.1, 95% CI 1.3–29), most subsequent studies demonstrated only non-statistically significant trends towards an increase in incidence of NHL with exposure to OCI. In conclusion, there is insufficient evidence at this time to determine if OCIs are associated with NHL.

Organophosphate Insecticides (OPI)
The OPIs are the most broadly used insecticides in the US. They were originally developed as byproducts of nerve-gas production in Nazi Germany. They function as neurotoxins by virtue of irreversibly inhibiting the enzyme acetylcholinesterase. The OPIs easily degrade with sunlight, prohibiting significant bioaccumulation. However, small amounts can be detected in food and drinking water.

Several studies have investigated the impact of OPIs on the development of NHL. The Nebraska study and a Canadian study established a statistically significant increase in NHL incidence and the use of OPIs. Most other investigations established a similar trend, although the findings were not statistically significant.

Overall, the OPI compounds can be regarded as potential culprits for lymphomagenesis.

Carbamates
The carbamates represent a heterogenous group of compounds that are used as herbicides and insecticides. They belong to the same class as the clinically used compounds neostigmine and rivastigmine, whose chemical structure is based on the natural alkaloid physostigmine.

A study from Nebraska described a statistically significant association of carbamate exposure and the development of NHL. Several later North American studies showed a positive association, which held statistical significance for only certain subclasses of carbamate insecticides and herbicides, which were not statistically significantly associated with the development of NHL in other studies.

Fungicides
Fungicides make up less than 10% of the pesticides used in the US. Association of fungicide use with the incidence of NHL in humans has been studied over more than two decades. Although in a Canadian study sulfur compound fungicides have been statistically significantly linked to an increased incidence of NHL, most other studies that studied sulfur compound and other fungicide use demonstrated either protective effects or lost statistical significance of an association when corrected for other pesticide use.

Lymphoma Subtypes
The inability of several of the above outlined studies to detect a statistically significant association between pesticide exposure and NHL development may partially be related to the fact that the incidence of NHL in general was examined as the outcome variable. As discussed previously, NHLs are a highly heterogeneous group of diseases. Even within the same subtype of NHL, the genetic profiles observed often vary widely. This prompts the question if lymphomas, harboring specific genetic abnormalities, are more likely to be associated with pesticide exposures than others.
One commonly detected genetic abnormality in NHL is the translocation 14;18 or t(14;18). This genetic event corresponds with the activation of Bcl-2, an anti-apoptotic protein. Cells with this mutation can be immortalized by virtue of the activity of this cell cycle relevant protein and this event has been directly linked with lymphomagenesis, mainly follicular lymphoma. Several preliminary retrospective studies identified a possible link between lymphomas containing t(14;18) and pesticide exposure.19

Two large population-based studies have specifically evaluated the association of t(14;18)-positive lymphomas in occupational pesticide exposure. In the first study by Schroeder and colleagues,18 the aggregate exposure OR for insecticides in t(14;18) showed a weakly positive trend without reaching statistical significance (OR 1.3, 95% CI 0.8-2.0). However, when examining specific OCI exposures, the associations observed were much stronger and reached statistical significance. A second population-based study by Chiu and colleagues found an association between pesticide exposure and t(14;18)-positive NHL.19 The association retained statistical significance for crop insecticides (OR=3.0, 95% CI 1.1-8.2), herbicides (OR=2.9, 95% CI 1.1-7.9) and fumigants (OR=5.0, 95% CI 1.7-14.5). No association between pesticide exposure and t(14;18)-negative NHL was found.

CONCLUSIONS

Several key points can be highlighted based on our review. First, the literature on the subject is complicated by the fact that several pesticides are often used simultaneously. This might obscure pathogenic relationships between certain pesticides and NHL development. Second, most of the epidemiological studies are biased secondary to retrospective cohort and case-control designs. For better study of the exposure disease relationship further prospective studies are required. Third, in spite of several methodological shortcomings, the literature suggests an association between the exposure to several pesticides and the development of NHL. Fourth, several other compounds such as carbamates, fungicides and glyphosate have no sufficient evidence on such a relationship. Lastly, the evolving knowledge about the molecular diversity and pathogenesis of lymphomas might allow for a more specific study of associations between pesticide exposures and certain NHL subtypes.

REFERENCES


David Berz, MD, PhD, is Assistant Professor of Medicine, The Warren Alpert Medical School of Brown University. Jorge J. Castillo, MD, is Assistant Professor of Medicine, The Warren Alpert Medical School of Brown University/Division of Hematology and Oncology, The Miriam Hospital.

Daniela N. Quilliam, MPH, REHS, is a Public Health Epidemiologist, Office of Food Protection, Rhode Island Department of Health, and Teaching Associate in Community Health, The Warren Alpert Medical School of Brown University.

Gerald Colvin, DO, is Adjunct Assistant Professor of Medicine, Brown University School of Medicine and Associate Professor of Medicine, Warren Alpert School of Medicine at Brown University (pending).

Disclosure of Financial Interests

The authors and/or spouses/significant others have no financial interests to disclose.

Correspondence

Gerald Colvin, DO
Rhode Island Hospital
593 Eddy Street, George 3
Providence, RI, USA 02903
Phone: (401) 444-5396
Email: gcolvin@lifespan.org