Integrative assessment of multiple pesticides as risk factors for non-Hodgkin’s lymphoma among men

A J De Roos, S H Zahm, K P Cantor, D D Weisenburger, F F Holmes, L F Burmeister, A Blair

Background: An increased rate of non-Hodgkin’s lymphoma (NHL) has been repeatedly observed among farmers, but identification of specific exposures that explain this observation has proven difficult.

Methods: During the 1980s, the National Cancer Institute conducted three case-control studies of NHL in the midwestern United States. These pooled data were used to examine pesticide exposures in farming as risk factors for NHL in men. The large sample size (n = 3417) allowed analysis of 47 pesticides simultaneously, controlling for potential confounding by other pesticides in the model, and adjusting the estimates based on a prespecified variance to make them more stable.

Results: Reported use of several individual pesticides was associated with increased NHL incidence, including organophosphate insecticides coumaphos, diazinon, and fonofos, insecticides chlorodane, dieldrin, and copper acetarsenite, and herbicides atrazine, glyphosate, and sodium chloride. A subanalysis of these “potentially carcinogenic” pesticides suggested a positive trend of risk with exposure to increasing numbers.

Conclusion: Consideration of multiple exposures is important in accurately estimating specific effects and in evaluating realistic exposure scenarios.

METHODS

Study population
The three case-control studies had slightly different methods of subject recruitment. In Nebraska, all cases of NHL diagnosed between July 1983 and June 1986 among white subjects 21 years of age and older, and living in one of the 66 counties of eastern Nebraska were identified through the Nebraska Lymphoma Study Group and area hospitals. In Iowa and Minnesota, all newly diagnosed cases of NHL among
white men aged 30 years or older were ascertained from records of the Iowa State Health Registry from 1981 to 1983, and a special surveillance system of Minnesota hospitals and pathology laboratories from 1980 to 1982. In Kansas, a random sample of cases diagnosed between 1979 and 1981 among white men age 21 years or older was selected from the statewide cancer registry run by the University of Kansas Cancer Data Service. Population based controls were randomly selected from the same geographical areas as the cases, frequency matched to cases by race, sex, age, and vital status at the time of interview. Potential controls were identified by random digit dialing and from Medicare records, and for deceased cases, from state mortality files.

Only one study included women; in this pooled analysis we excluded female cases and controls. Those who lived or worked on a farm when younger than 18 years of age, but not after age 18, were not asked about their pesticide use in the Nebraska study; persons with this history from any of the three studies were therefore excluded from analyses of the pooled data. Following exclusions, the study population included 870 cases and 2569 controls.

**Interviews**

Interviews were conducted with the subjects or their next of kin if the subjects were dead or incapacitated. In each study, detailed questions were asked about the use of agricultural pesticides as well as other known or suspected risk factors for NHL. In Nebraska, information was obtained through questioning about the use of any pesticide, followed by prompting for specific pesticides, with details on the total number of years of use and average number of days per year. In Iowa and Minnesota, use was assessed by a direct question about a selected list of specific pesticides. Pesticide users were also asked the first and last year each pesticide was used. In Kansas, use of pesticides was assessed by an open ended question without prompting for specific pesticides, and duration of use and days per year were obtained for groups of pesticides (herbicides, insecticides, and fungicides), but not for each pesticide individually.

**Statistical analyses**

Each pesticide for which there were data from all three studies, and to which 20 or more persons were exposed, was included in the pooled analysis. The set of pesticides examined included 47 insecticides and herbicides. Exposure to each pesticide was coded as an indicator variable for exposed (1) or not exposed (0). Because these analyses of multiple pesticides modelled the pesticides simultaneously, any subject with a missing or “don’t know” response for any one of the 47 pesticides of interest was excluded from all analyses. Following exclusion of subjects with missing data, analyses of multiple pesticides included 650 cases (74.7%) and 1933 controls (75.2%). We employed two approaches to our analyses: standard logistic regression (maximum likelihood estimation) and hierarchical regression, calculating odds ratios to estimate the relative risk associated with each pesticide. All models included variables for age (censored as a quadratic spline variable with knots at 50 years and 80 years) and indicator variables for study site. Other factors known or suspected to be associated with NHL, including first degree relative with haematopoietic cancer, education, and smoking, were evaluated and found not to be important confounders of the associations between NHL and pesticides. The standard logistic regression models did not assume any prior distribution of pesticide effects, in contrast to the hierarchical regression modelling.

**Hierarchical regression of multiple pesticide exposures**

In the first-level model of the hierarchical regression analysis, NHL disease status was regressed simultaneously on the 47 pesticide exposures, age, and study site. The maximum likelihood estimates for the 47 pesticides from the first-level model were regressed in a second-level linear regression model as a function of prespecified prior covariates for each of the pesticides. The second-level model should incorporate what is known about each true effect parameter prior to seeing the study data. Information derived from the second-level model was used to adjust the beta coefficient for each pesticide exposure according to its “prior distribution”; the beta for each pesticide was adjusted in the direction of its prior mean, or expected value (from the second-level model), with the magnitude of shrinkage dependent on the precision of its likelihood estimate (from the first-level model) and a prespecified variance of the assumed normal distribution for that parameter. SAS Proc GLIMMIX was used to run the hierarchical models. This program can be adapted for the purpose of hierarchical modelling of multiple exposures, and uses a penalised likelihood function to fit the first- and second-level models by an iterative procedure.

Information on pesticides that would give a priori reason to believe that the true effect parameters for certain specific pesticides would be more or less similar to each other was constructed into a matrix for use in the second level of the hierarchical regression analysis (table 1). The second-level, or prior covariates, were factors hypothesised to determine the magnitude of, or explain some of the variability between, the individual true effects. The covariates were indicators of pesticide class, structure, and toxicity, used to define categories of pesticide effects which would be regarded as “exchangeable”, or as draws from a common prior distribution. These “categories of exchangeability” included the groupings: insecticides (versus herbicides), organochlorines, organophosphates, carbamates, phenoxyacetic acids, triazines, amides, and benzoic acids (see table 1). In addition to categories of exchangeability, we defined a prior covariate incorporating prior evidence for carcinogenicity of the pesticide. Based on data from the United States Environmental Protection Agency’s (US EPA) Integrated Risk Information System (http://www.epa.gov/iris/) and the International Agency for Research on Cancer’s Program on the Evaluation of Cancer Risks to Humans (http://monographs.iarc.fr/), carcinogenic probability for any cancer (not limited to NHL), was defined as a continuous variable ranging between 0 and 1 (algorithm for variable definition is included as footnote to table 1).

Another component of each pesticide effect’s prior distribution was a value for the residual variance, which captures effects above and beyond those accounted for by the “group” effects of the second-level covariates, and determines the degree of shrinkage of a likelihood estimate toward its prior mean. This residual variance was defined as a value relating to a range of probable values for the true effect parameter. We assumed, with 95% certainty, that the rate ratio for each pesticide, after adjusting for the second-level covariates, would fall within a 10-fold range around its prior mean (for example, between 0.5 and 5.0), by defining the prior residual variance as 0.35 (note: for a 10-fold range, residual variance = (ln(10)/3.92)^2 ≤ 0.35, assuming normality).

Because our prior covariates were crudely defined, and because there is little information on factors that would be expected to affect the magnitude of the effect of pesticides on NHL incidence, we also performed a hierarchical regression analysis of multiple pesticides using an intercept-only model, in which all pesticide effects were assumed to arise from a common prior distribution, with a prior residual variance of 0.35. In other words, this modelling strategy assumed that there was no a priori reason to believe that any specific pesticide was more likely to be associated with NHL incidence than any other pesticide in the model.

**Number of pesticides used**

We conducted analyses to estimate NHL incidence associated with the number of pesticides used, out of the total number of...
86 pesticides reported in all three of the pooled studies (many of these 86 pesticides were not included in the multivariable analysis of the set of 47 specific pesticides because of their infrequent use). The number of pesticides was coded using indicator variables (1 pesticide, 2–4 pesticides, 5 or more pesticides). Similar analyses were conducted for the number of insecticides and herbicides used. For those pesticides showing positive associations with NHL in the hierarchical regression analysis of 47 specific pesticides (nine pesticides total, see table 3), we conducted a similar analysis of the number of pesticides used, restricted to these “potentially carcinogenic” pesticides. In addition to logistic regression analyses, we evaluated the effect of the number of pesticides used by hierarchical regression with an intercept-only model, in which all pesticide effects (those indicating number of pesticides, as well as the 47 specific pesticides) were assumed to have been sampled from a common prior distribution with an unknown mean and a residual variance of 0.35.

**Combined pesticide exposures**

We explored the risk associated with combined pesticide exposures, defined as two pesticides used by the same person, but not necessarily at the same time. For any two pesticides for which more than 75 persons reported use of both (representing the 5% most common of all possible combinations of the 47 pesticides), and at least 20 persons reported use of each of the two individual pesticides not in combination, we evaluated potential superadditivity of pesticide effects on NHL (the appendix contains a list of the pesticide combinations evaluated). Individual and joint effects were first estimated.
using logistic regression in models including variables for the joint exposure and two individual exposures, the 45 other specific pesticides, age, and study site. Where the OR for the joint effect was 1.3 or higher, positive interaction on the additive scale was evaluated using the interaction contrast ratio (ICR = ORjoint exposure – ORindividual exposure #1 + ORindividual exposure #2 + 1). ICR values above 0.5 were considered indicative of superadditivity, and these pesticide combinations were further analysed using hierarchical regression with an intercept-only model, in which all pesticide effects (those indicating joint and individual exposures to the two pesticides, as well as the other 45 specific pesticides) were assumed to have been sampled from a common prior distribution with an unknown mean and a residual variance of 0.35.

**RESULTS**

Table 2 shows characteristics of men in the pooled studies. In the control population, which was representative of this part of the midwestern United States, approximately 70% of the men had lived or worked on a farm as an adult. There was a 10% increased NHL incidence associated with living or working on a farm as an adult; this increase is similar in magnitude to meta-analyses of farming and NHL mortality and morbidity. Cases were slightly more likely than controls to have been directly interviewed, to be between the ages of 40 and 79, and they were more than twice as likely to have a first degree relative with haematopoietic cancer. The subset of subjects included in analyses of multiple pesticides was less likely than those in the overall study population to be from the Kansas or Nebraska studies, to have lived or worked on a farm as an adult, or to have had a proxy respondent, and they were slightly more likely to be more highly educated; however, the relation of these factors with case status did not differ between the overall study and the subset included in the analyses of multiple pesticides.

Use of most specific pesticides was more frequent among cases than controls; however, most of the odds ratios were not increased in the multivariable models (table 3), primarily due to adjustment for study site, since both the frequency of pesticide use and case-to-control ratios differed by study site. The results of the hierarchical regression analysis of 47 pesticides were generally similar to, but had somewhat more narrow confidence intervals than results from the logistic regression model. Only a few pesticides were associated with a possible increased NHL incidence (judged by OR >1.3 and lower confidence limit <0.8), including the organophosphate (OP) insecticides coumaphos, fonofos, and diazinon, the organochlorine insecticides chlordane and dieldrin, the insecticide copper acetarsenate, and the herbicides atrazine, glyphosate, and sodium chloride. There was also a significantly decreased risk associated with aldrin exposure. These suggested effects occurred in both the logistic and hierarchical regression analyses. For pesticides that had wider confidence intervals in the logistic regression model, odds ratios from the hierarchical model were generally closer to the null value, based on a priori assumptions about the probable magnitudes of effect. For example, we assumed that the effect of sodium chloride would be similar to that of other herbicides and other pesticides for which there was a low carcinogenic probability, and that after accounting for these prior covariates, the rate ratio would be similar to that of other herbicides and other pesticides for which there was a low carcinogenic probability, and that after accounting for these prior covariates, the rate ratio would likely fall within a 10-fold range around its expected value. Based on these assumptions, a fourfold risk associated with the use of sodium chloride in the logistic regression analysis was adjusted to a 1.8-fold risk using hierarchical regression.

![Table 2](http://www.occenvmed.com)
There was no association between NHL incidence and the total number of pesticides or herbicides used (see table 4). There was a 40% increased incidence associated with the use of five or more insecticides; however, there was no apparent exposure-response trend. In an analysis of the number of “potentially carcinogenic” pesticides, NHL incidence increased by the number of pesticides used by the subject. Subjects who reported using any five or more “potentially carcinogenic” pesticides were twice as likely to be NHL cases compared to those using no pesticides. The results for “potentially carcinogenic” pesticides were highly sensitive to removal of certain pesticides from the count, including dieldrin, atrazine, or glyphosate. For example, removal of glyphosate from the count resulted in a lack of trend for increasing number of “potentially carcinogenic” pesticides (1 pesticide: OR = 1.2; 2–4 pesticides: OR = 1.2; ≥5 pesticides: OR = 1.1).
The analysis of 48 pesticide combinations in relation to NHL incidence revealed few joint effects of 1.3 or higher that were indicative of superadditivity (table 5). Combined exposures to carbofuran and atrazine, diazinon and atrazine, and alachlor and atrazine had estimated joint effects that were more than additive (ICR >0.5), even following shrinkage in hierarchical regression analyses. Other joint pesticide effects which seemed indicative of superadditivity in results from logistic regression analyses, such as that for atrazine and dicamba, were probably misleading due to imprecision of estimates; these results did not hold up following shrinkage in hierarchical regression analyses, according to our prior distribution of complete exchangeability.

**DISCUSSION**

Incidence and mortality rates for NHL have been generally increasing in the United States and in most industrialised countries for several decades, with an 85–100% increase in...
mortality among whites and non-whites from the late 1940s
to the late 1980s, a time period relevant for this study. This
increase may be partially attributed to improved diagnosis and
in later years to AIDS related lymphomas, but cannot be com-
pletely explained by these factors. Environmental factors
such as pesticides could play a role in this persistent increase,
since their use became more widespread during this time
period. Several aetiological mechanisms of pesticides in
relation to NHL have been proposed, including genotoxicity
and immunotoxicity, increased cell proliferation, and
chromosomal aberrations. In our analysis of multiple
pesticides in farming, we found only a small number of the
pesticides to be risk factors for NHL, with the highest
increased risks among subjects exposed to five or more of
these “potentially carcinogenic” pesticides, or those with cer-
tain combined pesticide exposures.

The large number of exposed subjects in this pooled analy-
sis allowed adjustment for the use of other pesticides, and
hierarchical regression modelling resulted in estimates that
were in some instances more stable than those from logistic
regression models. However, the effect estimates from the
logistic and hierarchical analyses were quite similar overall,
with a few standout exceptions. The hierarchical results are
more conservative than those from the logistic regressions,
given the uninformed nature of the prior distributions we
specified, particularly in analyses of the number of pesticides
used and combined pesticide exposures. For example, in the
hierarchical regression analysis of the number of pesticides
used, we assumed that the use of any five or more pesticides
was no more likely to be associated with NHL than use of any
one pesticide. A less conservative prior distribution could have
been specified in which a higher probability would be placed
on a positive association for the greater number of pesticides
used. However, the uninformed nature of these priors seemed
appropriate in a largely exploratory analysis of multiple expo-
sures for which there is little prior knowledge about how pes-
ticide exposures interact in relation to the risk of NHL. Both
analyses showed increasing odds ratios with the number of
“potentially carcinogenic” pesticides used, but the relative
risks in the upper category were substantially different—25.9
for the logistic regression and 2.0 for the hierarchical
analysis—probably indicating inappropriate use of logistic
regression for these sparse data.

Adjustment for multiple pesticides suggested that there
were few instances of substantial confounding of pesticide
effects by other pesticides. Nevertheless, some previous
findings in our data appear to be due to confounding by cor-
related pesticide exposures. In particular, a previously reported
positive association for carbaryl was not replicated in the
adjusted analyses. Further analysis here revealed that carbaryl
and diazinon use were highly associated (p < 0.001), and pre-
viously reported associations of different carbaryl measures
with NHL were eliminated by adjustment for diazinon,
including carbaryl use, personal handling of carbaryl, and use
longer than 10 years. In the previous analysis, estimates were
adjusted for groups of pesticides, including a group for
organophosphate insecticides, but adjustment for specific
pesticides gave different results. Similarly, previous
observations of increased NHL risk associated with use of the
OP insecticides dimethoate and tetrachlorvinphos were neg-
ligible on inclusion of other OP insecticides in the model.
These findings underscore the importance of considering cor-
related pesticide exposures.

Our observation of increased risk associated with the use of
certain OP insecticides, including coumaphos, diazinon, and
fonofos, is consistent with previous analyses of the pooled
data and also corroborates findings of other studies. OP
insecticides are known to cause cyto genetic damage, and
could thereby contribute to NHL aetiology. There are data
from in vitro, animal, and human studies that show effects of
several OP insecticides on the immune system, indicating
another potential mechanism. OP compounds may impair
immune function through pathways involving cholinergic
stimulation, or inhibition of choline acetyltransferase.
However, it is unknown whether such immune effects might be
chemical specific or related to general OP toxicity. Our data do not indi-
cate an aetiological mechanism for NHL common to all OP
insecticides, since increased NHL incidence was associated
only with certain OPs evaluated.

We observed a possible effect of the organochlorine insecti-
cides chlordane and dieldrin. There is some evidence that
chlordane is immunotoxic, causing decreased lymphocyte
function in vitro. The concentration of chlordane in adipose
was higher among NHL cases than controls in a small
control study in Sweden, but a larger study in the
United States found no such association. Although these
chemicals have been banned in the United States, their
continued use in some developing countries, and bioaccumu-
lation of their chemical residues in the food chain, justify
further research on health effects.

Use of the herbicide atrazine was associated with increased
risk of NHL. Increased risk was observed in each of the three
pooled studies separately, but a previous analysis of the
Iowa study found that the risk was diminished on adjustment for
use of OP insecticides and 2,4-D. There have been few other epidemiological studies of atrazine in relation to
NHL. In a cohort of triazine herbicide manufacturing work-
ers, there was an excess number of deaths from NHL (n = 3)
among a group of men with definite or probable exposure;
however, some of the cases worked in triazine related jobs for
short time periods, thus clouding interpretation. A recent
NHL study where cases were further distinguished by presence or absence of the t(14;18) chromosomal transloca-
tion found that the risk of NHL associated with atrazine use
was solely observed among t(14;18) positive cases, suggesting
a cytogenetic mechanism. However, there is only very limited
evidence for genotoxicity of atrazine, although there are no
studies in humans. A small number of studies of atrazine on
immune function in rodents and in vitro suggest a decreased
lymphocyte count and cytokine production following expo-
sure; however, these effects were not always dose dependent or
statistically significant. In our data, there was an indica-
tion of superadditive effects of atrazine in combination with
carbofuran, diazinon, or alachlor. This is a factor to consider in
future studies of this widely used pesticide.

Glyphosate, commercially sold as Roundup, is a commonly
used herbicide in the United States, both on crops and on
non-cropland areas. An association of glyphosate with NHL
was observed in another case-control study, but the estimate
was based on only four exposed cases. A recent study across
a large region of Canada found an increased risk of NHL asso-
ciated with glyphosate use that increased by the number of
days used per year. These few suggestive findings provide
some impetus for further investigation into the potential
health effects of glyphosate, even though one review
concluded that the active ingredient is non-carcinogenic and
non-genotoxic.

Much attention in NHL research has focused on the herbi-
cide 2,4-D as a potential risk factor, and several studies have
observed positive associations with 2,4-D exposure. Whereas
an indicated effect of 2,4-D exposure on NHL was
reported in NCI’s Nebraska and Kansas studies, this analysis of
the pooled data found no association with having ever used
2,4-D. The null association does not result from adjustment for
other pesticides, missing data, or from the hierarchical
regression modelling approach, but is rather due to pooling
data from the Iowa and Minnesota study, in which no associ-
ation of 2,4-D with NHL incidence was observed, with data
from the Nebraska and Kansas studies. The literature on the
relation between 2,4-D and NHL is not consistent. Some
recent studies have reported excess risk among
The study in Nebraska, however, observed that NHL risk increased by number of days per year of 2,4-D use, which were unable to duplicate in the pooled analysis because of lack of such data from the other two studies. It is possible that a more refined metric incorporating frequency of use better captures relevant exposure. Some recent studies may shed light on potential mechanisms of 2,4-D in relation to NHL. A study of 10 farmers who applied 2,4-D and MCPA observed a significant reduction of several immune parameters, including CD4, CD8, natural killer cells, and activated CD8 cells (expressing the surface antigen HLA-DR), and a reduction in lymphoproliferative response. Furthermore, a study of professional 2,4-D applicators in Kansas observed an increase in the lymphocyte replication index following application.

This pooled study of multiple agricultural pesticides provided an opportunity to estimate the effect of each specific pesticide and certain pesticide combinations on NHL incidence, adjusted for the use of other pesticides. Overall, few pesticides and pesticide combinations were associated with increased NHL risk; this has several implications. First, it is consistent with results from bioassays where only a few of the pesticides tested have caused cancer in laboratory animals. Although epidemiological data on cancer risks from exposure to specific pesticides are scant, it also suggests that while some pesticides may present a cancer risk to humans, many, maybe even most, pesticides do not. Second, the fact that there were few associations suggests that the positive results we observed are not likely to be due to a systematic recall bias for pesticide exposures, or selection bias for the subgroup included in the analyses of multiple pesticides. Third, although some of the positive results could be due to chance, the hierarchical regression analysis placed some restriction on the variance of estimates, theoretically decreasing the chances of obtaining false positive results. On the other hand, it is possible that the assumptions for the hierarchical regression are too restrictive and that this has increased the number of false negatives.

Certain limitations of our data hinder the inferences we can make regarding specific pesticides in their association with NHL. Our exposure metric of having ever used a pesticide is rather crude, offering no distinctions based on use by the number of years or the number of days per year. Further exploration of observed associations by more refined exposure metrics is warranted. In addition, this analysis provides no information on the timing of pesticide use in relation to disease onset or in conjunction with the timing of other pesticides used. This has particular relevance in our analysis of “combined pesticide exposures”, in which two pesticides may or may not have been used at the same time or even during the same year. Lastly, if a study subject had a missing value for any one of the 47 pesticides evaluated, that person was excluded from analyses, resulting in analyses on a limited subset (about 75%) of the pooled study population. Although we have no way to evaluate potential bias due to missing data, some assurances are provided by the fact that cases and controls were equally likely to be included in analyses, and that there were similarities between the entire group of study subjects and subjects included in our analyses, in terms of NHL status in relation to demographic factors (table 2). If simultaneous analysis of multiple exposures is to become standard, statistical techniques to impute values for subjects with “don’t know” or missing responses should be further developed in order to prevent biased results.

Despite limitations of our study, certain inferences are possible. Our results indicate increased NHL incidence by number of pesticides used, only for the subgroup of “potentially carcinogenic” pesticides, suggesting that specific chemicals, not pesticides, insecticides, or herbicides, as groups, should be examined as potential risk factors for NHL. In addition, argument against an analysis approach focused on classes or groups of pesticides is provided by the fact that our prior covariates of pesticide classes and groups in the hierarchical regression model were not important predictors of the magnitude of observed pesticide effects. A chemical specific approach to evaluating pesticides as risk factors for NHL should facilitate interpretation of epidemiological studies for regulatory purposes. However, the importance of additionally considering multiple correlated exposures is clear.

**APPENDIX**

Table A1 shows the pesticide combinations considered in analyses of joint and individual exposures.

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<tr>
<th>Insecticides</th>
<th>Insecticide and herbicide</th>
<th>Herbicides</th>
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<tr>
<td>DDT and chlorpyrifosine</td>
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<td>DDT and fly, lice, or tick spray</td>
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<tr>
<td>Lindane and malathion</td>
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Table A1: Pesticide combinations considered in analyses of joint and individual exposures
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