DRAFT-
Lymphoma risk and pesticide use in the Agricultural Health Study

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ABBREVIATIONS

Agricultural Health Study (AHS)

Rate ratios (RR)

95% confidence intervals (CI)

Organochlorine insecticides (OC)

Organophosphate insecticides (OP)

United States Environmental Protection Agency (U.S. EPA)

International Agency for Research on Cancer (IARC)

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Running Title: Pesticides and Non-Hodgkin Lymphoma

Abstract: 247 words: 250 word limit for EHP.

Manuscript, references and tables 1-5: 8,162 including title page etc.. [narrative (abstract & main manuscript 3,717, references 1,411, tables 2942] 7000 word limit for EHP.

> **Comment [a1]:** If we have the message and analyses right we have to cut 1,200 words for EHP. We may want to go to another journal.
>
> **Comment [AB2]:** I suggest go to another journal.

ABSTRACT

Background: Farming and eExposure to pesticides haves been linked to non-Hodgkin

lymphoma (NHL) in a number of previous studies. **Objective**: To evaluate specific pesticides for

associations with NHL and NHL subtypes in a prospective cohort of farmers and commercial

pesticide applicatorsregistered pesticide applicators. **Methods**: We examined NHL incidence in a

prospective cohort of 57,310 licensed pesticide applicators in Iowa and North Carolina from

1993- 2008. Information on pesticide and other agricultural eExposure, information lifestyle and

medical historyhealth histories wasere obtained from a self-administered questionnaires

administered at enrollment (1993-1997) and in a telephone follow-up questionnaire administered

approximately five years later (1998-2004). Poisson regression modeling was used to evaluate

the association between use of specific pesticides and the rate ratios of NHL and NHL subtypes

while adjusting for age and other potential confounding variables. **Results**: A statistically

significant monotonic increase in the risk of overall NHL with increasing life-time exposure-

days for lindane (organochlorine insecticide) was observed and a significant positive non-

monotonic trend was observed for butylate (thiocarbamate herbicide), among 50 pesticides

evaluated. Significantly increasing risk of specific NHL subtypes with increasing life-time

exposure-days of use were observed for lindane, butylate, dicamba, terbufos, alachlor, EPTC,

imazethapyr and trifluralin. The total number of different pesticides used was not associated with

NHL risk overall, but the number of different triazine/triazone herbicides was significantly

associated NHL. Chlorinated and organophosphate insecticide and triazine/triazone herbicides

used, was related to risk in specific NHL subtypes. **Conclusions**: A wide variety of chemically-

distinct herbicides and insecticides were significantly associated with different NHL subtypes.

Most pesticides are associated with only one NHL subtype.

Comment [AB3]: Need to indicate which subtypes were associated with which pesticides.

Comment [AB4]: Mention the chemical class – subtype associations before the specific pesticide associations. Go from the general to the specific.

Comment [AB5]: I am not sure we want to deliver this message. As written it says we believe we found a number of meaningful pesticide – subtype links and that the links were specific. This implies we believe these findings are probably "real." I think the message should be – this is one of the few studies (and the only prospective study I think) that has looked at specific pesticide – subtype associations. Since different subtypes may have different etiologies these findings provide leads for future evaluations.

12/5/2016

12/5/2016

INTRODUCTION

Non-Hodgkin lymphomas (NHLs) are a heterogeneous group of over ~~20~~ different B and T-cell neoplasms affecting the immune system/ lymphatic system arising primarily in the lymph nodes (Swerlow et al. 2008; Shankland et al., 2012). M~~Numerous~~ eta-analyses (Blair et al., 1985; Blair et al., 1993; Beane Freeman, 2009) studies relate lymphohaematopoietic cancers with farming (~~Blair A et al., 1993; Blair and~~ Beane Freeman, 2009), with exposure to pesticides being a hypothesized etiologic agent. Since the 1980s a number of studies have been conducted to evaluate possible links between specific pesticides and NHL. A meta-analysis of 13 case-control studies published between1993-2005 observed an overall significant meta-odds ratio between occupational exposure to pesticides and NHL (OR=1.35; 95% CI: 1.2-1.5). When observations were limited to those that had more than 10 years of exposure the risk increased (OR=1.65; 95% CI: 1.08-1.95) (Merhi M, et al., 2007). While the meta-analysis supports the hypothesis that pesticides are associated with NHL, it did not~~they lack sufficient detail about~~ evaluate exposure to specific pesticide exposure and other information on risk factors for hematopoietic cancers to identify specific causes (Merhi M, et al., 2007). In individual studies of NHL have reported links a number of specific pesticides including phenoxy acid herbicides (Dich et al 1997; Hardell L et al., 1981; Hoar SK et al., 1986; Zahm et al, 1990, Miligi et al, 2006, McDuffie et al, 2001Eriksson M et al., 2008; Burns et al., 2011; 8). ~~and~~ chlorinated pesticides (McDuffie et al, 2001, Colt et al., 2006; Spinelli JJ et al 2007, Purdue et al, 2007, Brauner EV, et al., 2012; Quintana et al., 2004; Coco et al., 2004), organophosphates (Waddell et al., 2001; Hohenadel et al., 2011)dicamba (McDuffie et al., 2001; nitro-derivaties (Miligi et al., 2003); and triazole fungicides and urea herbicides (Orsi et al., 2009)~~have been suggested as causes of NHL.~~ ~~-~~but the evidence has been inconsistent. Little evidence of an association between phenoxy acid herbicides and NHL was observed in New Zealand (Pearce NE et al 1987), Washington state (USA) (Woods JS, et al 1987), or Minnesota and Iowa (USA) (Cantor KP et al, 1992) and little evidence for chlorinated pesticides was observed in a European study that measure pesticide metabolites in plasma samples (Cocco P et al, 2008). A variety of other pesticides have also been associated with NHL but the evidence available to date does not conclusively link a specific pesticide to NHL (Alavanja M et al., 2012; Cocco P et al., 2013). In a study from the six Canadian provinces case-control study, the risk of NHL increased with the number of different pesticides used (Hohenadel K et al., 2011).(I think the flow of this first

Comment [AB6]: References are numbered in the reference list, but not in the test

Comment [AB7]: Is the Beane Freeman article cited here Laura's livestock article? It is the only one in the references

Comment [a8]: Moved the Merhi study up to mention the general association first and later the pesticide class specific-Done

Comment [a9]: Added reference

Comment [a10]: Added reference

Comment [a11]: Added reference

Comment [a12]: Added Purdue

Comment [a13]: Sentence added in reference to Laura's comment to mention other chemical associations by way of citing a review article -Done We are >8,100 words, EHP limit 7,000

Comment [a14]: Cindy suggests cutting down the introduction. --Done

paragraph can be modified to make it clearer. Start with farming, then list pesticides that have been linked to NHL in some studies. This should cover the different pesticides that have been linked to NHL. Then list your review and Cocco (2013) to indicate that the evidence is not conclusive for any pesticide).

In the Agricultural Health Study (AHS) we had the opportunity to evaluate the risk of NHL overall and by cell type by ~~both the association of~~ lifetime use of individual pesticides obtained from enrollment and follow-up questionnaires ~~and the number of different pesticides used and NHL incidence overall and by cell type~~ in a prospective cohort study of licensed pesticide applicators in Iowa and North Carolina.

~~We evaluated potential confounders including a previous history of malignant disease (Wang et al., 2007), different immunosuppressive states (Simard JF, et al., 2012), and body mass index (BMI) (Patel et al., 2013) and other factors observed to be associated with NHL in the AHS cohort.~~

MATERIALS & METHODS

Study Population

The AHS is a prospective cohort study of 52,394 licensed private pesticide applicators in Iowa and North Carolina and 4,916 licensed commercial applicators from Iowa. The cohort has been described in detail (Alavanja et al., 1996). Briefly, the cohort included individuals seeking licenses for restricted use pesticides from December 1993 through December 1997 (82% of the target population enrolled). The protocol was approved by relevant institutional review boards. We obtained cancer incidence information by regular linkage to cancer registry files in Iowa and North Carolina. In addition, we matched cohort members to state residential mortality registries and the National Death Index to identify vital status, and to address records of the Internal Revenue Service, motor vehicle registration files, and pesticide license registries of state

Comment [a15]: Infor about cancer registries deleted as suggested by Laura

agricultural departments to determine residence in Iowa or North Carolina. The current analysis

included all incident primary non-Hodgkin lymphomas (*n*=333) diagnosed from enrollment

(1993-1997) through December 31, 2008. We censored follow-up at diagnosis of NHL or any

other cancer, date of death, movement out of state, or December 31, 2008, whichever was earlier.

Person-years of follow-up summed to 714,770.

Tumor Characteristics

Information on tumor characteristics was obtained from state cancer registries. Cases were

classified into 5 groups of cell types according to the Surveillance Epidemiology and END

Result (SEER) coding scheme (http://seer.cancer.gov/lymphomarecode) SEER recodes of cell

type are listed in appendix 1.-_The first group (n=117) includes chronic B-cell lymphocytic

lymphomas (CLL) /small B-cell lympocytic lymphomas (SLL) [n=101], and mantle-cell

lymphomas (MCL) (n=16). The second group includes 94 diffuse large B-cell lymphomas; the

third group includes 53 follicular lymphomas. There were 34 'other B-cell lymphomas'

consisting of a diverse set of B-cell lymphomas including precursor acute lymphoblastic

leukemia/lymphoma (n=4), Waldenstrom macro globulinemia (n=2), lymphoplasmacytic

lymphoma (n=2), hairy-cell leukemia (n=6), B-cell non-Hodgkin lymphoma not otherwise

specified(n=6), Burkitt lymphoma/leukemia (n=1), and extra-nodal Marginal Zone Lymphomas

(MZL)/ MALT type/ Nodal MZL(n=13). The fifth grouping included 35 cases consisting of T-

cell lymphomas (n=12) and non-Hodgkin lymphoma of unknown lineage (n=23). The fifth

grouping was excluded from cell type-specific analyses because of small numbers of cases with

identified cell types. Although multiple myeloma (MM) (n=77) and plasmacytomas (n=6) are

Comment [lbf16]: Did you remove prevalent cancers? Does this mean that you also included second cancers if they were NHL? Eg. If someone had an incident prostate cancer and then was diagnosed with an NHL, do you consider them to be an NHL case? Or, did you censor them at their diagnosis of prostate cancer? I would remove all prevalent cancers (n=1,074) and only include first primary NHL diagnoses, censoring at diagnosis of any cancer.

Comment [a17]: Yes, we removed all prevalent cancers and included only primary NHL cases - clarification made in sentence -no other change necessary.

Comment [a18]: Cindy would like the 5 groups to be named. They do not have names so it is may be inappropriate to give them non-standard names. I gave the SEER recode number in the table as a means of identification

Comment [lbf19]: Since you present them in the appendix, I would suggest taking them out of the text here—it'shard to read with all these numbers. You could also add them to the relevant tables under the specific sub-types

Comment [a20]: SEER recodes deleted as recommended by Laura

now classified as a type of non-Hodgkin lymphoma (Morton LM et al., 2007), the pesticide

literature prior to 2008 (including the AHS) examined multiple myeloma (and plasmacytomas)

separately. (AB - I wonder if the decision not to include myeloma might seem inconsistent with

our decision to go with the new definition of NHL. We say we are changing the cancers we

characterize as NHL to fit the new definition, but then we promptly say we are not going to

follow the new definition for all of the new inclusions, i.e., myeloma will not be included. It is

inconsistent and seems gerrymandered. The reason given also does not seem adequate (myeloma

has been analyzed separately for pesticides) because there have also been studies that looked a

pesticides and chronic lymphocytic leukemia, yet it is included as NHL here. Not sure what to

do but the whole thing just seems messy. We need to talk about this on an EC call.) We continue

to examine MM separately to facilitate comparisons to the previous literature. We provide

supplemental table 7 which shows NHL risk (previous definition, ICD-O-3) and lifetime use of

individual pesticides (AB - I think to make clear the possible the impact, or lack of it, of

changing the NHL definition. Table 7 needs to include ORs from both definitions of NHL for

the same length of follow up. This would make it clear that any difference regarding specific

pesticides would be due to differences in disease classification.   A comparison of cell types in

the previous (ICD-O-3) and recent Inter Lymph hierarchical classification of NHL is provided in

appendix 2.

> **Comment [a21]:** We added the phrase 'prior to 2008" to avoid a large increase in citations which would contribute an additional 90 words or more (approximately).
>
> **Comment [lbf22]:** You will need to cite these papers in the discussion.

Exposure Assessment

Information on lifetime use of 50 pesticides was captured in two self-administered questionnaires (http://aghealth.org/questionnaires.html) completed during cohort enrollment (Phase 1). All 57,310 applicators completed the first enrollment questionnaire, which inquired about ever/never use of the 50 pesticides, as well as duration (years) and frequency (average days/year) of use for a subset of 22 pesticides. In addition, 25,291 (44.1%) of the applicators returned the second (take-home) questionnaire, which inquired about duration and frequency of use for the remaining 28 pesticides.

A follow-up questionnaire, which ascertained pesticide use since enrollment, was administered about five5 years after enrollment (1998-2003, Phase 2) and completed by 36,342 (63%) of the original participants. For participants who did not complete a Phase 2 questionnaire (20,968 applicators, 37%), a data-driven multiple imputation procedure based on logistic regression and stratified sampling was employed to impute likely use of specific pesticides in Phase 2 (Heltshe et al.,2012) which used logistic regression and stratified sampling to impute the use of specific pesticides in phase 2.

> **Comment [a23]:** Description of imputation procedure shortened considerable per suggestion - Done

Information on pesticide use obtained from Phase 1 and Phase 2 interviews was used to construct two individual pesticide exposure metricsWe used 2 exposure metrics to assess cumulative exposure to each pesticide: (i) lifetime days of pesticide use, i.e. the product of years of use of a specific pesticide and the number of days used per year; and (ii) intensity-weighted lifetime days of use, i.e. the product of lifetime days of use and a measure of exposure intensity. Intensity of exposure was derived from an algorithm using questionnaire data on mixing status, application method, equipment repair and use of personal protective equipment (Coble et al. 2011).

> **Comment [a24]:** Dropped Dosemeci as suggested. Dosemeci is referenced in Coble et al. No additional changes made to this section.

We analyzed total NHL risk and specific cell type NHL by pesticide classes, individual

pesticides use, and by the number of different pesticides used within a chemical/functional class

and the total number of different pesticides used in a working lifetime.

> **Comment [a25]:** Analysis requested by Aaron.

Statistical Analyses

We used Poisson regression to calculate rate ratios (RR) and 95% confidence intervals (95% CI)

for overall NHL and four NHL subtypes in relation to pesticide use. Data were obtained from

AHS data release versions P1REL201005.00 (for Phase 1) and P2REL201007.00 (for Phase 2).

We evaluated pesticides with 15 or more exposed cases of total NHL, thereby excluding

aldicarb, aluminum phosphide, carbon tetrachloride/carbon disulfide, dieldrin,(Might look

specifically at dieldrin even though it is below your cutpoint because it has been linked to NHL

in the past.) ethylene dibromide, maneb, parathion, 2,4,5-TP, trichlorofon, and ziram (This list is

different than that provided in the first draft. Why the change?). For each pesticide analyzed, we

> **Comment [a26]:** Correction suggested by Cindy.

categorized exposure into non-exposed and tertiles of exposure based on the distribution of

exposed cases. A first set of rate ratios were adjusted for age and a second set of rate ratios were

adjusted for age and other statistically significant (α=0.05) predictors of NHL in the AHS. We

evaluated several lifestyle and demographic measures and identified the following as potential

confounding variables: age at enrollment (<40, 40-49, 50-59, 60-70, $\geq$70), race (White, Black,

other, missing), state (Iowa, North Carolina), family history of lymphoma in first-degree

relatives (yes, no, missing), body mass index (BMI <25, 25-<30, $\geq$30), cigarette smoking history

(never, former, current, missing), alcohol consumption per week (none, < once per week, $\geq$ once

> **Comment [a27]:** We analyzed BMI and it was not a confounder. We added to table 1.
>
> We examined available pack-years and there was no confounding.

per week) and several occupational exposures (i.e., number of livestock, poultry, acres planted, welding, diesel use, number of different pesticides used, and pesticides shown to be associated with NHL in the current analysis)(So all of these factors all significantly associated with risk of NHL here? From Table 1 it looked like most of the other adjustment factors were not significantly associated with NHL.). Tests for trend used the midpoint value of each exposure category, and the Likelihood Ratio tests were used to assess differences between strata (p-interaction). All tests were two-sided and conducted at the α=0.05 level. (I do not quite understand the rationale for the tables. The above indicates ORs were adjusted for several factors. The first set of tables say they are "age adjusted." The supplemental tables have more extensive adjustment. If it is important to adjust for factors other than age, why are these analyses in supplemental tables. If they are not important, why are they done at all. In any case I am not sure you need two tables. Often you see age adjusted and more extensively adjusted ORs in the same table. That would be better because it allows the reader to see if the additional adjusment made any difference in the ORs.)

We also conducted various sensitivity analyses. We analyzed Phase 1 data alone to assess the impact of the additional information collected or imputed from Phase 2. We also explored the effect of lagging exposure data 5 and 15 years since recent these recent exposures may not have had an impact on the development of cancer. Reported results show un-lagged exposure data from Phase 1 and Phase 2 combined for cumulative intensity-weighted and un-weighted days of use. (AB - I think we should start doing some analyses by type of protective equipment used. I know it is supposedly taken into account in the intensity score, but it would be informative if there were differences in OR by different protective approaches. It could be used with number

> **Comment [AB28]:** Probably need to add you chose to show these data because the other analyses had not impact.

of days of pesticide use where it has not been taken into account. It provides information that is useful to farmers and extension agents.)

RESULTS

The risk of NHL increased significantly and in a near monotonic fashion with age in the AHS cohort (Table 1). The age-adjusted risk of NHL is significantly lower in NC compared to IA and among current smokers compared to nonsmokers. Other demographic factors including gender, license type, educational level, alcohol consumption, BMI, and a family history of lymphomas were not significant risk factors of NHL in this cohort. We evaluated whether other occupational factors were associated with NHL. Of those evaluated, the number of livestock on the farm and whether cohort members drove farm equipment with diesel engines significantly increased risk of NHL.

The age-adjusted risk of NHL and NHL subtypes from possible exposure to~~associated with~~ 16 insecticides and herbicides ~~associated with NHL or NHL subtypes or~~ previously associated with NHL are listed in Table 2 (age-adjusted risk of NHL for all other evaluated pesticides in the AHS may be found in supplemental table 1 and fully-adjusted risk of NHL in supplemental table 2). Lindane, an organochlorine insecticide, is the only pesticide showing a monotonic rise in overall NHL risk with increasing life-time days of use (p trend=0.003) and intensity-weighted lifetime days of use (p trend=0.05). Butylate, a thiocarbamate herbicide, showed a significant increasing trend in life-time days of use (p trend=0.004) and intensity-weighted lifetime days of

Comment [lbf29]: I think that you can cut down on reporting the results that are presented in the tables, but I would like to see some more results in the text that aren't in the tables. E.g., what happens when you put both lindane and butylate in the model? What is frequency of use of chemicals, etc.?

Comment [a30]: Narrative now mentions that there is no apparent confounding between lindane and butylate. Only pesticides with 15 or more exposed cases are listed in the tables for analysis. Space limits more extensive discussion of frequency of pesticide use in the AHS, although this can be ascertained from use in controls.

Comment [AB31]: The Methods says they were significant risk factors.

Comment [a32]: Previous table 2 deleted and discussion of potential confounding variables shortened as suggested by Laura.

Comment [t33]: It's not clear why you are showing these 22 pesticides

Comment [AB34]: I think it would help the reader if you presented ever/never results for all pesticides analyzed. This would set the stage for the exposure response analyses. You would largely include only those pesticides with some excess in the ever category in the trend analyses. Now it is not clear why some are listed and others are not. As of now the Results just sort of jump into detailed exposure-response analyses.

Comment [t35]: If there's not a big difference between age and fully adjusted models I would delete fully adjusted

use (p trend=0.04) but the associations were not monotonic. Some other pesticides -had

individual point estimates that were significant but did not show a significant pattern of

increasing risk with increasing exposure. Lindane and butylate did not show confounding with

each other when they were put in the same model. The significant increasing trend of NHL risk

with exposure to lindane and butylate was also not changed with the adjustment days of all other

pesticide use, nor with adjustment for days of use of organophosphate insecticides, carbamate

insecticides, other insecticides, triazine/triazone herbicides, other herbicides, fungicides, or

fumigants. The results from fully adjusted risk of NHL (i.e., Age [<45,45-49,50-54,55-59,60-

64,65-69,≥70], smoking status(current, former, never), number of livestock (0,,<100,100-

999,>999), drove diesel tractor (<weekly,≥weekly, state (NC, IA) [data not shown were

comparable to the age-adjusted risk]. Also, these unlagged results were comparable (not shown)

to 5 year and 15 year lagged exposures, therefore we present RRs for unlagged exposure only.

Comment [lbf36]: I find these lists of RR and 95% CI throughout to be a bit hard to read, plus they take up a lot of words. I think it would be better to provide more information in the text about results that aren't presented in the tables. E.g., for lindane,, how many people reported using it in Phase 1 vs. Phase 2 as it was approaching phase out. This will help to set the stage for putting the results in context later in the discussion.

Comment [a37]: Point estimates deleted to reduce word count as recommended.

Comment [a38]: Need to define the pesticides included in each group appendix 2-done

Comment [AB39]: Supplement Table 2 does show the fully adjusted model, right?

We also analyzed Phase 1 data only to assess the impact of the additional information collected

or imputed from Phase 2, although there was an increase in precession including phase 2

estimates, no meaningful change was observed in the risk estimates. ,

Comment [lbf40]: I don't think you mention this in the results.

Comment [lbf41]: How did you choose the 22 pesticides in this table? Why not 28 as in table 2? Regardless, need to explain rationale/criteria for presenting some and not others

The risk of the four major categories of B cell lymphomas by number of days of use of

individual pesticide is shown in Table 3. For the CLL/SLL/MCL group of lymphomas, dicamba,

a carbamate herbicide (p trend=0.03) and butylate, a thiocarbamate herbicide (p trend=0.04), and

lindane, a chlorinated insecticide, (p trend=0.005) were observed to have a significant increased trend of risk with increasing lifetime-days of use. Metribuzin, a triazone herbicide, (p trend=0.06) had a near significant relationship with this group of lymphomas. Carbaryl, a carbamate insecticide, was observed to have a significant inverse relationship (p trend=0.007).

> **Comment [a42]:** Metribuzin, is a triazone herbicide not a triazine herbicide.-corrected

A significant increase in the risk of Other B-cell Lymphomas was associated with the number of life-time days of use of six herbicides and one insecticide: alachlor (p trend=0.02); butylate, (p trend=0.0499); dicamba (p trend=0.02); EPTC use (p trend=0.01): imazethapyr (p trend=0.03); trifluralin use (p trend=0.01); and terbufos (p trend=0.01) (Table 3).   Risk of other B-cell lymphomas was also associated with a non-significant elevated risk for the low and medium exposure categories and was significantly associated with the highest category of exposure for atrazine use (RR=3.6 [95% CI: 1.2-10.8]; p trend=0.06).

> **Comment [AB43]:** Since insecticides come before the herbicides in the table discuss terbufos before the herbicides here in the text.

No pesticide had a significant exposure response pattern with either diffuse large B-cell lymphomas or follicular B-cell lymphomas, although significant point estimates of risk were identified for butylate, terbufos, and methyl bromide.

> **Comment [AB44]:** Glyphosate had a significant trend for diffuse and chlordane and malathion were borderline. EPTC and butylate had borderline trends for follicular.

The number of different triazine/triazone herbicides used, adjusted for age and lifetime days of use of triazine/triazone herbicides was associated with a significant increasing trend with total NHL risk (p trend=0.04) (Table 4). No other chemical/functional class showed a significant pattern of NHL risk.   The association between the age-adjusted risk of the four NHL B-cell sub-types and the total number of different pesticides by chemical class used is presented in Table 5. For the CLL/SLL/MCL group of lymphomas, the number of different chlorinated insecticides (p

> **Comment [AB45]:** Not sure what is meant here. Triazine/triazones adjusted for triazine/triazone?

trend=0.02) and the number of different organophosphate insecticides (p trend= 0.03) showed a

significant trend of increase risk with increasing number of insecticides from these

chemical/functional classes. Similar trends were observed for the number of different

Comment [a46]: Typo corrected as suggested

triazine/triazone herbicides (p trend=0.07), other herbicides (p trend=0.06) and fungicides (p

trend=0.11) but the trends were not statistically significant.

For either diffuse large B-cell lymphomas or follicular B-cell lymphomas, no pesticide class had

a significant pattern of increasing risk with number of pesticides used, although a significant

decreased risk with increasing number of pesticides used was observed for chlorinated

pesticides (p trend=0.05) and other insecticides (p trend= 0.04) with the diffuse large B-cell

lymphoma group.

For the other B-cell lymphoma group, the number of different triazine/triazone herbicides (p

trend=0.006) and the number of different acetamide herbicides (p trend= 0.009) both were

observed to have a significant trend of increasing risk with increasing days of use. Similar trends

were observed for the number of different carbamate herbicides (p trend=0.11) and 'other

herbicides' (p trend=0.06) but these trends were not statistically significant.

Comment [a47]: These will be adjusted for total number of exposure days to chemicals in this class.- Done

Comment [lbf48]: Throughout , you need to reference the previous analyses of AHS data and specific chemicals. You reference Mark Purdue's paper in the intro, but no others

Comment [a49]: See changes made throughout to address these points.

Comment [lbf50]: *This paper just came out and used the most recent definitions of NHL. Actually supportive of these AHS findings. Occup Environ Med*2013;**70**:91-98 doi:10.1136/oemed-2012-100845

Lymphoma risk and occupational exposure to pesticides: results of the Epilymph study

DISCUSSION

AB – I think we need to start with the big picture comparisons first. I suggest the order for the

discussion should be: (1) Ever/never comparisons for NHL overall. (2) Then move to trends for

NHL overall. (3) Then trends for subtypes. (4) Next have a discussion of how the change in

NHL definition might affect comparison of our results with those from the literature. (5) Comparison of these results with literature pesticide by pesticide (or pesticide group). (6) Strengths and limitations. (7) Conclusions.

In this analysis, we observed a significant increase in the risk of overall NHL with two pesticides, lindane an organochlorine insecticide no longer registered for use in the U.S and butylate a thio-carbamate herbicide widely used in the United States and other countries.   Our findings for total NHL are inconsistent with a number of other studies which found increased risks with a variety of chlorinated and organophosphate insecticides and triazine and phenoxy acid herbicides (Dich et al 1997; Hardell L et al., 1981; Hoar SK et al., 1986; Zahm et al, 1990). However, we did find significantly increasing risk of specific NHL subtypes with increasing life-time exposure days of individual pesticides use. Butylate and dicamba, carbamate herbicides, and lindane, a chlorinated insecticide, were observed to have a significant increasing risk of the CLL/SLL/ MCL lymphomas sub-types with increasing lifetime-days of use. (This first paragraph just sort of jumps into the subtype/specific pesticide links. I think a smoother opening paragraph would be to comment on ever/never for specific pesticides, then exposure trends by specific pesticide, and finally exposure trends by NHL subtypes. This summary of the findings should then be followed by a discussion of the effects, or lack of them, from the change in the definition of NHL. Then the findings from this analysis can be compared to the previous literature.)

 Other B-cell lymphomas are a varied group including 8 different cell types of lymphomas. Excess risks of other B-cell lymphomas were observed for several widely-used pesticides including: the organophosphorous insecticide terbufos, for alachlor, an acetanilide-herbicide, imazethapyr, an imidazoline-herbicides, and trifluralin, a dinitroaniline-herbicide, and for

Comment [lbf51]: What was percentage of use in P1 vs. P2? If people aren't still using, but we still have excess then we need to explore this further. Do we see stronger effects in earlier time periods? Do we expect this to not be aproblem since lindane is no longer on the market? Or, is this going to be a persistent problem? We also need to say something about when lindane was taken off the market.

Comment [AB52]: There is a bit of an inconsistency here. Says there is an excess for lindane, but these findings differ from earlier work that saw excesses for a variety of chlorinated insecticides. Lindane is a chlorinated insecticide.

Comment [lbf53]: This sounds like all the other studies are positive, which isn't actually true. I think that you need to have a more in-depth discussion of specific pesticides and findings.

Comment [AB54]: I do not think we can make this statement of differences with past studies without immediately including a discussion of the difference in disease definition and whether or not this might account for the differences/or similarities with past research. Probably need to start the discussion with comparison of results of analyses for the two different definitions to orient the reader regarding what changes occurred simply because of the change in definition. Then this should be followed with a discussion of findings from an ever/never comparison. Then you go to trends.

butylate, dicamba, and, EPTC which all belong to the family of carbamate herbicides. The triazine herbicides atrazine and cyanazine had specific point estimates that were elevated but the trends of risk were neither significant nor monotonic. ~~Metribuzin, a triazone herbicide, had too few other B-cell lymphomas to evaluate.~~ The wide array of functional groups and chemical classes that are associated with an increased risk of Other B-cell lymphomas does not suggest a single known mechanism of action. Multiple pathways seem to be involved.

In a Swedish case-control study a significant excess risk of NHL was associated with the phenoxy herbicide MCPA and glyphosate (Ericksson et al., 2008). 2,4-D and 2,4,5-T (2,4,5-trichlorophenoxyacetic acid) have been banned from Sweden and could not be evaluated (Eriksson M et al.,2008). In our study we could not evaluate MCPA but found no excess risk of NHL or its subtypes with the use of glyphospate, 2,4-D or 2,4,5-T.

In a population-based case-control study conducted in six Canadian provinces increased risk to NHL was associated with a positive family history of cancer both with and without pesticide exposure [OR=1.72 (95% CI 1.21-2.45) and OR=1.43 (95% CI: 1.12-1.83), respectively] (McDuffie HH, et.al, 2009). In this same case-control study six pesticides/pesticide analytes also showed a significant association with NHL [beta-hexachlorocyclohexane, *p, p'*- dichloro-diphenyl-dichloroethylene (DDE), hexachlorobenzene, mirex, oxychlordane and trans-nonachlor] (Spinelli et al., 2007). The strongest association was found for oxychlordane, a metabolite of the pesticide chlordane (highest vs. lowest quartile OR=2.68, 95% CI 1.69-4.2). These finding were not confirmed in a recent analysis of plasma samples from 174 NHL cases and 203 controls from France, Germany and Spain. The risk of NHL did not increase with

Comment [AB55]: I am not sure you want to talk about pathways. This assumes that the links observed here are real. Perhaps the wide array of function groups and chemical classes is just noise. You might try to dissect the individual histologies in this "Other B-cell" to see if any one stands out with a particular pesticide

Comment [AB56]: Check to make sure 2,4-D was banned during the time of pesticide use by people in Eriksson's study. My impression is that it just was not used much in Scandinavia, but was not banned until later

Comment [AB57]: Not sure we need this sentence. Certainly should not lead with it because family history was not evaluate our NHL study.

plasma levels of hexachlorobenzene, beta-hexachlorobenzene or DDE (Cocco P et al., 2008). In our study NHL was associated with lindane but no excess risk was observed for chlordane and no excess risk was observed among those with a family history of lymphoma. The other chemicals evaluated in the Canadian six province study were not evaluated in the AHS cohort.

New evidence linking NHL with chlorinated pesticide use (Brauner EV, et al., 2012) and a study linking the number of different pesticides used with NHL (Hohenadel K et al., 2011) are somewhat supported by our findings in the AHS cohort. While the number of different pesticides used overall was not associated with NHL risk in the AHS, a significant increase in the CLL/SLL/MCL sub-group of NHL was observed with the number of different chlorinated pesticides used and the number of different organophosphate chemicals used. A similar pattern of increase risk was observed in the other B-cell lymphoma subgroup of NHL with an increasing number of triazine/triazone pesticides used.

> **Comment [lbf58]:** Expand to discuss what these actually show—similar to ours? Not similar to ours?
>
> **Comment [a59]:** Modified sentence in response to comment

> **Comment [AB60]:** I have a hard time following the discussion. I wonder if it might not be clearing if the link to previous literature is done pesticide by pesticide. Then you could indicate what is found here and follow that with findings for that pesticide in the literature. This means previous studies could be cited numerous times, but it would be easier to see the relationship between our findings and those from other studies for individual pesticides.

A strength of this investigation is that a relatively large population of licensed pesticide applicators provided reliable information regarding their pesticide application history (Blair et al. 2002; Coble et al. 2011, should cite Jane's paper on reliability also). In the AHS, a priori derived algorithm scores that incorporated several exposure determinants were found to be able to used to predict urinary pesticide levels (Thomas et al., Coble 2011). Few? studies of pesticide use with a prospective design have been large enough or had sufficiently detailed exposure information, to evaluate the potential link between NHL, NHL subtypes and specific pesticide exposures (Are there any other prospective studies that could look at specific pesticides?). Also, because occupational pesticide users are seldom exposed to a single agent, we controlled for the total pesticide exposure days and total pesticide exposure days by chemical/functional class and found

no meaningful change in the associations. Additionally, potential confounding of pesticides by other occupational exposures was reported to be minimal in the AHS (Coble et al., 2002) and adjustment for various agricultural exposures did not fundamentally change calculated RR for NHL from various pesticide exposures. – (Mention ability to control of possible non-occupational confounders, use of incidence rather than mortality)

> **Comment [AB61]:** I have a real problem with this approach and the interpretation of the findings from it. Is total pesticide exposure days associated with NHL? If not, then it clearly does not control from individual pesticides because some individual pesticides are associated with NHL. This would work if most pesticides were associated with NHL, but most are not Thus, this total pesticide scale is so water down that it cannot control for anything. This said, I doubt that there is confounding among the pesticides, but we cannot us this approach as evidence for no confounding. The most straightforward, and usual approach, is to adjust the RR for one pesticide by each individual pesticide thought to be a potential confounder

Although this is a large prospective study, there are limitationslimitations should be acknowledged. Cell-type information in the AHS was obtained from the cancer registry database and did not involve pathologic re-review of diagnostic slides. Other limitations including a small number of exposed cases for certain chemical of interest.

> **Comment [AB62]:** I do not think I would list this These are data that are used to establish cancer patterns by the NCI I think the reliability/validity of the diagnosis from tumor registries is well accepted

Need to add a paragraph of exposure assessment. Discuss the information on our exposure scale in relation to the monitoring work. Discuss the likely magnitude of misclassification and its likely impact on the estimates of RR. Might also want to say something about multiple exposures. Cannot look only at a single exposure. This is an issue raised by critics. Just as well address it here.

AB – This next paragraph seems part of the conclusions. I would try to merge it with the conclusions paragraph.

In our study no pesticide had a significant exposure response pattern with either diffuse large B-cell lymphoma or follicular B-cell lymphoma, although significant relativepoint estimates of risks were identified for butylate (a carbamate herbicide), terbufos (an organophosphate insecticide), and methyl bromide (an organic halide)(Not clear what you are trying to say here – No exposure-response pattern, but significant RRs.). Previously, NHL subtypes with t (14;18) translocations were associated with the chlorinated insecticides dieldrin, lindane, and toxaphene

> **Comment [AB63]:** But there were borderline trends for these subtypes

and the triazine herbicide atrazine (chiu BCH et al., 2006 and Chiu BCH and Blair A 2009). We were unable to evaluate translocations in this analysis. Although it is possible that t (14;18) translocations are an initiating event of a causative cascade leading to an NHL subtype, follicular lymphoma (FL), much more work needs to be done to establish this etiologic pathway. (Not sure mentioning t(14;18) is worthwhile here. This study sheds no light on this issue. This point might be combined in a paragraph that discusses future research, but it does not fit by itself)—.

Conclusion:

(I do not think you should start the conclusion with comments about subtypes. Start with NHL overall. In summary, our results suggest that there is subtype specificity in associations between NHL and pesticides exposures. The varying etiology of NHL sub-types may have masked real associations between pesticides and NHL in previous studies where NHL sub-type information was not available (Not sure how varying etiology by subtype would mask associations with NHL overall. If each study had all the subtypes then either the subtype links power through to overall NHL or they do not. The reverse is true. Looking only at NHL overall would hide associations with specific subtypes.). Although the epidemiological evidence for associations between specific pesticides and specific cell types is growing (probably should cite the other papers that have information on specific pesticides and subtypes), the observation that pesticides of different chemical and functional classes and different known toxicological properties are associated with the same cell type (Is it know that different pesticides are associated with the same cell type?) indicates that relatively little is known about the biological/toxicological mechanisms by which these compounds may be contributing to this disease. Cautious interpretation of these results is advised since the number of exposed-cases for

each subgroup of NHL in the AHS is still relatively small. (Overall I think the conclusion is too

strong. It seems to say that the links between specific pesticides and certain NHL subtypes

observed in this study are real and this is why we do not understand the mechanisms for

pesticides causing cancer. The findings here are interesting, but they are leads to be confirmed.

I do not think they are strong enough to be making statements about what this says about

mechanisms. I think the tone should be – few studies have been able to look at specific

pesticides and NHL subtypes. What we found is interesting. Need to see if other studies will

have similar findings. I may be in a minority about this, but I would like to have a discussion

about this on an EC call.)

> **Comment [AB64]:** This affiliation does not cover ally coauthors. Don't we usually put some comment of appreciation to the participants in the AHS in the acknowledgements?

> **Comment [a65]:** Get correct contract numbers here.

The authors have no conflicts of interest in connection with this manuscript.

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Table 1. Baseline characteristics of AHS study participants in the NHL incidence analysis from 1993 through 2008				
	All NHL cases	Cohort Person-years.	RR[1]	95% CI
Age at Enrollment				
<45	51	368,766.80	1.0 (ref)	
45-49	34	88,648.48	2.8	1.8-4.3
50-54	51	75,781.37	4.9	3.3-7.2
55-59	59	67,981.37	6.3	4.3-9.1
60-64	46	53,346.73	6.2	4.2-9.3
65-69	46	34,532.71	9.6	6.5-14.4
≥70	46	25,713.12	12.9	8.7-19.3
Gender				
Male	328 (ref)	695,190.90	1.0 (ref)	
Female	5	19,579.34	0.5	0.2-1.3
State				
IA	213 (ref)	461,697.24	1.0 (ref)	
NC	120	253,072.27	0.8	0.6-0.97
License type				
Private	318	652,562.25	1.0 (ref)	
Commercial	15	62,207.89	0.9	0.5-1.5
Education				
<12 yrs.	57	61,656.39	1.0 (ref)	
HS/GED	143	326,344.92	0.8	0.6-1.1
>12 yrs.	121	297,437.85	1.0	0.7-1.4
Smoking Status				

Never	165	371,929.66	1.0 (ref)	
Former	127	203,445.28	0.93	0.7-1.2
Current	29	116,254.87	0.6	0.4-0.9
Body Mass Index (BMI)				
<25	58		1.0 (ref)	
25-<30	138		1.1	0.8-1.5
≥30	61		0.94	0.7-1.4
Alcohol consumption per week				
None	128	212,928.70	1.0 (ref)	
<once a week	89	217,015.35	1.0	0.8-1.4
≥once a week	89	240,745.51	1.0	0.8-1.4
First degree relative with lymphoma				
No	291	639,748.82	1 (ref)	
Yes	7	12,606.85	1.1	0.5-2.4

[1] All variables except age are age adjusted (<45,45-49,50-54,55-59,60-64,65-69,≥70)

[2] Numbers do not sum to totals (333 cases, 714,770 person-years) due to missing data.

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Table 2. Pesticide exposure (Lifetime Days [LD] & intensity weighted Lifetime Days [IWLD]) and the age-adjusted risk of NHL incidence (1993 through 2008)				
Insecticides				
Pesticide (chemical-functional class) [median days of lifetime exposure for each category]	NHL Cases	RR[1] (95%) by Total Days of Exposure	NHL Cases	RR[1] (95% CI) Intensity-weighted days of exposure
Carbaryl **(carbamate-insecticide)**				
None	81	1.0 (ref)	81	1.0 (ref)
Low [8.75]	31	0.9 (0.5-1.5)	27	0.9 (0.5-1.5)
Medium [56]	23	0.7 (0.4-1.1)	26	0.8 (0.5-1.4)
High [124.5]	25	0.9 (0.6-1.5)	26	0.8 (0.5-1.3)
		P trend=0.86		P trend=0.47
Malathion **(organophosphorous-insecticide)**				
None	55	1.0 (ref)	55	1.0 (ref)
Low [8.75]	46	1.0 (0.7-1.5)	37	1.0 (0.7-1.6)
Medium [42.75]	28	0.7 (0.4-1.2)	38	0.8 (0.5-1.3)
High [103.75]	36	1.0 (0.7-1.6)	35	0.91 (0.6-1.4)
		P trend=0.74		P trend=0.71
Terbufos **(organophosphorous-insecticide)**				
None	157	1.0 (ref)	157	1.0 (ref)
Low [24.5]	58	1.4 (1.1-1.9)	43	1.3 (0.92-1.8)
Medium [56]	38	2.0 (1.4-2.8)	43	2.0 (1.4-2.8)
High [116]	34	1.2 (0.8-1.7)	42	1.2 (0.9-1.8)

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		P trend=0.23		P trend=0.19
Chlorinated Insecticide				
Chlordane **(Chlorinated Insecticide)**				
None	223	1.0 (ref)	223	1.0 (ref)
Low [8.75]	23	0.9 (0.6-1.4)	13	1.1 (0.7-2.0)
Medium [20]	6	1.7 (0.8-3.8)	13	0.9 (0.5-1.6)
High [38.75]	9	0.8 (0.4-1.6)	12	0.9 (0.5-1.6)
		P trend=0.89		P trend=0.77
DDT **(Chlorinated Insecticide)**				
None	194	1.0 (ref)	194	1.0 (ref)
Low [8.75]	20	0.8 (0.5-1.3)	19	0.9 (0.6-1.5)
Medium [56]	18	0.9 (0.6-1.6)	18	0.8 (0.5-1.4)
High [116]	17	1.5 (0.9-2.5)	18	1.4 (0.8-2.2)
		P trend=0.14		P trend=0.28
Lindane **(Chlorinated Insecticide)**				
None	209	1.0 (ref)	209	1.0 (ref)
Low [17.75]	11	1.0(0.5-2.0)	10	1.1(0.6-2.0)
Medium [56]	10	1.2(0.6-2.3)	11	1.4(0.7-2.6)
High [116]	10	2.7(1.4-5.1)	9	1.9(0.95-3.7)
		P trend=0.003		P trend=0.04
Herbicides				
Alachlor **(acetamide-herbicide)**				
None	138	1.0 (ref)	138	1.0 (ref)

Comment [lbf66]: I like this heading—suggest using them throughout the tables and then deleting the chemical class in parentheses

Low [24.5]	65	1.0 (0.7-1.3)	53	1.0 (0.7-1.3)
Medium [116]	49	0.9(0.6-1.2)	50	0.9 (0.6-1.2)
High [224.75]	43	1.3(0.9-1.9)	51	1.2 (0.9-1.7)
		P trend=0.12		P trend=0.19
Atrazine **(triazine-herbicide)**				
None	85	1.0 (ref)	85	1.0 (ref)
Low [38.75]	88	1.2(0.8-1.7)	79	1.1(0.8-1.6)
Medium [114.5]	72	1.3(0.96-1.9)	78	1.4(1.0-2.0)
High [224.75]	77	1.2(0.9-1.6)	78	1.2(0.8-1.6)
		P trend=0.56		P trend=0.68
Butylate **(thiocarbamate-herbicide)**				
None	107	1.0 (ref)	107	1.0 (ref)
Low [24.5]	22	1.0(0.6-1.5)	16	0.9(0.5-1.5)
Medium [56]	18	2.8(1.7-4.7)	16	2.1(1.2-3.5)
High [56]	7	1.1(0.5-2.4)	15	1.5(0.9-2.6)
		P trend=0.004		P trend=0.04
Dicamba **(benzoic-herbicide)**				
None	121	1.0 (ref)	121	1.0 (ref)
Low [20]	66	1.3(0.94-1.8)	56	1.2(0.9-1.8)
Medium [56]	52	1.5(1.1-2.1)	54	1.5(1.1-2.1)
High [128.5]	47	1.2(0.9-1.7)	55	1.3(0.9-1.8)
		P trend=0.38	P trend=0.23	
2,4-D **(phenoxy-herbicide)**				

None	71	1.0 (ref)	71	1.0 (ref)
Low [46.75]	83	1.0(0.7-1.4)	82	1.0(0.7-1.4)
Medium [133.35]	83	1.2(0.8-1.6)	83	1.1(0.8-1.6)
High [371.75]	82	1.0(0.7-1.4)	81	1.0(0.7-1.4)
		P trend=0.96		P trend=0.94
EPTC **(thiocarbamate-herbicide)**				
None	229	1.0 (ref)	229	1.0 (ref)
Low [8.75]	28	1.3(0.9-2.0)	20	1.3(0.8-2.1)
Medium [50.75]	14	1.0(0.6-1.7)	20	1.2(0.7-1.8)
High [108.5]	18	1.3(0.8-2.0)	19	1.1(0.7-1.8)
		P trend=0.35		P trend=0.54
Glyphosate **(phosphinic acid-herbicide)**				
None	70	1.0 (ref)	70	1.0 (ref)
Low [20]	89	0.8(0.6-1.2)	83	0.9(0.6-1.3)
Medium [65.75]	78	0.8(0.6-1.2)	84	0.8(0.5-1.1)
High [173.25]	83	1.0(0.7-1.4)	82	1.0(0.7-1.3)
		P trend=0.58		P trend=0.81
Imazethapyr **(imidazolinone-herbicide)**				
None	181	1.0 (ref)	181	1.0 (ref)
Low [8.75]	39	0.9(0.6-1.3)	36	1.0(0.7-1.4)
Medium [28.75]	34	0.9(0.6-1.4)	37	0.9(0.6-1.3)
High [56]	35	1.2(0.8-1.7)	35	1.2(0.8-1.7)
		P trend=0.54		P trend=0.55
Metribuzin				

(triazine-herbicide)				
None	94	1.0 (ref)	94	1.0 (ref)
Low [8.75]	28	1.0 (0.7-1.7)	21	1.2(0.7-2.0)
Medium [50.75]	15	0.9(0.5-1.6)	23	1.1(0.7-1.7)
High [56]	20	1.7(1.0-2.7)	19	1.3(0.8-2.2)
		P trend=0.06		P trend=0.28
Trifluralin **(dinitroaniline-herbicide)**				
None	140	1.0 (ref)	140	1.0 (ref)
Low [25]	51	1.0 (0.7-1.4)	50	1.0(0.7-1.4)
Medium [108.5]	58	1.1(0.8-1.5)	52	1.1(0.8-1.5)
High [224.75]	43	1.0(0.7-1.3)	48	0.9(0.7-1.3)
		P trend=0.81		P trend=0.65

[1] Age adjusted (<45,45-49,50-54,55-59,60-64,65-69,≥70)

[2] Numbers do not sum to total number of NHL cases (n=333) due to missing data.

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Table 3. Pesticides exposure (Lifetime-days and the age-adjusted risk of NHL by cell type (1993-2008).

	Insecticides, fungicide and fumigant							
	CLL, SLL, MCL		Diffuse Large B-cell		Follicular B-cell		Other B-cell types	
	RR[1] (95% CI)	n	RR[1] (95% CI)	n	RR[1] (95% CI)	n	RR[1] (95% CI)	N
Carbaryl								
None	1.0 (ref)	32	1.0 (ref)	23	1.0 (ref)	9	1.0 (ref)	9
Low	1.1(0.5-2.2)	15	0.7(0.3-1.5)	10	1.1(0.3-4.0)	5	Xxx	6
Medium	1.0(0.2-4.2)	2	1.3(0.6-3.0)	8	1.8(0.6-5.9)	4	Xxx	0
High	0.4(0.2-0.8)	8	1.5(0.7-3.5)	8	1.3(0.4-4.1)	4	xxx-	1
	P trend=0.007		P trend=0.19		P trend=0.66		P trend=xxx	
Malathion								
None	1.0 (ref)	21	1.0 (ref)	16	1.0 (ref)	5	1.0 (ref)	6
Low	0.94(0.5-1.8)	17	0.8(0.4-1.7)	16	1.0(0.3-3.6)	6	xxx-	8
Medium	0.8(0.4-1.7)	11	0.9(0.4-2.1)	8	1.2(0.3-4.3)	5	-xxx	0
High	0.8(0.4-1.7)	11	1.7(0.8-3.8)	11	1.5(0.4-4.9)	5	-xxx	3
	P trend=0.52		P trend=0.07		P trend=0.48		P trend=xxx	
Terbufos								
None	1.0 (ref)	53	1.0 (ref)	47	1.0 (ref)	26	1.0 (ref)	10
Low	1.8(1.0-3.1)	17	0.9(0.4-1.7)	12	2.5(1.1-5.4)	8	2.3 (0.8-6.6)	6
Medium	2.2(1.3-3.6)	21	2.2(1.2-4.2)	12	1.8(0.7-4.3)	7	3.1(1.1-9.2)	5
High	1.4(0.8-2.6)	13	1.1(0.5-2.3)	10	0.7(0.3-1.8)	6	4.1(1.4-11.9)	5
	P trend=0.16		P trend=0.34		P trend=0.54		P trend=0.01	
	Chlorinated pesticides							
Chlordane								
None	1.0 (ref)	74	1.0 (ref)	68	1.0 (ref)	35	1.0 (ref)	21

Comment [lbf67]: Insert the codes here and then you can remove them from the text.

Comment [lbf68]: Would suggest using the headings as suggest in Table 2 to orient people to chemical class.

Low	1.4 (0.7-2.7)	10	0.8 (0.4-2.0)	6	1.6 (0.4-6.9)	2	Xxx	1
Medium	2.8 (0.9-9.0)	3	1.8 (0.6-5.1)	4	0.8 (0.2-3.4)	2	Xxx	2
High	0.8 (0.3-2.7)	3	1.0 (0.2-4.1)	2	0.7 (0.1-5.1)	1	Xxx	0
	P trend=0.56		P trend=0.09		P trend=0.92		P trend=xxx	
DDT								
None	1.0 (ref)	62	1.0 (ref)	53	1.0 (ref)	36	1.0 (ref)	22
Low	0.91 (0.4-2.0)	8	1.1 (0.5-2.6)	7	1.1 (0.4-3.4)	4	0.4 (0.1-1.9)	2
Medium	1.1 (0.5-2.4)	8	2.3 (1.0-5.4)	7	0.3 (0.1-2.6)	1	1.4 (0.3-6.2)	2
High	2.3 (1.0-5.3)	7	1.2 (0.5-2.9)	6	0.7 (0.1-5.0)	1	0.9 (0.1-6.7)	1
	P trend=0.45		P trend=0.31		P trend=0.72		P trend=0.77	
Lindane								
None	1.0 (ref)	41	1.0 (ref)	39	1.0 (ref)	14	1.0 (ref)	14
Low	1.6(0.7-3.6)	8	0.7(0.2-3.0)	9	2.7(0.8-9.4)	3	Xxx	1
Medium	1.1(0.3-4.8)	3	1.1(0.3-3.7)	6	3.6(0.8-15.9)	2	Xxx	0
High	3.8(1.5-9.6)	5	1.3(0.2-9.7)	5	2.4(0.5-10.4)	2	Xxx	0
	P trend=0.005		P trend=0.25		P trend=0.25		P trend=xxx	
				Herbicides				
Alachlor (acetanilide)								
None	1.0 (ref)	53	1.0 (ref)	42	1.0 (ref)	22	1.0 (ref)	9
Low	0.9(0.6-1.5)	23	0.9(0.5-1.6)	13	1.3(0.6-2.6)	10	1.6 (0.6-4.4)	7
Medium	0.8(0.5-1.4)	18	0.7(0.4-1.3)	14	0.8(0.3-1.6)	9	2.1 (0.8-5.3)	10
High	1.1(0.6-2.1)	14	0.8(0.4-1.6)	10	1.1(0.4-2.7)	6	4.0 (1.2-13.0)	4
	P =0.67		P trend=0.52		P trend=0.99		P trend=0.02	
Atrazine (triazine)								
None	1.0 (ref)	34	1.0 (ref)	26	1.0 (ref)	12	1.0 (ref)	5

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Low	1.0 (0.6-1.7)	29	1.1(0.6-2.0)	21	1.7(0.7-3.9)	17	2.4 (0.9-6.8)	13
Medium	1.2 (0.7-2.0)	25	1.1(0.6-2.2)	23	1.3(0.5-3.4)	10	1.7(0.5-5.9)	6
High	1.0 (0.6-1.7)	26	0.9(0.5-1.7)	19	1.4(0.6-3.4)	13	3.6 (1.2-10.8)	9
	P trend=0.90		P trend=0.62		P trend=0.83		P trend=0.06	
Butylate (thio-carbamate-)								
None	1.0 (ref)	40	1.0 (ref)	33	1.0 (ref)	14	1.0 (ref)	8
Low	0.8(0.4-1.9)	7	1.1(0.4-3.0)	4	0.8(0.2-2.9)	3	3.0 (0.8-11.3)	3
Medium	3.5(1.6-7.6)	8	1.2(0.4-3.5)	4	6.3(2.1-19.3)	4	4.0(1.2-13.7)	4
High	1.3(0.4-4.3)	3	0.8(0.2-2.5)	3	1.0(0.1-7.9)	1	2.4 (0.3-19.7)	1
	P trend=0.04		P trend=0.69		P trend=0.07		P trend=0.0499	
2,4-D (Chlorinated Phenoxy)								
None	1.0 (ref)	25	1.0 (ref)	23	1.0 (ref)	9	1.0 (ref)	5
Low	0.90(0.5-1.5)	31	0.9(0.5-1.7)	23	1.8(0.8-4.4)	14	1.9 (0.6-6.2)	10
Medium	1.2(0.7-2.0)	29	1.0(0.6-1.9)	21	1.0(0.4-2.4)	14	1.7 (0.5-5.6)	9
High	1.3(0.7-2.2)	29	0.7(0.4-1.3)	21	1.4(0.6-3.4)	12	2.2 (0.7-7.2)	9
	P trend=0.20		P trend=0.23		P trend=0.84		P trend=0.35	
Dicamba (benzoic acid)								
None	1.0 (ref)	39	1.0 (ref)	40	1.0 (ref)	22	1.0 (ref)	6
Low	1.5 (0.9-2.6)	23	1.1 (0.6-2.1)	12	1.5(0.7-3.4)	9	3.2 (1.0-9.9)	8
Medium	1.5 (0.9-3.4)	20	1.1 (0.6-2.1)	13	1.8(0.90-4.0)	10	5.2(1.6-16.6)	7
High	2.0 (1.1-3.4)	20	0.7 (0.4-1.4)	11	0.7(0.3-1.5)	8	5.1(1.6-16.1)	7
	P trend=0.03		P trend=0.26		P trend=0.32		P trend=0.02	

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EPTC (thio-carbamate)								
None	1.0 (ref)	86	1.0 (ref)	62	1.0 (ref)	40	1.0 (ref)	19
Low	1,2(0.6-2.3)	9	1.2(0.6-2.7)	7	xxx	3	2.1 (0.7-6.0)	4
Medium	1.2(0.6-2.5)	8	1.7(0.7-4.2)	5	xxx	0	2.1 (0.6-7.1)	3
High	1.4(0.6-3.4)	5	0.8(0.3-2.3)	4	xxx	1	4.9 (1.4-16.7)	3
	P trend= 0.41		P trend=0.98		P trend=0.10		P trend=0.01	
Glyphosate (isopropyl-amine)								
None	1.0 (ref)	25	1.0 (ref)	19	1.0 (ref)	13	1.0 (ref)	10
Low	0.6(0.4-1.1)	32	1.3(0.7-2.6)	23	0.7(0.3-1.7)	15	0.4 (0.1-1.2)	9
Medium	1.1(0.6-1.9)	29	1.1(0.5-2.1)	23	0.6(0.2-1.4)	11	0.6 (0.2-1.6)	7
High	1.1(0.6-1.8)	29	0.7(0.4-1.3)	22	0.7(0.3-1.8)	12	0.6 (0.2-1.8)	7
	P trend=0.21		P trend=0.05		P trend=0.66		P trend=0.98	
Imazethapyr (imid-azolinone)								
None	1.0 (ref)	68	1.0 (ref)	57	1.0 (ref)	29	1.0 (ref)	12
Low	1.0(0.6-1.8)	16	0.7(0.3-1.4)	10	0.7(0.3-1.7)	6	1.6 (0.6-3.8)	8
Medium	0.8(0.4-1.6)	11	0.6(0.3-1.4)	6	1.1(0.3-3.5)	6	5.2 (1.6-16.6)	4
High	1.2(0.6-2.2)	12	0.5(0.2-1.2)	5	1.0(0.4-2.8)	5	3.2 (1.0-10.0)	4
	P trend=0.71		P trend=0.16		P trend=0.90		P trend=0.03	
Metribuzin (Triazone)								
None	1.0 (ref)	30	1.0 (ref)	35	1.0 (ref)	13	1.0 (ref)	9
Low	1.5(0.7-2.9)	11	0.5(0.2-1.4)	5	1.4(0.5-3.9)	5	1.0 (0.2-4.9)	3

Medium	2.1(1.1-4.0)	13	0.5(0.1-2.0)	3	0.8(0.2-2.9)	3	2.8 (0.9-8.9)	5
High	1.8(0.6-5.2)	4	0.4(0.1-1.6)	2	1.3(0.2-9.8)	1	-	0
	P trend=0.06		P trend=0.13		P trend=0.88		P trend=0.60	
Trifluralin (dinitro-aniline)								
None	1.0 (ref)	45	1.0 (ref)	43	1.0 (ref)	25	1.0 (ref)	10
Low	1.1(0.7-1.9)	23	0.9(0.5-1.7)	14	0.9(0.4-1.9)	8	1.2 (0.4-3.2)	7
Medium	1.6(0.9-2.6)	21	0.8(0.4-1.7)	11	0.8(0.4-1.8)	8	2.7 (1.0-7.0)	7
High	1.1(0.6-1.9)	15	0.6(0.3-1.2)	11	0.8(0.3-1.9)	7	3.3 (1.2-9.1)	6
	P trend= 0.81		P trend=0.13		P trend=0.62		P trend=0.01	

[1]Age adjusted (<45,45-49,50-54,55-59,60-64,65-69,$\geq$70)
[2] Numbers do not sum to NHL subtype totals due to missing data.

Table 4: The number of different pesticides in a pesticide class used and the risk of NHL (95% CI)

Number pesticides in a pesticide class	All NHL Cases[1]	Cohort Person-Years	RR[2]	95% CI
All pesticide				
0-4	36	46,624	1.0 (ref)	
5-8	58	62,304	1.2	(0.8-1.9)
9-11	50	56,373	1.2	(0.8-2.0)
12-16	65	93,714	0.9	(0.5-1.4)
17-20	48	57,874	1.1	(0.7-1.8)
>20	75	71,281	1.1	(0.7-1.8)
			P trend=0.53	
Chlorinated Insecticides				
0	111	344,026	1.0 (ref)	
1	63	131,439	1.1	(0.6-1.9)
2	42	77,989	1.1	(0.6-2.0)
≥3	89	122,276	0.9	(0.5-1.7)
			P trend=0.45	
Organophosphate insecticides				
0	38	90,621	1.0 (ref)	
1	59	128,694	1.2	(0.7-1.8)
2	69	146,183	1.3	(0.8-2.0)
3	56	133,273	1.1	(0.6-1.8)
≥4	107	208,634	1.2	(0.7-2.1)
			P trend=0.59	
Carbamate insecticide				
0	104	231,849	1 (ref)	
1	126	294,727	0.7	(0.5-1.0)
≥2	89	163,706	0.9	(0.6-1.4)
			P trend=0.64	
Other insecticides				
0	251	532,835	1.0 (ref)	
>1	43	112,489	1.1	(0.6-1.8)
			P trend=0.36	
Triazine herbicides				
0	67	161,040	1.0	
1	92	187,057	1.2	(0.6-2.4)
2	78	185,777	1.0	(0.5-2.1)
3	92	173,920	1.4	(0.7-3.0)
			P trend=0.04	
Acetamide herbicides				
0	90	206,537	1.0	
1	115	236,407	1.6	(0.8-3.4)
2	102	219,200	1.7	(0.7-3.7)

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			P trend=0.10	
Carbamate herbicides				
0	193	414,729	1.0 (ref)	
1	79	179,871	0.8	(0.5-1.2)
2	40	84,589	0.8	0.8 (0.4-1.4)
			P trend=0.80	
Other herbicides				
0	13	25,880	1.0 (ref)	
1-2	67	131,595	1.1	(0.5-2.7)
3-4	76	162,359	1.0	(0.4-2.4)
5-6	78	185,337	1.0	(0.4-2.5)
≥7	97	205,915	1.1	(0.4-2.6)
			P trend=0.19	
Fungicides				
0	203	442,307	1.0 (ref)	
1	73	152,882	1.1	(0.8-1.5)
≥2	52	110,590	1.5	(0.99-2.3)
			P trend=0.31	
Fumigants				
0	240	538,867	1.0 (ref)	
1	73	123,473	1.4	(0.9-2.1)
≥2	15	42,165	0.9	(0.4-1.9)
			P trend=0.24	

[1] Numbers do not sum to totals (333 cases, 714,770 person-years) due to missing data
[2] NHL risks are age adjusted (<45,45-49,50-54,55-59,60-64,65-69,≥70)and adjusted for lifetime days of use of pesticides in the specific pesticide class

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Table 5. Number of different pesticides used by pesticide type (in the NHL incidence analysis from 1993 through 2008) for B cell sub-types.[1,2]

	CLL, SLL, PLL, MCL		Diffuse Large B-cell		Follicular B-cell		Other B-cell types	
	RR [1] (95% CI)	n	RR[1] (95% CI)	n	RR[1] (95% CI)	n	RR[1] (95% CI)	n
Insecticides								
Carbamate insecticides[3]								
0	1.0 (ref)	34	1.0(ref)	33	1.0(ref)	12	1.0 (ref)	13
1	0.8 (0.5-1.3)	45	0.7(0.4-1.2)	36	1.5(0.8-3.0)	26	0.3 (0.1-0.8)	7
2-3	1.1 (0.7-1.7)	32	0.7(0.4-1.2)	20	1.2(0.5-2.7)	12	1.2 (0.5-2.5)	13
	P trend= 0.82		P trend=0.21		P trend=0.63		P trend= 0.75	
Chlorinated insecticides[4]								
None	1.0 (ref)	8	1.0(ref)	16	1.0(ref)	3	1.0 (ref0	6
1	1.6 (0.7-3.8)	17	0.9 (04-1.7)	18	4.1(1.2-14.1)	15	0.9 (0.3-2.7)	7
2	2.2 (0.95-5.0)	19	0.6(0.3-1.3)	10	2.5(0.6-9.6)	7	0.5 (0.1-1.9)	3
3	2.4 (1.2-5.2)	41	0.5(0.3-1.0)	17	1.7(0.5-6.5)	9	0.8 (0.3-2.3)	10
	P trend=0.02		P trend=0.05		P trend=0.73		P trend= 0.48	
Organophosphate Insecticides[5]								
0	1.0 (ref)	13	1.0 (ref)	14	1.0(ref)	5	1.0	5
1	0.93(0.4-2.0)	15	1.2(0.6-2.4)	21	1.3(0.4-3.9)	8	0.8 (0.2-2.8)	5
2	1.4 (0.7-2.7)	25	1.0(0.5-2.0)	20	1.7(0.6-4.7)	12	1.3 (0.4-4.0)	9
3	1.3 (0.6-2.5)	20	0.8(0.4-1.7)	14	1.4(0.5-4.1)	9	0.5 (0.1-2.1)	3
>4	1.7 (0.92-3.2)	42	0.8(0.4-1.6)	23	1.6(0.6-4.4)	17	1.3 (0.5-3.7)	12

Comment [lbf69]: Interesting results

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	P trend =0.03		P trend= 0.28		P trend=0.38		P trend=0.67	
Other Insecticides[6]								
0	1.0 (ref)	86	1.0 (ref)	71	1.0(ref)	35	1.0 (ref)	22
1	0.94 (0.6-1.6)	19	0.5(0.2-1.0)	9	1.3(0.6-2.4)	12	1.1 (0.5-2.8)	6
	P trend=0.78		P trend= .04		P trend=0.49	6	P trend=0.82	
Herbicides								
Acetamide Herbicide[7]								
0	1.0 (ref)	37	1.0(ref)	32	1.0(ref)	14	1.0	6
1	0.97 (0.6-1.5)	35	1.0(0.6-1.6)	32	1.3(0.7-2.6)	19	1.4 (0.5-4.0)	8
2	1.2 (0.8-2.0)	39	0.6(0.4-1.1)	18	1.2(0.6-2.4)	15	3.9 (1.2-8.2)	16
	P trend=0.35		P trend=0.16		P trend=0.72		P trend= 0.009	
Carbamate Herbicide[8]								
0	1.0 (ref)	67	1.0(ref)	58	1.0(ref)	27	1.0	16
1	0.98 (0.6-1.5)	27	0.7(0.4-1.2)	17	1.3(0.7-2.5)	16	1.5 (0.7-3.4)	10
2	1.5 (0.9-2.5)	17	0.9(0.4-1.7)	9	0.6(0.2-1.8)	3	2.2 (0.9-5.7)	6
	P trend=0.29		P trend=0.33		P trend=0.71		P trend=0.11	
Other herbicides[9]								
0	1.0 (ref)	6	1.0(ref)	6	1.0(ref)	1	1.0	2
1-2	1.2(0.5-2.8)	25	1.0(0.4-2.5)	22	3.2(0.5-27.0)	13	0.6 (0.1-3.1)	4
2-4	0.9 (0.4-2.2)	20	1.4(0.6-3.4)	33	2.5(0.3-19.2)	10	0.94(0.2-4.6)	7
5-6	1.2 (0.5-2.8)	26	0.7(0.3-1.7)	16	4.0(0.5-29.8)	17	1.2(0.3-5.7)	9
≥7	1.7 (0.7-4.1)	38	0.7(0.3-1.7)	16	2.5(0.3-19.3)	11	1.7(0.4-7.6)	12
	P trend=0.06		P trend=0.08		P trend=0.84		P trend= 0.06	
Triazine/Triazone herbicides[10]								
0	1.0	29	1.0 (ref)	22	1.0(ref)	6	1.0 (ref)	4
1	0.8 (0.5-1.4)	24	1.5(0.9-2.6)	34	3.2(1.3-8.0)	20	2.0 (0.6-6.6)	8

Comment [lbf70]: Interesting results

2	1.0(0.6-1.7)	27	0.8(0.4-1.5)	17	2.1(0.8-6.7)	13	2.5 (0.8-8.3)	9
3	1.5 (0.91-2.5)	35	1.1(0.6-2.0)	20	2.3(0.9-6.1)	13	4.2 (1.4-13.1)	13
	P trend=0.07		P trend=0.64		P trend=0.30		P trend=.006	
Fungicides and Fumigants								
Fungicides[11]								
0	1.0 (ref)	4	1.0 (ref)	6	1.0(ref)	3	1.0	2
1	1.3 (0.4-3.6)	29	0.7(0.3-1.8)	28	1.1(0.3-3.6)	23	1.2 (0.3-5.6)	14
2	1.7 (0.6-4.6)	81	0.8(0.3-1.8)	58	0.6(0.2-2.1)	26	0.8 (0.2-3.4)	18
	P trend=0.11		P trend=0.75		P trend=0.10		P trend=0.29	
Fumigants[12]								
0	1.0 (ref)	43	1.0 (ref)	30	1.0(ref)	25	1.0	9
1	1.0 (0.6-1.9)	13	2.0(1.1-3.7)	17	0.6(0.2-1.7)	4	2.8 (1.0-7.4)	7
≥2	0.95(0.6-1.4)	58	1.1(0.7-1.8)	45	0.7(0.4-1.2)	22	1.5(0.7-3.3)	18
	P trend=0.81		P trend=0.75		Ptrend=0.20		P trend=0.43	

[1]Age adjusted (<45,45-49,50-54,55-59,60-64,65-69,≥70 [2] Numbers do not sum to NHL subtype totals due to missing data [3]Carbamate insecticides: carbofuran, aldicarb, carbaryl [4]Chlorinated insecticides: aldrin, chlordane, dieldrin, DDT, heptachlor, lindane, toxaphene [5]Organophosphate insecticides: Chlorpyrifos, coumaphos, diazinon, dichlorvos, fonofos, malathion, parathion, phorate, terbufos, [6]Other insecticides: permethrin [7]Acetamide: metolachlor, alachlor [8]Carbamate herbicide: Butylate: EPTC [9]Other herbicides: Glyphosate, imazethapyr, herbicide oil, paraquat, chlorimuron ethyl, dicamba, pendimethalin, trifluralin, 2,4-D, 2,4,5-T, 2,4-TP[10]Triazine herbicides: Atrazine, cyanazine, metribuzin [11]Fungicides: Benomyl, chlorthalonil, captan, maneb/macozeb, metalaxyl, ziram [12]Fumigants: methyl bromide, aluminum phosphate, ethylene dibromide, carbon tetra chloride/carbon disulfide

12/5/2016

Supplemental Table 1 Other pesticide exposures (lifetime days [LD} and intensity weighted total days) and age-adjusted risk of NHL incidence (1993 through 2008).				
Pesticide (chemical-functional class) [median days of lifetime exposure for each category]	NHL Cases	RR (95%) by Lifetime- Days of Exposure	NHL Cases	RR (95% CI) Intensity weighted Lifetime-Days of exposure
Benomyl **(carbamate-fungicide)**				
None	134	1.0 (ref)	134	1.0 (ref)
Low [0.5]	6	5.6 (2.4-12.6)	6	4.1(1.8-9.3)
Medium [12.25]	5	1.0 (0.4-2.6)	5	1.0 (0.4-2.6)
High [108.5]	5	0.8 (0.3-1.9)	5	0.8 (0.3-1.9)
		P for trend=0.50		P for trend=0.57
Captan **(dicarboximide-fungicide)**				
None	258	1.0 (ref)	258	1.0 (ref)
Low [4]	8	0.6 (0.3-1.3)	8	0.7 (0.4-1.5)
Medium [12.25]	8	1.6 (0.6-4.1)	7	1.2 (0.5-2.9)
High [124]	7	0.6 (0.3-1.5)	7	0.5 (0.2-1.3)
		P for trend=0.33		P for trend=0.20
Carbofuran **(carbamate-insecticide)**				
None	199	1.0 (ref)	199	1.0 (ref)
Low [8.75]	35	1.1 (0.8-1.6)	29	1.2 (0.8-1.8)
Medium [38.75]	25	1.0 (0.7-1.6)	29	0.9 (0.6-1.3)
High [56]	28	1.0 (0.7-1.5)	28	1.1 (0.8-1.7)

Comment [lbf71]: I think that you need to put number of days for each pesticide. Low/Med/High is not the same for each pesticide under study and this leaves the impression that they are.

Comment [a72]: Lifetime days added as suggested.

		P trend=0.81		P trend=0.74
Chlorpyrifos **(organophosphate-insecticide)**				
None	189	1.0 (ref)	189	1.0 (ref)
Low [14.75]	44	1.1 (0.7-1.5)	40	1.1 (0.8-1.5)
Medium [38.75]	45	1.3(0.9-1.8)	41	1.0 (0.7-1.5)
High [116]	43	0.9 (0.7-1.3)	39	1.1 (0.8-1.5)
		P trend=0.57		P trend=0.67
Chlorthalonil **(thalonitrile-fungicide)**				
None	301	1.0 (ref)	301	1.0 (ref)
Low [8]	7	1.3 (0.6-2.7)	7	1.1 (0.5-2.4)
Medium [54.25]	6	0.6 (0.2-1.6)	6	0.6 (0.2-1.5)
High [79]	6	0.6 (0.2-1.2)	6	0.7 (0.3-1.5)
		P for trend=0.12		P for trend=0.23
Coumaphos **(0rganophosphate-insecticide)**				
None	258	1.0(ref)	258	1.0 (ref)
Low [8.75]	12	1.2 (0.7-2.2)	10	1.6 (0.8-2.9)
Medium [38.75]	10	1.4 (0.8-2.7)	11	1.2 (0.6-2.1)
High [63.75]	8	1.2 (0.6-2.4)	9	1.2 (0.6-2.3)
		P for trend=0.41		P for trend=0.55
DDVP **(dimethyl phosphate-insecticide)**				
None	261	1.0 (ref)	261	1.0 (ref)

Low [8.75]	10	1.2 (0.6-2.2)	10	1.2 (0.7-2.3)
Medium [108.5]	11	1.1 (0.6-2.0)	9	0.8 (0.4-1.6)
High [457.25]	7	0.7 (0.3-1.5)	9	1.0 (0.5-1.9)
		P for trend=0.42		P for trend=0.95
Diazinon **(organophosphosphorous-insecticide)**				
None	113	1.0 (ref)	113	1.0 (ref)
Low [8.75]	19	1.2 (0.7-2.0)	14	1.3 (0.7-2.2)
Medium [30]	10	0.7 (0.3-1.7)	15	0.9 (0.5-1.7)
High [56]	13	1.1 (0.6-2.1)	13	1.1 (0.6-1.9)
		P trend=0.73		P trend=0.92
Fonofos **(phosphonothioate-insecticide)**				
None	220	1.0 (ref)	220	1.0 (ref)
Low [20]	28	1.3 (0.9-1.9)	23	1.2 (0.8-1.9)
Medium [50.75]	19	1.2 (0.8-2.0)	23	1.4 (0.93-2.2)
High [108.5]	22	1.1 (0.7-1.7)	22	1.0 (0.6-1.5)
		P for trend=0.67		P for trend=0.98
Matalaxyl **(analine methyl ester-fungicide)**				
None	126	1.0 (ref)	126	1.0 (ref)
Low [3.5]	10	1.2 (0.6-2.2)	10	1.8 (0.95-3.4)
Medium [24.5]	11	0.9 (0.5-1.7)	11	0.7 (0.4-1.4)
High [50]	9	0.8 (0.4-1.5)	9	0.8 (0.4-1.5)

		P for trend=0.43		P for trend=028
Methyl bromide **(methyl halide-fumigant)**				
None	268	1.0 (ref)	268	1.0 (ref)
Low [8]	25	1.9 (1.2-2.8)	17	1.9 (1.2-3.1)
Medium [15.5]	9	0.9 (0.4-1.7)	16	1.3 (0.8-2.1)
High [28]	16	0.6 (0.3-0.9)	16	0.5 (0.3-0.9)
		P for trend=0.03		P for trend=0.02
Permethrin Animals **(pyrethroid-insecticide)**				
None	263	1.0 (ref)	263	1.0 (ref)
Low [8.75]	15	1.3 (0.8-2.3)	10	1.3 (0.7-2.5)
Medium [24]	5	0.8 (0.3-2.5)	10	0.8 (0.4-1.7)
High [56]	9	0.6 (0.3-1.2)	9	0.8 (0.4-1.5)
		P trend= 0.18		P trend=0.43
Permethrin Crops **(pyrethroid-insecticide)**				
None	249	1.0 (ref)	249	1.0 (ref)
Low [8.75]]	17	1.0 (0.6-1.7)	12	1.1 (0.5-2.2)
Medium [24.5]	9	1.1 (0.5-2.3)	12	1.2 (0.7-2.2)
High [59]	10	0.7 (0.4-1.4)	11	0.6 (0.3-1.1)
		P for trend=0.36		P for trend=0.15
Phorate **(organophosphate-insecticide)**				
None	102	1.0 (ref)	102	1.0 (ref)
Low [20]	20	1. (0.6-1.6)	17	0.9(0.5-1.5)

Comment [lbf73]: Do you show permethrin on crops anywhere?

Medium [24.5]	20	2.2 (1.4-3.5)	17	1.9 (1.1-3.1)
High [56]	10	0.7 (0.4-1.3)	16	1.0(0.6-1.7)
		P for trend=0.80		P for trend=0.67

Herbicide exposures				
	Life-time days of Exposure		Intensity weighted days of exposure*	
	NHL Cases	RR (95%)	NHL Cases	RR (95% CI)
Chlorimuron-ethyl **(benzoic acid ester-herbicide)**				
None	105	1.0 (ref)	105	1.0 (ref)
Low [8.75]	28	1.2(0.9-1.8)	18	1.1(0.6-1.9)
Medium [24.5]	18	1.9(1.2-3.2)	18	1.5(0.9-2.5)
High [24.5]	7	0.7(0.3-1.5)	17	1.1(0.7-1.9)
		P for trend=0.83		P for trend=0.60
Cyanazine **(triazine-herbicide)**				
None	162	1.0 (ref)	162	1.0 (ref)
Low [20]	58	1.4(0.9-1.9)	45	1.3(0.8-1.7)
Medium [56]	43	1.2(0.8-1.7)	45	1.4(1.0-1.9)
High [116]	35	1.1(0.8-1.6)	44	1.1(0.8-1.5)
		P for trend=0.81		P for trend=0.67
Herbicide Oil **(Petroleum oils-herbicide)**				
None	120	1.0 (ref)	120	1.0 (ref)
Low [20]	14	1.0(0.6-1.9)	13	1.3(0.7-2.3)
Medium [56]	13	1.8(1.0-1.1)	12	1.1(0.6-1.9)

High [173.25]	10	1.0(0.5-2.0)	12	1.3(0.7-2.4)
		P for trend=0.84		P for trend=0.36
Metolachlor **(acetamide-herbicide)**				
None	145	1.0 (ref)	145	1.0 (ref)
Low [20]	50	1.2(0.9-1.7)	49	1.2(0.8-1.6)
Medium [56]	54	1.3(0.94-1.5)	49	1.4(1.0-2.0)
High [116]	44	1.1(0.8-1.5)	48	1.1(0.8-1.5)
		P for trend=0.67		P for trend=0.28
Paraquat				
None	127	1.0 (ref)	127	1.0 (ref)
Low [7]	10	1.5(0.8-2.8)	10	1.9(1.0-3.7)
Medium [24.5]	10	0.8(0.4-1.5)	9	0.5(0.3-1.1)
High [116]	8	1.0(0.5-2.0)	9	1.5(0.8-3.0)
		P for trend= 0.88		P for trend=0.26
Pendimethalin				
None	96	1.0 (ref)	96	1.0 (ref)
Low [8.75]	32	1.1(0.7-1.6)	25	1.1(0.6-1.8)
Medium [24.5]	23	1.2(0.7-2.0)	26	1.0(0.7-1.6)
High [56]	20	1.0(0.6-1.6)	24	1.2(0.7-1.8)
		P for trend=0.87		P for trend=0.52
2,4,5 T **(phenoxyacetic acid)**				
None	71	1.0 (ref)	71	1.0 (ref)
Low [8.75]	30	1.7(1.1-2.5)	17	1.6(0.9-2.8)
Medium [8.75]	4	1.2(0.4-3.3)	16	1.9(1.1-3.2)
High [20]	15	1.2(0.7-2.2)	16	1.0(0.6-1.7)

		P for trend=0.52		P for trend=0.51

[1]Age adjusted (<45,45-49,50-54,55-59,60-64,65-69,≥70)

	NHL Cases	RR (95%) by Total Days of Exposure	NHL Cases	RR (95% CI) Intensity weighted days of exposure
Supplemental Table 2. Pesticide exposures (total days and intensity weight total days) fully adjusted risks of NHL incidence (1993 through 2008).				
Benomyl				
none	134	1.0 (ref)	134	1.0 (ref)
Low	6	6.1(2.7-13.8)	6	4.6 (2.0-10.6)
medium	5	1.0(0.4-2.6)	5	1.4 (0.6-3.5)
High	5	1.0(0.4-2.6)	5	1.1 (0.4-2.8)
		P trend (full)=0.98		P trend (full)=0.94
Captan				
none	258	1.0 (ref)	258	1.0 (ref)
Low	8	0.6(0.3-1.2)	8	0.7 (0.3-1.4)
medium	8	1.7(0.7-4.3)	7	1.2 (0.5-2.0)
High	7	0.7(0.3-1.6)	7	0.6 (0.2-1.4)
		P trend (full)=0.45		P trend (full)=0.28
Carbaryl				
none	81	1.0(ref)	81	1.0 (ref)
Low	31	0.96(0.6-1.6)	27	0.91 (0.6-1.5)
medium	23	0.8(0.5-1.4)	26	0.99 (0.6-1.6)
High	25	1.3(0.8-2.2)	26	1.1 (0.7-1.9)
		P trend (full)=0.26		P trend (full)=0.54
Carbofuran				
none	199	1.0 (ref)	199	1.0 (ref)
Low	35	1.0(0.7-1.5)	29	1.1(0.8-1.6)
medium	25	0.97(0.6-1.5)	29	0.8(0.5-1.2)
High	28	0.96(0.6-1.4)	28	1.1(0.7-1.6)

		P trend (full)=0.83		P trend (full)=0.95
Chlorthalonil				
none	301	1.0 (ref)	301	1.0 (ref)
Low	7	1.4(0.7-3.0)	7	1.2 (0.6-2.6)
Medium	6	0.7(0.3-1.8)	6	0.6 (0.2-1.9)
High	6	0.6 (0.3-1.4)	6	0.7 (0.3-1.6)
		P trend (full)=0.21		P trend (full)=0.37
Chlorpyrifos				
None	189	1.0 (ref)	189	1.0 (ref)
Low	44	1.0(0.7-1.5)	40	1.0 (0.7-1.5)
Medium	45	1.2(0.9-1.7)	41	0.94 (0.7-1.3)
High	43	0.8(0.6-1.2)	39	1.0 (0.7-1.4)
		P trend (full)=0.31		P trend (full)=0.99
Coumaphos				
none	258	1.0 (ref)	258	1.0 (ref)
Low	12	1.1(0.6-2.0)	10	1.4 (0.8-2.7)
medium	10	1.3 (0.7-2.5)	11	1.1 (0.6-2.0)
High	8	1.1(0.5-2.2)	9	1.1 (0.6-2.1)
		P trend (full)=0.62		P trend (full)=0.75
Diazinon				
None	113	1.0 (ref)	113	1.0 (ref)
Low	19	1.3(0.8-2.1)	14	1.3 (0.7-2.2)
medium	10	0.8(0.3-1.8)	15	0.9 (0.5-1.7)
High	13	1.3(0.7-2.5)	13	1.3 (0.7-2.3)
		P trend (full)=0.41		P trend (full)=0.50

DDVP				
none	261	1.0 (ref)	261	1.0 (ref)
Low	10	1.0 (0.5-1.9)	10	1.1 (0.6-2.1)
medium	11	0.92 (0.5-1.7)	9	0.7 (0.4-1.4)
High	7	0.6 (0.3-1.3)	9	0.9 (0.4-1.7)
		P trend (full)=0.22		P trend (full)=0.61
Fonofos				
None	220	1.0 (ref)	220	1.0 (ref)
Low	28	1.2(0.8-1.7)	23	1.1(0.7-1.7)
medium	19	1.1(0.7-1.7)	23	1.2(0.8-1.9)
High	22	0.9 (0.6-1.5)	22	0.9(0.5-1.3)
		P trend (full)=0.76		P trend (full)=0.51
Lindane				
None	122	1.0 (ref)	122	1.0 (ref)
Low	11	0.9(0.5-1.8)	10	1.0(0.5-1.8)
medium	10	1.0(0.5-2.0)	11	1.2(0.6-2.3)
High	10	2.3(1.2-4.5)	9	1.7(0.9-3.3)
		P trend (full)=0.01		P trend (full)=0.12
Malathion				
none	55	1.0 (ref)	55	1.0 (ref)
Low	46	0.9(0.6-1.3)	37	0.9 (0.6-1.4)
medium	28	0.7(0.4-1.1)	38	0.8 (0.5-1.1)
High	36	1.0(0.7-1.5)	35	0.9 (0.6-1.4)
		P trend (full)=0.68		P trend (full)=0.91
Metalaxyl				
none	126	1.0 (ref)	126	1.0 (ref)
Low	10	1.2(0.6-2.4)	10	1.7 (0.9-3.4)

medium	11	1.1(0.6-2.2)	11	0.9 (0.4-1.7)
High	9	1.1(0.5-2.3)	9	1.0 (0.5-2.2)
		P trend (full)=0.89		P trend (full)=0.93
Methyl bromide				
none	268	1.0 (ref)	268	1.0 (ref)
Low	25	2.2 (1.4-3.4)	17	2.3 (1.4-3.8)
medium	9	1.1 (0.5-2.1)	16	1.5 (0.9-2.6)
High	16	0.7 (0.4-1.2)	16	0.7 (0.4-1.1)
		P trend (full)=0.13		P trend (full)=0.07
Permethrin Animals				
None	263	1.0 (ref)	263	1.0 (ref)
Low	15	1.1(0.7-1.9)	10	1.1(0.6-2.1)
medium	5	0.7(0.2-2.1)	10	0.7(0.3-1.4)
High	9	0.5(0.3-1.0)	9	0.6(0.3-1.2)
		P trend (full)=0.055		P trend (full)=0.15
Permethrin Crops				
None	249	1.0 (ref)	249	1.0 (ref)
Low	17	0.9(0.5-1.6)	12	1.0(0.5-2.0)
medium	9	1.1(0.5-2.2)	12	1.2(0.7-2.2)
High	10	0.8(0.4-1.5)	11	0.6(0.3-1.2)
		P trend (full)=0.44		P trend (full)=0.18
Phorate				
none	102	1.0 (ref)	102	1.0 (ref)
Low	20	0.8(0.5-1.3)	17	0.7 (0.4-1.2)
medium	20	1.7(1.0-2.8)	17	1.5 (0.9-2.5)
High	10	0.6(0.3-1.0)	16	0.8 (0.5-1.4)
		P trend (full)=0.26		P trend (full)=0.70

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Terbufos				
None	157	1.0 (ref)	157	1.0 (ref)
Low	58	1.3(0.9-1.8)	43	1.2(0.8-1.7)
medium	38	1.7(1.2-2.5)	43	1.7(1.2-2.4)
High	34	1.0(0.7-1.5)	42	1.1(0.8-1.6)
		P trend (full)=0.78		P trend (full)=0.65

	Herbicide exposures			
	Life-time days of Exposure		Intensity weighted days of exposure*	
	NHL Cases	RR (95%)	NHL Cases	RR (95% CI)
Alachlor				
None	138	1.0 (ref)	138	1.0 (ref)
Low	65	0.9 (0.7-1.2)	53	0.9(0.7-1.2)
medium	49	0.8((0.6-1.1)	50	0.8 (0.6-1.1)
High	43	1.2((0.9-1.8)	51	1.2 (0.8-1.6)
		P trend (full)=0.20		P trend (full)=0.27
Atrazine				
None	85	1.0 (ref)	85	1.0 (ref)
Low	88	1.1(0.8-1.5)	79	1.0(0.7-1.4)
medium	72	1.2 (0.8-1.6)	78	1.2(0.9-1.7)
High	77	1.0 (0.7-1.4)	78	0.98(0.7-1.4)
		P trend (full)= 0.72		P trend (full)=0.73
Butylate				
None	107	1.0 (ref)	107	1.0 (ref)
Low	22	0.9(0.5-1.4)	16	0.8 (0.5-1.3)
medium	18	2.4(1.4-4.0)	16	1.8 (1.0-3.0)
High	7	1.0(0.4-2.1)	15	1.3 (0.8-2.3)

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		P trend (full)=0.03		P trend (full)=0.14
Chlorimuron-ethyl				
None	105	1.0 (ref)	105	1.0 (ref)
Low	28	1.1 (0.7-1.7)	18	1.0 (0.6-1.7)
medium	18	1.7 (1.0-2.9)	18	1.3(0.8-2.2)
High	7	0.7 (0.3-1.5)	17	1.1(0.6-1.8)
		P trend (full)=0.69		P trend (full)=0.68
Cyanazine				
None	162	1.0 (ref)	162	1.0 (ref)
Low	58	1.3(0.94-1.8)	45	1.2(0.8-1.7)
medium	43	1.1(0.8-1.6)	45	1.3(0.9-1.8)
High	35	1.0(0.7-1.4)	44	1.0(0.7-1.4)
		P trend (full)=0.65		P trend (full)=0.76
Dicamba				
None	121	1.0 (ref)	121	1.0 (ref)
Low	66	1.2 (0.8-1.7)	24	1.1(0.7-1.6)
medium	52	1.3 (0.9-1.9)	54	1.3(0.9-1.9)
High	47	1.1 (0.7-1.6)	55	1.1(0.8-1.6)
		P trend (full)=0.99		P trend (full)=0.76
2,4-D				
None	71	1.0 (ref)	71	1.0 (ref)
Low	83	0.9(0.6-1.3)	82	0.9 (0.6-1.2)
medium	83	1.0(0.7-1.4)	83	0.97 (0.7-1.4)
High	82	0.8(0.6-1.2)	81	0.9 (0.6-1.2)
		P trend (full)=0.35		P trend (full)=0.46
EPTC				
None	229	1.0 (ref)	229	1.0 (ref)

Low	28	1.2(0.8-1.8)	20	1.2 (0.8-2.0)
medium	14	0.9(0.7-1.9)	20	1.1 (0.7-1.7)
High	18	1.2(0.7-1.9)	19	1.0 (0.6-1.7)
		P trend (full)=0.56		P trend (full)=0.85
Glyphosate				
None	70	1.0 (ref)	70	1.0 (ref)
Low	89	0.8(0.6-1.2)	83	0.91 (0.6-1.3)
medium	78	0.8(0.6-1.2)	84	0.8 (0.5-1.1)
High	83	1.0(0.7-1.4)	82	0.97 (0.7-1.4)
		P trend (full)=0.63		P trend (full)=0.69
Herbicide Oil				
None	120	1.0 (ref)	120	1.0 (ref)
Low	14	1.0(0.6-1.7)	13	1.2 (0.6-2.1)
medium	13	1.7(0.93-2.9)	12	1.0 (0.5-1.8)
High	10	0.9((0.5-1.8)	12	1.2 (0.7-2.2)
		P for trend (full)=0.88		P for trend (full)=0.56
Imazethapyr				
None	181	1.0 (ref)	181	1.0 (ref)
Low	39	0.8(0.5-1.2)	36	0.8 (0.6-1.2)
medium	34	0.8(0.5-1.2)	37	0.7 (0.5-1.1)
High	35	1.0(0.7-1.5)	35	0.99 (0.7-1.5)
		P trend (full)=0.90		P trend (full)=0.92
Metolachlor				
None	145	1.0 (ref)	145	1.0 (ref)
Low	50	1.2 (0.8-1.6)	49	1.1(0.8-1.5)
medium	54	1.2 (0.8-1.7)	49	1.3(0.9-1.9)
High	44	1.0 (0.7-1.4)	48	0.98(0.7-1.4)

		P trend (full)=0.90		P trend (full)=0.81
Metribuzin				
None	94	1.0 (ref)	94	1.0 (ref)
Low	28	1.0(0.6-1.5)	21	1.0 (0.6-1.7)
medium	15	0.8(0.4-1.3)	23	0.91 (0.6-1.5)
High	20	1.4(0.8-2.3)	19	1.1 (0.7-1.9)
		P trend (full)=0.29		P trend (full)=0.66
Paraquat				
None	127	1.0 (ref)	127	1.0 (ref)
Low	10	1.6(0.8-3.0)	10	2.0 (1.0-3.7)
medium	10	0.9(0.5-1.7)	9	0.6 (0.3-1.3)
High	8	1.2(0.6-2.5)	9	1.9 (0.9-3.9)
		P trend (full)=0.72		P trend (full)=0.08
Pendimethalin				
None	96	1.0 (ref)	96	1.0 (ref)
Low	32	1.0(0.6-1.5)	25	0.9 (0.5-1.6)
medium	23	1.0(0.6-1.8)	26	0.9 (0.6-1.4)
High	20	1.0(0.6-1.5)	24	1.1 (0.7-1.8)
		P trend (full)=0.72		P trend (full)=0.60
Trifluralin				
None	140	1.0 (ref)	140	1.0 (ref)
Low	51	0.9(0.7-1.3)	50	0.9 (0.6-1.2)
medium	58	1.0(0.7-1.3)	52	1.0 (0.7-1.4)
High	43	0.8(0.6-1.2)	48	0.8 (0.6-1.1)
		P trend (full)=0.41		P trend (full)=0.30
2,4,5 T				
None	71	1.0 (ref)	71	1.0 (ref)

Low	30	1.6(1.0-2.4)	17	1.6 (0.9-2.6)
medium	4	1.1(0.4-3.0)	16	1.7 (1.0-2.9)
High	15	1.1(0.7-2.0)	16	1.0 (0.6-1.7)
		P trend (full)=0.78		P trend (full)=0.23

[1]Age adjusted (<45,45-49,50-54,55-59,60-64,65-69,$\geq$70), smoking status(current, former, never), number of livestock (0,<100,100-999,>999), drove diesel tractor(<weekly,$\geq$weekly), state (NC, IA)

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Supplemental Table 1A. Chlorinated Insecticide exposure (in total days and intensity weighted days) and NHL age-adjusted relative risk(1993 through 2008).				
	Total exposure days		Intensity weight exposure days	
	NHL cases	RR (95% CI)[1]	NHL cases	RR (95% CI)
Aldrin **(Chlorinated Insecticide)**				
None	232	1.0 (ref)	232	1.0 (ref)
Low [8.75]	14	0.8 (0.5-1.6)	12	0.9(0.5-1.6)
Medium [56]	14	0.8(0.5-1.4)	12	0.8(0.4-1.4)
High [116]	7	1.6(0.7-3.4)	11	1.0(0.6-1.9)
		P trend=0.70		P trend=0.86
Aldrin				
None	232	1.0 (ref)	232	1.0 (ref)
Low	14	0.8 (0.5-1.4)	12	0.9 (0.5-1.6)
medium	14	1.6 (0.8-3.4)	12	1.0 (0.6-1.9)
high	7	0.9 (0.7-1.2)	11	0.9 (0.7-1.2)
		P for trend=0.42		P for trend=0.95
		P for trend (full)=0.34		P for trend (full)=0.60
Heptachlor **(Chlorinated Insecticide)**				
None	240	1.0 (ref)	240	1.0 (ref)
Low [8.75]	11	2.1 (1.3-3.6)	10	2.8 (1.5-5.3)
Medium [24.5]	15	0.9 (0.3-2.1)	10	1.0 (0.5-1.9)
High [24.5]	5	1.0 (0.7-1.3)	10	1.0 (0.7-1.30
		P trend=0.26		P trend=0.42

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Heptachlor				
None	240	1.0 (ref)	240	1.0 (ref)
Low	11	0.9 (0.5-1.6)	11	0.9 (0.5-1.7)
medium	15	2.1 (1.3-3.6)	10	2.8 (1.5-5.3)
high	5	0.9 (0.4-2.1)	10	1.0 (0.5-1.9)
		P for trend=0.11		P for trend=0.41
		P for trend (full)=0.19		P for trend (full)=0.16
2,4,5 TP				
None	276	1.0 (ref)	276	1.0 (ref)
Low	8	1.8 (0.9-3.7)	4	1.6 (0.6-4.3)
medium	0	0.6 (0.2-1.9)	4	1.4 (0.5-3.8)
high	3	0.9 (0.6-1.2)	3	0.8 (0.2-2.4)
		P for trend=0.40		P for trend=0.75
		P for trend (full)=0.27		P for trend (full)=0.74
Toxaphene **(Chlorinated Insecticide)**				
None	250	1 .0 (ref)	250	1.0 (ref)
Low [8.75]	10	3.4(1.4-8.3)	7	0.8(0.4-1.6)
Medium [20]	5	0.6(0.3-1.3)	8	0.7(0.3-1.6)
High [50.75]	6	1.0(0.7-1.3)	6	1.0(0.7-1.3)
	P trend=0.66		P trend=0.83	
Toxaphene				
None	250	1.0 (ref)	250	1.0 (ref)
Low	10	3.4 (1.4-8.3)	7	1.6 (0.8-3.5)
medium	5	0.6 (0.3-1.3)	8	0.8 (0.4-1.6)
high	6	1.0 (0.7-1.3)	6	0.7 (0.3-1.6)

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	P for trend=0.33		P for trend=0.31
	P for trend (full)= 0.12		P for trend (full)=0.69

[1]Age adjusted (<45,45-49,50-54,55-59,60-64,65-69,≥70)

Supplemental Table 2A. Chlorinated Insecticide exposure (in total days and intensity weighted days) and NHL fully adjusted relative risk (1993 through 2008).				
	Life-time exposure days		Intensity weight exposure days	
	NHL cases	RR (95% CI)[1]	NHL cases	RR (95% CI)
Aldrin				
None	232	1.0 (ref)	232	1.0 (ref)
Low	14	0.7 (0.4-1.3)	12	0.8 (0.5-1.5)
medium	14	0.7 (0.4-1.2)	12	0.7 (0.4-1.3)
high	7	1.4 (0.7)	11	0.9 (0.5-1.7)
		P for trend (full)=0.34		P for trend (full)=0.60
Chlordane				
None	223	1.0 (ref)	223	1.0 (ref)
Low	23	1.0 (0.6-1.6)	13	1.2 (0.7-2.2)
medium	6	1.8 (0.8-4.2)	13	0.9 (0.5-1.7)
high	9	0.4 (0.4-1.7)	12	1.0 (0.6-1.8)
		P for trend (full)=0.63		P for trend (full)=0.90
DDT				
None	194	1.0 (ref)	194	1.0 (ref)
Low	20	0.8 (0.5-1.3)	19	0.9 (0.6-1.5)

medium	18	1.0 (0.6-1.6)	18	0.9 (0.5-1.4)
high	17	1.5 (0.9-2.5)	18	1.4 (0.9-2.4)
		P for trend (full)=0.48		P for trend (full)=0.61
Heptachlor				
None	240	1.0 (ref)	240	1.0 (ref)
Low	11	0.8 (0.4-1.5)	11	0.8 (0.5-1.6)
medium	15	1.9 (1.1-3.3)	10	2.4 (1.3-4.7)
high	5	0.8 (0.3-1.9)	10	0.9 (0.5-1.8)
		P for trend (full)=0.19		P for trend (full)=0.16
Lindane				
None	122	1.0 (ref)	122	1.0 (ref)
Low	11	0.9 (0.5-1.8)	10	1.0(0.5-1.8)
medium	10	1.0 (0.5-2.0)	11	1.2(0.6-2.3)
high	10	2.4 (1.2-4.5)	9	1.7(0.9-3.3)
		P for trend (full)=0.01		P for trend (full)=0.12
Toxaphene				
None	250	1.0 (ref)	250	1.0 (ref)
Low	10	0.91 (0.5-1.7)	7	1.6 (0.7-3.3)
medium	5	3.4 (1.4-8.3)	8	0.8 (0.4-1.6)
high	6	0.6 (0.3-1.3)	6	0.7 (0.3-1.7)
		P for trend (full)= 0.12		P for trend (full)=0.69

Supplemental Table 3. Herbicide exposures (Life-time days) and age-adjusted NHL risk by cell type (1993 through 2008).

Pesticide (chemical class)	CLL, SLL, PLL, MCL		Diffuse Large B-cell		Follicular B-cell		Other B-cell types	
	RR (95% CI)	n	RR (95% CI)	n	RR (95% CI)	n	RR (95% CI)	n
Alachlor (acetanilide)								
None	1.0 (ref)	53	1.0 (ref)	43	1.0 (ref)	22	1.0 (ref)	9
low	0.9(0.6-1.5)	23	0.9(0.5-1.6)	13	1.3(0.6-2.6)	10	1.6 (0.6-4.4)	7
medium	0.8(0.5-1.4)	18	0.7(0.4-1.3)	14	0.8(0.3-1.6)	9	2.1 (0.8-5.3)	10
high	1.1(0.6-2.1)	14	0.8(0.4-1.6)	10	1.1(0.4-2.7)	6	4.0 (1.2-13.0)	4
	LD P =0.67		LD P trend=0.52		LD P trend=0.99		LD P trend=0.02	
	IWLD P=0.49		IWLD P trend=0.092		IWLD P trend=0.97		IWLD P trend= 0.20	
Atrazine (triazine)								
None	1.0 (ref)	34	1.0 (ref)	26	1.0 (ref)	12	1.0 (ref)	5
low	1.0 (0.6-1.7)	29	1.1(0.6-2.0)	21	1.7(0.7-3.9)	17	2.4 (0.9-6.8)	13
medium	1.2 (0.7-2.0)	25	1.1(0.6-2.2)	23	1.3(0.5-3.4)	10	1.7(0.5-5.9)	6
high	1.0 (0.6-1.7)	26	0.9(0.5-1.7)	19	1.4(0.6-3.4)	13	3.6 (1.2-10.8)	9
	LD P trend=0.90		LD P trend=0.62		LD P trend=0.83		LD P trend=0.06	
	IWLD P trend=0.75		IWLD P trend=0.87		IWLD P trend=0.76		IWLD P trend=0.22	

Butylate (thio-carbamate-)								
None	1.0 (ref)	40	1.0 (ref)	33	1.0 (ref)	14	1.0 (ref)	8
low	0.8(0.4-1.9)	7	1.1(0.4-3.0)	4	0.8(0.2-2.9)	3	3.0 (0.8-11.3)	3
medium	3.5(1.6-7.6)	8	1.2(0.4-3.5)	4	6.3(2.1-19.3)	4	4.0(1.2-13.7)	4
high	1.3(0.4-4.3)	3	0.8(0.2-2.5)	3	1.0(0.1-7.9)	1	2.4 (0.3-19.7)	1
	LD P trend=0.04		LD P trend=0.69		LD P trend=0.07		LD P trend=0.05	
	IWLD P trend=0.19		IWLD P trend=0.89		IWLD P trend=0.12		IWLD P trend=0.13	
Chlorimuron-ethyl (Sulfonylurea)								
None	1.0 (ref)	38	1.0 (ref)	29	1.0 (ref)	14	1.0 (ref)	14
low	1.3(0.7-2.6)	11	1.4(0.7-3.0)	9	0.9(0.3-3.1)	3	-	1
medium	2.9(1.4-6.6)	9	1.2(0.4-4.0)	3	2.8(0.9-8.7)	4	-	1
high	0.3(0.1-2.5)	1	1.4(0.5-3.9)	4	0.7(0.9-5.1)	1	-	0
	LD P for trend=0.91		LD P trend=0.21		LD P trend=0.56		LD P for trend=xx	
	IWLD P trend=0.56		IWLD P trend=0.92		IWLD P trend=0.62		IWLD P trend=	
Cyanazine (triazine)								
None	1.0 (ref)	65	1.0 (ref)	46	1.0 (ref)	24	1.0 (ref)	10
low	1.2 (0.7-2.2)	15	1.4 (0.8-2.4)	16	1.9(0.9-3.8)	12	3.7(1.4-9.7)	7
medium	0.9 (0.5-1.6)	16	0.8 (0.4-1.8)	8	1.7(0.8-3.6)	9	2.9 (1.5-7.5)	8
high	1.1(0.6-2.0)	14	1.0 (0.5-2.1)	8	0.8(0.3-2.2)	4	2.6(0.9-7.5)	5
	LD P trend=0.93		LD P trend=0.93		LD P trend=0.87		LD P trend=0.17	

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	IWLD P trend=0.35		IWLD P trend=0.47		IWLD P trend=0.68		IWLD P trend=0.15	
2,4-D **(Chlorinated Phenoxy)**								
None	1.0 (ref)	25	1.0 (ref)	23	1.0 (ref)	9	1.0 (ref)	5
low	0.90(0.5-1.5)	31	0.9(0.5-1.7)	23	1.8(0.8-4.4)	14	1.9 (0.6-6.2)	10
medium	1.2(0.7-2.0)	29	1.0(0.6-1.9)	21	1.0(0.4-2.4)	14	1.7 (0.5-5.6)	9
high	1.3(0.7-2.2)	29	0.7(0.4-1.3)	21	1.4(0.6-3.4)	12	2.2 (0.7-7.2)	9
	LD P trend=0.20		LD P trend=0.23		LD P trend=0.84		LD P trend=0.35	
	IWLD P trend=0.83		IWLD P trend=0.41		IWLD P trend=0.22		IWLD P trend=0.75	
Dicamba **(benzoic acid)**								
None	1.0 (ref)	39	1.0 (ref)	40	1.0 (ref)	22	1.0 (ref)	6
low	1.5 (0.9-2.6)	23	1.1 (0.6-2.1)	12	1.5(0.7-3.4)	9	3.2 (1.0-9.9)	8
medium	1.5 (0.9-3.4)	20	1.1 (0.6-2.1)	13	1.8(0.90-4.0)	10	5.2(1.6-16.6)	7
high	2.0 (1.1-3.4)	20	0.7 (0.4-1.4)	11	0.7(0.3-1.5)	8	5.1(1.6-16.1)	7
	LD P trend=0.03		LD P trend=0.26		LD P trend=0.32		LD P trend=0.02	
	IWLD P trend=0.04		IWLD P trend=0.35		IWLD P trend=0.22		IWLD P trend=0.02	
EPTC **(thio-carbamate)**								
None	1.0 (ref)	86	1.0 (ref)	62	1.0 (ref)	40	1.0 (ref)	19
low	1,2(0.6-2.3)	9	1.2(0.6-2.7)	7	-	3	2.1 (0.7-6.0)	4
medium	1.2(0.6-2.5)	8	1.7(0.7-4.2)	5	-	0	2.1 (0.6-7.1)	3
high	1.4(0.6-3.4)	5	0.8(0.3-2.3)	4	-	1	4.9 (1.4-16.7)	3
	LD P trend= 0.41		LD P trend=0.98		LD P trend=0.10		LD P trend=0.01	
	IWLD P trend=0.43		IWLD P trend=0.59		IWLD P trend=0.14		IWLD P trend=0.15	

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Glyphosate (isopropyl-amine)								
None	1.0 (ref)	25	1.0 (ref)	19	1.0 (ref)	13	1.0 (ref)	10
low	0.6(0.4-1.1)	32	1.3(0.7-2.6)	23	0.7(0.3-1.7)	15	0.4 (0.1-1.2)	9
medium	1.1(0.6-1.9)	29	1.1(0.5-2.1)	23	0.6(0.2-1.4)	11	0.6 (0.2-1.6)	7
high	1.1(0.6-1.8)	29	0.7(0.4-1.3)	22	0.7(0.3-1.8)	12	0.6 (0.2-1.8)	7
	LD P trend=0.21		LD P trend=0.05		LD P trend=0.66		LD P trend=0.98	
	IWLD P trend=0.18		IWLD P trend=0.19		IWLD P trend=0.83		IWLD P trend=0.75	
Herbicide Oil (petroleum oil)								
None	1.0 (ref)	42	1.0 (ref)	35	1.0 (ref)	17	1.0 (ref)	14
low	1.8(0.8-4.3)	7	1.0(0.4-2.5)	6	1.4(0.3-5.9)	2	-	1
medium	2.6(1.0-6.7)	5	2.8(0.7-11.9)	2	1.1(0.1-8.4)	1	-	1
high	1.0(0.4-2.6)	5	1.4(0.4-4.5)	3	0.5(0.1-3.6)	1	0	0
	LD P trend=0.76		LD P trend=0.55		LD P trend=0.46		LD P trend=xxx	
	IWLD P trend=0.88		IWLD P trend=0.16		IWLD P trend=0.40		IWLD P trend=xxx	
Imazethapyr (imid-azolinone)								
None	1.0 (ref)	68	1.0 (ref)	57	1.0 (ref)	29	1.0 (ref)	12
low	1.0(0.6-1.8)	16	0.7(0.3-1.4)	10	0.7(0.3-1.7)	6	1.6 (0.6-3.8)	8
medium	0.8(0.4-1.6)	11	0.6(0.3-1.4)	6	1.1(0.3-3.5)	6	5.2 (1.6-16.6)	4
high	1.2(0.6-2.2)	12	0.5(0.2-1.2)	3	1.0(0.4-2.8)	5	3.2 (1.0-10.0)	4
	LD P trend=0.71		Ld P trend=0.16		LD P trend=0.90		LD P trend=0.03	
	IWLD P trend=0.95		IWLD P trend=0.34		IWLD P trend=0.83		IWLD P trend=0.03	

Metolachlor (chlor-acetanilide)									
None	1.0 (ref)	52	1.0 (ref)	48	1.0 (ref)	20	1.0 (ref)	10
low	1.2(0.7-2.0)	23	0.9(0.4-2.1)	11	1.4(0.6-3.2)	9	2.7 (1.0-7.0)	9
medium	1.7(0.95-3.2)	17	1.3(0.7-2.4)	12	1.4(0.6-3.7)	9	2.1 (0.6-7.7)	4
high	1.3(0.8-2.3)	18	0.4(0.2-0.9)	9	1.5(0.7-3.6)	8	2.6 (0.9-7.2)	6
	LD P trend=0.19		LD P trend=0.07		LD P trend=0.43		LD P trend=0.19	
	IWLD P trend=0.20		IWLD P trend=0.23		IWLD P trend=0.33		IWLD P trend=0.64	
Metribuzin (Triazinone)									
None	1.0 (ref)	30	1.0 (ref)	35	1.0 (ref)	13	1.0 (ref)	9
low	1.5(0.7-2.9)	11	0.5(0.2-1.4)	5	1.4(0.5-3.9)	5	1.0 (0.2-4.9)	3
medium	2.1(1.1-4.0)	13	0.5(0.1-2.0)	3	0.8(0.2-2.9)	3	2.8 (0.9-8.9)	5
high	1.8(0.6-5.2)	4	0.4(0.1-1.6)	2	1.3(0.2-9.8)	1	-	0
	LD P trend=0.06		LD P trend=0.13		LD P trend=0.88		LD P trend=0.60	
	IWLD P trend=0.03		IWLD P trend=0.21		IWLD P trend=0.10		IWLD P trend=0.43	
Paraquat (bi-pyridylium)									
None	1.0 (ref)	48	1.0 (ref)	37	1.0 (ref)	15	1.0 (ref)	14
low	1.0(0.4-2.4)	5	2.4(0.9-6.7)	4	2.9(0.7-12.7)	2	-	1
medium	1.0(0.2-4.0)	2	0.7-0.2-2.3)	3	1.2(0.3-5.3)	2	-	1
high	1.0(0.3-3.2)	3	0.8(0.2-3.4)	2	1.0(0.1-7.6)	1	-	0
	Ld P trend=0.99		LD P trend=0.23		LD P trend=0.94		LD P trend=xxx	
	IWLD P trend=0.44		IWLD P trend=0.78		IWLD P trend=0.75		IWLD P trend=xxx	

Pendi-methalin (dinitro-aniline)								
None	1.0 (ref)	38	1.0 (ref)	28	1.0 (ref)	11	1.0 (ref)	8
low	1.2(0.6-2.2)	12	1.0(0.4-2.2)	9	1.4(0.5-4.2)	6	1.8 (0.5-6.2)	5
medium	1.2(0.6-2.7)	8	0.92(0.3-2.6)	6	1.5(0.4-5.4)	4	2.3 (0.6-8.9)	4
high	0.8(0.3-1.9)	6	0.8(0.3-2.1)	5	1.4(0.5-4.5)	4	1.8 (0.5-6.9)	3
	LD P trend=0.66		LD P trend=0.66		LD P trend=0.57		LD P trend=0.42	
	IWLD P trend=0.44		IWLD P trend= 0.88		IWLD P trend=0.49		IWLD P trend=0.70	
Trifluralin (dinitro-aniline)								
None	1.0 (ref)	45	1.0 (ref)	43	1.0 (ref)	25	1.0 (ref)	10
low	1.1(0.7-1.9)	23	0.9(0.5-1.7)	14	0.9(0.4-1.9)	8	1.2 (0.4-3.2)	7
medium	1.6(0.9-2.6)	21	0.8(0.4-1.7)	11	0.8(0.4-1.8)	8	2.7 (1.0-7.0)	7
high	1.1(0.6-1.9)	15	0.6(0.3-1.2)	11	0.8(0.3-1.9)	7	3.3 (1.2-9.1)	6
	LD P trend= 0.08		LD P trend=0.13		LD P trend=0.62		LD P trend=0.01	
	IWLD P trend=0.80		IWLD P trend=0.11		IWLD P trend=0.65		IWLD P trend=0.08	
2,4,5 T								
None	1.0 (ref)	37	1.0 (ref)	33	1.0 (ref)	14	1.0 (ref)	12
low	2.1(1.1-3.9)	14	1.3(0.6-3.0)	7	4.6(1.3-16.1)	3	-	3
medium	2.4(0.7-7.00)	3	0.9(0.2-3.7)	2	2.1(0.6-7.2)	3	-	0
high	1.1(0.4-2.8)	5	1.3(0.4-4.3)	3	1.1(0.2-4.8)	2	-	1
	LD P trend= 0.33		LD P trend=0.71		LD P trend=0.73		LD P trend=xxx	
	IWLD P trend=0.83		IWLD P trend=0.90		IWLD P trend=0.80		IWLD P trend=0.97	

[1] Age adjusted (<45,45-49,50-54,55-59,60-64,65-69,≥70)

[2] Numbers do not sum to NHL subtype totals due to missing data

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Supplemental Table 4. Insecticides, fungicide and fumigant exposure (life-time days) and age-adjusted risk of NHL by cell type (1993 through 2008).

	CLL, SLL, PLL, MCL		Diffuse Large B-cell		Follicular B-cell		Other B-cell types	
	RR (95% CI)	**n**	**RR (95% CI)**	**n**	**RR (95% CI)**	**n**	**RR (95% CI)**	**n**
Aldicarb								
None	1.0 (ref)	51	1.0 (ref)	40	1.0 (ref)	19	1.0 (ref)	15
low	1.9(0.3-13.4)	1	1.7(0.4-7.2)	2	6.1(0.8-45.7)	1	-	1
medium	0.95(0.1-6.9))	1	4.8(1.2-19.8)	2	1.2(0.2-9.4)	2	-	1
high	-	0	0.5(0.1-4.1)	1	-	0	-	0
	LD P trend=0.15		LD P trend=0.72		LD P trend=0.63		LD P trend=xxx	
	IWLD P trend=0.14		IWLD P trend=0.89		IWLD P trend=0.64		IWLD P trend=xxx	
Carbaryl								
None	1.0 (ref)	32	1.0 (ref)	23	1.0 (ref)	9	1.0 (ref)	9
low	1.1(0.5-2.2)	15	0.7(0.3-1.5)	10	1.1(0.3-4.0)	5	xxx-	6
medium	1.0(0.2-4.2)	2	1.3(0.6-3.0)	8	1.8(0.6-5.9)	4	xxx-	0
high	0.4(0.2-0.8)	8	1.5(0.7-3.5)	8	1.3(0.4-4.1)	4	xxx-	1
	LD P trend=0.007		LD P trend=0.19		LD P trend=0.66		LD P trend=xxx	
	IWLD P trend=0.02		IWLD P trend=0.27		IWLD P trend=0.81		IWLD P trend=xxx	
Carbofuran								
None	1.0 (ref)	67	1.0 (ref)	58	1.0 (ref)	33	1.0 (ref)	19
low	1.4(0.8-2.5)	15	0.9(0.4-1.9)	8	0.96(0.4-2.5)	5	1.0 (0.4-2.7)	5

Comment [lbf74]: It looks like in the main tables you have restricted presenting results when there aren't 5 cases in a cell. You should use the same rules in the supplemtnal tables.

medium	1.2(0.6-2.4)	10	0.9(0.4-1.8)	9	1.6(0.7-3.9)	6	1.4(0.2-10.7)	1
high	1.3(0.7-2.4)	12	1.1(0.5-2.9)	5	0.6(0.2-2.0)	3	0.94(0.2-4.1)	2
	LD P trend=0.36		LD P trend=0.81		LD P trend=0.79		LD P trend=0.99	
	IWLD P trend=0.79		IWLD P trend=0.71		IWLD P trend=0.72		IWLD P trend=xxx	
Chlorpyrifos								
None	1.0 (ref)	69	1.0 (ref)	55	1.0 (ref)	26	1.0 (ref)	18
low	0.9(0.5-1.7)	15	1.2(0.6-2.1)	13	1.4(0.7-3.1)	10	0.9(0.3-2.6)	5
medium	1.1(0.7-2.0)	16	1.0(0.5-1.7)	15	1.2(0.5-2.9)	7	4.2(1.7-10.6)	6
high	1.0(0.5-1.7)	14	0.9(0.6-4.0)	7	1.4(0.6-3.4)	6	0.8(0.3-2.3)	4
	LD P trend=0.99		LD P trend=0.66		LD P trend=0.56		LD P trend=0.97	
	IWLD P trend=0.88		IWLD P trend=0.67		IWLD P trend=0.22		IWLD P trend=	
Chlorthalonil								
None	1.0 (ref)	107	1.0 (ref)	84	1.0 (ref)	45	1.0 (ref)	32
low	0.9(0.3-2.9)	3	1.6(0.4-6.6)	2	3.1(0.7-12.6)	2	-	1
medium	0.7(0.2-2.7)	2	1.4(0.3-5.6)	2	1.2(0.3-4.8)	2	-	0
high	0.7(0.2-2.7)	2	0.2(0.1-1.4)	1	0.6(0.1-4.4)	1	-	0
	LD P trend=0.46		LD P trend=0.11		LD P trend=0.61		LD P trend=xxx	
	IWLD P trend=0.96		IWLD P trend=0.17		IWLD P trend=0.41		IWLD P trend=xxx	
Coumaphos								
None	1.0 (ref)	92	1.0 (ref)	72	1.0 (ref)	42	1.0 (ref)	22
low	1.1(0.4-3.1)	4	0.7(0.2-2.3)	3	1.9(0.6-6.0)	3	xxx-	4
medium	2.0(0.8-4.9)	5	2.1(0.5-8.5)	2	0.5(0.1-4.0)	1	xxx-	0

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high	1.3(0.4-4.0)	3	1.5(0.4-5.9)	2	2.2(0.3-16.3)	1	-	1
	LD P trend=0.36		LD P trend=0.47		LD P trend=0.43		LD P trend=xxx	
	IWLD P trend=0.53		IWLD P trend=0.74		IWLD P trend=0.82		IWLD P trend=xxx	
Diazinon								
None	1.0 (ref)	40	1.0 (ref)	33	1.0 (ref)	13	1.0 (ref)	12
low	1.5(0.7-3.1)	9	1.2(0.4-3.1)	5	1.6(0.4-5.5)	3	xxx-	2
medium	1.2(0.4-3.6)	5	0.9(0.3-2.8)	4	1.6(0.4-7.4)	3	xxx-	1
high	1.2(0.5-3.0)	5	1.2(0.4-3.8)	3	2.0(0.4-10.0)	2	xxx-	0
	LD P trend=0.72		LD P trend=0.84		LD P trend=0.35		LD P trend=xxx	
	IWLD P trend=0.60		IWLD P trend=0.84		IWLD P trend=0.53		IWLD P trend=xxx	
DDVP								
None	1.0 (ref)	95	1.0 (ref)	74	1.0 (ref)	43	1.0 (ref)	24
low	1.3(0.5-3.5)	4	4.1(1.0-16.9)	2	0.7(0.2-3.1)	2	xxx-	1
medium	1.4(0.6-3.4)	5	0.5(0.1-1.9)	2	2.2(0.3-16.1)	1	xxx-	2
high	0.3(0.1-2.1)	3	0.3(0.1-2.2)	1	0.5(0.1-3.9)	1	-xxx	0
	LD P trend=0.46		LD P trend=0.25		LD P trend=0.54		LD P trend=xxx	
	IWLD P trend=0.85		IWLD P trend=0.54		IWLD P trend=0.53		IWLD P trend=xxx	
Fonofos								
None	1.0 (ref)	79	1.0 (ref)	61	1.0 (ref)	40	1.0 (ref)	17
low	1.6(.8-2.9)	12	1.5(0.8-3.1)	9	-	5	2.2(0.8-5.9)	5
medium	1.2(0.5-2.9)	5	1.0(0.4-2.3)	6	-	0	2.0(0.6-6.7)	3
high	0.9(0.5-2.0)	8	1.3(0.5-3.2)	5	-	2	2.3(0.3-17.0)	1
	LD P trend=0.88		LD P trend=0.62		LD P trend=0.20		LD P trend=0.19	

	IWLD P trend=0.94		IWLD P trend=0.77		IWLD P trend=0.18		IWLD P trend=xxx	
Lindane								
None	1.0 (ref)	41	1.0 (ref)	39	1.0 (ref)	14	1.0 (ref)	14
low	1.6(0.7-3.6)	8	0.7(0.2-3.0)	9	2.7(0.8-9.4)	3	xxx-	1
medium	1.1(0.3-4.8)	3	1.1(0.3-3.7)	6	3.6(0.8-15.9)	2	xxx-	0
high	3.8(1.5-9.6)	5	1.3(0.2-9.7)	5	2.4(0.5-10.4)	2	xxx-	0
	LD P trend=0.005		LD P trend=0.25		LD P trend=0.25		LD P trend=xxx	
	IWLD P trend=0.04		IWLD P trend=0.29		IWLD P trend=0.18		IWLD P trend=xxx	
Malathion								
None	1.0 (ref)	21	1.0 (ref)	16	1.0 (ref)	5	1.0 (ref)	6
low	0.94(0.5-1.8)	17	0.8(0.4-1.7)	16	1.0(0.3-3.6)	6	-xxx	8
medium	0.8(0.4-1.7)	11	0.9(0.4-2.1)	8	1.2(0.3-4.3)	5	-xxx	0
high	0.8(0.4-1.7)	11	1.7(0.8-3.8)	11	1.5(0.4-4.9)	5	-xxx	3
	LD P trend=0.52		LD P trend=0.07		LD P trend=0.48		LD P trend=xxx	
	IWLD P trend=0.24		IWLD P trend=0.33		IWLD P trend=0.56		IWLD P trend=xxx	
Maneb								
None	1.0 (ref)	52	1.0 (ref)	37	1.0 (ref)	19	1.0 (ref)	16
low	2.9(0.9-9.4)	3	2.6(0.6-10.9)	2	2.6(0.4-19.8)	1	-xxx	0
medium	1.6(0.4-6.6)	2	1.3(0.4-4.2)	3	1.1(0.1-8.0)	1	-xxx	0
high	0.3(0.1-2.4)	1	3.5(0.5-25.4)	1	-	0	-xxx	0
	LD P trend=0.43		LD P trend=0.19		LD P trend=0.55		LD P trend=xxx	
	IWLD P trend=0.49		IWLD P trend=0.17		IWLD P trend=0.66		IWLD P trend=xxx	

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Metalaxyl								
None	1.0 (ref)	46	1.0 (ref)	34	1.0 (ref)	18	1.0 (ref)	
Low	3.9(1.7-9.3)	6	1.1(0.3-3.6)	4	0.8(0.2-3.4)	2	-xxx	
medium	1.3(0.3-5.4)	2	1.4(0.5-3.9)	5	2.1(0.5-9.2)	2	-xxx	
high	0.4(0.1-1.2)	3	0.9(0.2-4.0)	2	0.9(0.1-6.4)	1	-xxx	
	LD P trend=0.08		LD P trend=0.92		LD P trend=0.81		LD P trend=xxx	
	IWLD P trend=0.04		IWLD P trend=0.85		IWLD P trend=0.83		IWLD P trend=xxx	
Methylbromide								
None	1.0 (ref)	101	1.0 (ref)	65	1.0 (ref)	45	1.0 (ref)	14
low	0.8(0.3-2.1)	4	4.8(2.5-9.3)	10	1.4(0.3-5.8)	2	-xxx	1
medium	0.7(0.3-1.6)	5	1.3(0.6-3.1)	6	1.2(0.4-4.0)	3	-xxx	1
high	0.4(0.1-1.3)	3	1.2(0.5-2.6)	7	-	0	-xxx	0
	LD P trend=0.09		LD P trend=0.71		LD P trend=0.08		LD P trend=xxx	
	IWLD P trend=0.02		IWLD P trend=0.57		IWLD P trend=0.09		IWLD P trend=xxx	
Permethrin animals								
None	1.0 (ref)	95	1.0 (ref)	78	1.0 (ref)	38	1.0 (ref)	25
low	1.3(0.5-3.3)	5	0.2(0.1-1.3)	1	2.8(1.1-7.0)	5	-xxx	1
medium	0.9(0.2-3.7)	3	0.5(0.1-3.4)	1	2.9(0.7-12.0)	2	-xxx	2
high	0.8(0.3-2.5)	3	-	0	0.8(0.2-3.5)	2	-xxx	0
	LD P trend=0.75		LD P trend=0.19		LD P trend=0.93		LD P trend=0.87	
	IWLD P trend=0.70		IWLD P trend=0.29		IWLD P trend=0.73		IWLD P trend=xxx	
Permethrin crops								

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None	1.0 (ref)	86	1.0 (ref)	72	1.0 (ref)	39	1.0 (ref)	23
low	1.9(0.6-5.4)	6	0.6(0.1-2.2)	3	1.1(0.3-3.5)	3	-xxx	4
medium	0.8(0.4-1.9)	6	2.7(0.7-10.6)	2	1.5(0.4-6.4)	2	-xxx	0
high	1.2(0.4-4.0)	4	0.4(0.1-1.8)	2	0.5(0.1-3.9)	2	-xxx	0
	LD P trend=0.76		LD P trend=0.28		LD P trend=0.57		LD P trend=0.37	
	IWLD P trend=0.70		IWLD P trend=0.33		IWLD P trend=0.45		IWLD P trend=xxx	
Phorate								
None	1.0 (ref)	36	1.0 (ref)	29	1.0 (ref)	15	1.0 (ref)	10
low	1.4(0.7-3.0)	9	1.0(0.4-2.6)	5	0.6(0.1-2.7)	2	1.4 (0.4-4.6)	4
medium	1.4(0.6-3.2)	6	2.0(0.9-4.7)	7	2.9(0.96-8.7)	4	1.5 (0.2-11.6)	1
high	0.94(0.4-2.4)	5	0.7(0.2-2.4)	3	-	0	1.4 (0.2-11.2)	1
	LD P trend=0.90		LD P trend=0.92		LD P trend=0.82		LD P trend=XXX	
	IWLD P trend=0.53		IWLD P trend=0.98		IWLD P trend=0.33		IWLD P trend=xxx	
Terbufos								
None	1.0 (ref)	53	1.0 (ref)	47	1.0 (ref)	26	1.0 (ref)	10
low	1.8(1.0-3.1)	17	0.9(0.4-1.7)	12	2.5(1.1-5.4)	8	2.3 (0.8-6.6)	6
medium	2.2(1.3-3.6)	21	2.2(1.2-4.2)	12	1.8(0.7-4.3)	7	3.1(1.1-9.2)	5
high	1.4(0.8-2.6)	13	1.1(0.5-2.3)	10	0.7(0.3-1.8)	6	4.1(1.4-11.9)	5
	LD P trend=0.16		LD P trend=0.34		LD P trend=0.54		LD P trend=0.01	
	IWLD P trend=0.14		IWLD P trend=0.40		IWLD P trend=0.18		IWLD P trend=xxx	

[1]Age adjusted (<45,45-49,50-54,55-59,60-64,65-69,≥70)

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Supplemental Table 5. Estimated individual and joint effects of pesticide combinations and age-adjusted risk of NHL		
Individual and joint pesticide exposures	**Exposed cases**	**Poisson Regression RR (95% CI)[1]**
Chlordane and DDT		
--Neither	174	1.0 (reference)
--Chlordane only	19	0.6 (0.4-1.0)
--DDT only	49	0.8(0.6-1.2)
--Both	56	0.9 (0.7-1.3)
Chlordane and Lindane		
--Neither	200	1.0 (reference)
--Chlordane only	47	0.8(0.6-1.2)
--Lindane only	23	1.0(0.6-1.5)
--both	28	1.0(0.7-1.6)
Lindane and dicamba		
--Neither	113	1.0 (reference)
--Lindane only	15	1.0 (0.6-1.7)
--dicamba only	120	1.3 (0.98-1.6)
--both	32	1.2 (0.8-1.8)
Atrazine and Chlordane		
--Neither	58	1.0 (reference)
--atrazine only	162	1.3(0.97-1.8)
--Chlordane only	19	1.0(0.6-1.7)
--Both	57	1.1(0.8-1.6)
2,4,5 t and Lindane		
--Neither	190	1.0 (reference)
--2,4,5-t only	57	1.1(0.9-1.6)

Comment [a75]: Need to delete. No really interesting findings, no space. Timing of pesticides not possible.

--Lindane only	27	1.1(0.7-1.6)
--Both	25	1.2 (0.8-1.8)
Atrazine and Lindane		
--Neither	73	1.0 (reference)
--Atrazine only	173	1.1 (0.9-1.5)
--Lindane only	4	0.5 (0.2-1.3)
--both	47	1.3 (0.9-1.9)
Atrazine and Dicamba		
--Neither	61	1.0 (reference)
--Atrazine only	72	1.0 (0.7-1.4)
--Dicamba only	17	1.0 (0.6-1.7)
--both	140	1.3 (0.97-1.8)
Atrazine and Carbofuran		
--Neither	68	1.0 (reference)
--Atrazine only	132	1.1 (0.9-1.5)
--Carbofuran only	9	0.9 (0.4-1.8)
--Both	81	1.2 (0.9-1.6)
Atrazine and Diazinon		
--Neither	58	1.0 (reference)
--atrazine only	163	1.2 (0.9-1.7)
--Diazinon only	20	0.9 (0.5-1.5)
--Both	59	1.1 (0.8-1.6)
Atrazine and alachlor		
--Neither	65	1.0 (reference)
--atrazine only	73	1.1 (0.8-1.5)

--alachlor only	16	0.8 (0.5-1.4)
--Both	146	1.1 (0.8-1.5)
2,4, 5 t and dicamba		
--Neither	94	1.0 (reference)
--2,4,5-t only	32	1.3 (0.9-1.9)
--dicamba only	107	1.4 (1.0-1.8)
--Both	45	1.3 (0.9-1.8)
2,4-D and Chlordane		
--Neither	55	1.0 (reference)
--2,4-D only	164	1.1(0.8-1.5)
--Chlordane only	7	0.7(0.3-1.5)
--Both	70	1.0 (0.7-1.5)
Glyphosate and atrazine		
--Neither	30	1.0 (reference)
--Glyphosate only	60	0.96(0.6-1.5)
--atrazine only	63	1.4(0.9-2.1)
--Both	171	1.1(0.7-1.6)
Glyphosate and 2,4-D		
--Neither	32	1.0 (reference)
--Glyphosate only	44	1.1(0.7-1.7)
--2,4-D only	61	1.4(0.9-2.1)
--Both	188	1.1(0.7-1.5)
Glyphosate and Chlordane		
--Neither	72	1.0 (reference)
--Glyphosate only	147	0.9 (0.7-1.2)

--chlordane only	13	1.0 (0.5-1.7)
--Both	64	0.8 (0.6-1.1)
2,4-D and Lindane		
---Neither	60	1.0 (reference)
---only 2,4-D	180	1.1(0.8-1.4)
---only lindane	3	0.6(0.2-1.8)
---both	48	1.2(0.8-1.7)
2,4-D and atrazine		
---Neither	41	1.0 (reference)
---only 2,4-D	49	1.0(0.7-1.5)
---only atrazine	35	1.2(0.8-1.9)
---both	199	1.2(0.8-1.7)
2,4-D and dicamba		
---Neither	51	1.0 (reference)
---only 2,4-D	81	0.9(0.6-1.3)
---only dicamba	13	1.2(0.7-2.2)
---both	144	1.2(0.9-1.7)
2,4-D and cyanazine		
---Neither	58	1.0 (reference)
---only 2,4-D	104	0.9(0.6-1.2)
---only cyanazine	11	0.9(0.5-1.7)
---both	130	1.2(0.9-1.6)
2,4-D and terbufos		
---Neither	48	1.0 (reference)
---only 2,4-D	113	1.0(0.7-1.5)

---only terbufos	16	1.7(0.97-3.0)
---both	115	1.5(1.0-2.0)
Cyanazine and atrazine		
---Neither	72	1.0 (reference)
---only cyanazine	11	1.3(0.7-2.4)
---only atrazine	90	1.0(0.8-1.4)
---both	130	1.3(0.97-1.7)

[1]Age adjusted (<45,45-49,50-54,55-59,60-64,65-69,$\geq$70)

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Appendix 1.			
Frequency of NHL in Agricultural Health Study applying New (InterLymp hierarchial classification of lymphoid neoplasms) and Older Definitions (ICD-O-3)			
Lymphoma category and type (ICD-O-3 codes)[1]	**Number NHL cases, new definition (InterLymph hierarchical classification)[1]**	**Number cases NHL, older definition (ICD-O-3)[2]**	**SEER Recode[1]**
CLL/SLL/PLL/MCL (Mature NHL, B-cell)			
Small lymphocytic lymphoma (9670)	27	27	08
Chronic lymphocytic leukemia/small lymphocytic lymphoma (9823)	74	0	08
Mantle -cell lymphoma (9673)	16	16	10
Diffuse Large B-cell Lymphoma (Mature NHL, B-cell)			
DLBCL (9680)	94	94	13
Follicular Lymphoma (Mature NHL, B-cell)			
Follicular lymphoma (9690, 9691,9695,9698)	53	53	21
Other B-cell Types			
Precursor acute lymphoblastic leukemia/lymphoma (9835(B), 9836)	4	0	07
Waldenstrom macroglobulinemia (9761)	2	0	12
Lymphoplasmacytic lymphoma (9671)	2	2	11
Hairy-cell leukemia (9940)	6	0	22
NHL, NOS (9591(B), 9675(B))	6	6	26
Burkitt lymphoma/leukemia (9687)	1	1	17
Extranodal marginal zone lymphoma (MZL), Malt type & Nodal MZL (9699)	13	13	19, 20
Plasma cell neoplasms Plasmacytoma (9734, 9731)	6	0	23
Multiple myeloma (9732)	77	0	24
Other NHL Types			
Precursor acute lymphoblastic leukemia/lymphoma (9835(T), 9837)	1	0	27
Mycosis fungoides (9700)	6	6	28
Peripheral T-cell lymphoma, NOS (9702)	2	2	30
Anaplastic large cell lymphoma, T or null cell (9714)	2	2	33
Enteropathy type T-cell lymphoma (9717)	1	1	35
Primary cutaneous anaplastic large cell lymphoma (9718)	1	1	37
T-cell lymph, nasal-type/aggressive NK leukemia (9719)	1	1	39
NHL, NOS (9591(T))	1	1	42
Lymphoid leukemia, NOS (9820(U))	1	0	
Precursor acute lymphoblastic leukemia/lymphoma (9727(U), 9835(U))	3	1	43
NHL, NOS (9591(U), 9675(U))	6	6	45
Lymphoid neoplasm, NOS (9590(U))	10	10	47
Total	416	243	

Lineage: B=B-cell, T=T-cell, U=Unknown
[1] http://seer.cancer.gov/lymphomarecode based on Morton LM et al. Blood, 2007;110:695-708.
[2] Percy C. et al., Lyon, France: IARC Press: 2001.

Comment [CL76]: This was originally coded as 9713, which is an ICD-O-2 code, which becomes 9719 in ICD-O-3. Since we are presenting ICD-O-3 codes in this table, I have changed this code to 9719.

Comment [CL77]: Since IA and NC cancer registries are not yet using 2008 WHO codes, the reference for this table should be the Morton LM et al. publication noted here This reference should also be noted in the text. Reference to the 2010 blood paper should not be noted in regard to the NHL classification used in this paper.

Appendix 2. Pesticide Classification by Chemical/Functional Class	
Chemical/functional class	**Pesticide**
Acetamide herbicide	Metolachlor, alachlor
Carbamate herbicde	Butlylate, EPTC
Other herbicides	Chloromuron ethyl, 2,4-D, dicamba, glyphosate, herbicide oil, imazethapyr. Paraquat, pendimethalin, 2,4,5-T, 2,4,5TP, trifluralin
Triazine/triazinone herbicides	Atrazine, cyanazine, metribuzin
Carbamate insecticides	Carbofuran, aldicarb, carbaryl
Chlorinated insecticides	Aldrin, chlordane, DDT, dieldrin, heptachlor, lindane, toxaphine
Organophosphate insecticides	Chlorpyrifos, coumaphos, diazinon, dichlorvos, fonofos, malathion, parathion, phorate, terbufos
Other insecticides	Permethrin (crops & animals), trichlorfon
Fungicides	Benomyl, chlorthalonil, captan, maneb/mancozeb, methylaxyl, ziram
Fumigants	Methyl bromide, aluminum phosphate, ethylene dibromide, carbon tetra chloride/carbondisulfide

Supplemental table 7: Pesticide exposures (total days and intensity weight total days) age- adjusted risks of NHL incidence (1993 through 2008)[old nhl definition; n=243].

	NHL Cases	RR[1] (95%) by Total Days of Exposure	NHL Cases	RR[1] (95% CI) Intensity-weighted days of exposure
Insecticides, Fungicides and Fumigants				
		P trend=		
Carbaryl **(carbamate-insecticide)**				
None	56	1.0 (ref)	56	1.0 (ref)
Low	19	0.8 (0.5-1.3)	19	0.9(0.6-1.6)
Medium	20	0.9(0.5-1.5)	20	0.7(0.4-1.2)
High	18	1.1(0.6-1.8)	18	1.2(0.7-2.0)
		P trend=0.64		P trend=0.42
Carbofuran **(carbamate-insecticide)**				
None	140	1.0 (ref)	140	1.0 (ref)

Low	26	1.2(0.8-1.8)	22	1.0(0.7-1.7)
Medium	18	1.1 (0.7-1.7)	21	1.0 (0.6-1.6)
High	21	1.1(0.7-1.7)	21	1.3(0.8-2.0)
		P trend=0.70		P trend=0.37
Chlorpyrifos **(organophosphate-insecticide)**				
None	134	1.0 (ref)	134	1.0 (ref)
Low	33	1.2(0.8-1.8)	30	1.2(0.8-1.8)
Medium	33	1.2(0.8-1.8)	30	0.9 (0.6-1.3)
High	32	0.9(0.6-1.3)	29	1.2 (0.8-1.7)
		P trend=0.50		P trend=0.56
Coumaphos				
None	186	1.0(ref)	186	1.0 (ref)
Low	9	1.3(0.7-2.5)	7	1.6(0.7-3.3)
Medium	7	1.1(0.5-2.3)	8	1.1(0.5-2.2)
High	5	1.4(0.6-3.4)	6	1.2(0.5-2.7)
		P trend=0.45		P trend=0.65
Diazinon **(organophosphosphorous-insecticide)**				
None	80	1.0 (ref)	80	1.0 (ref)
Low	12	1.0(0.6-1.9)	10	1.0(0.5-2.0)
Medium	8	0.9(0.4-1.9)	10	1.1(0.6-2.1)
High	9	1.2(0.6-2.4)	9	1.1(0.5-2.1)
		P trend=0.66		P trend=0.82
DDVP				
None	190	1.0(ref)	190	1.0 (ref)
Low	6	1.0(0.4-2.1)	6	1.1 (0.5-2.5)
Medium	6	0.9(0.4-2.0)	6	0.6(0.3-1.3)

High	5	0.6(0.3-1.6)	5	1.0(0.4-2.4)
		P trend=0.30		P trend=0.99
Fonofos				
None	163	1.0(ref)	163	1.0 (ref)
Low	18	1.1(0.7-1.8)	15	1.3(0.8-2.2)
Medium	13	1.1(0.6-2.0)	15	1.3(0.8-2.2)
Low	13	0.9(0.5-1.5)	14	0.7(0.4-1.2)
		P trend=0.		P trend=0.19
Malathion **(organophosphorous-insecticide)**				
None	39	1.0 (ref)	39	1.0 (ref)
Low	32	1.0(0.6-1.6)	26	1.1(0.7-1.8)
Medium	23	0.8(0.5-1.3)	27	0.7(0.4-1.2)
High	23	1.0 (0.6-1.7)	25	1.0(0.6-1.7)
		P trend=0.70		P trend=0.79
Metalaxyl				
None	91	1.0 (ref)	91	1.0 (ref)
Low	12	1.0 (0.5-1.8)	7	0.8(0.4-1.7)
Medium	3	0.7 (0.2-2.1)	7	1.1(0.5-2.4)
High	5	0.8 (0.3-2.0)	6	0.8(0.3-1.7)
		P trend=0.56		P trend=0.62
Methylbromide				
None	189	1.0 (ref)	189	1.0 (ref)
Low	16	2.7(1.6-4.5)	15	2.6 (1.6-4.5)
Medium	13	1.3(0.7-2.2)	13	1.5(0.8-2.6)
High	13	0.7(0.4-1.2)	13	0.6(0.4-1.1)
		P trend=0.24		P trend=0.07
Permethrin Animals				

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(pyrethroid-insecticide)				
None	189	1.0 (ref)	189	1.0 (ref)
Low	9	1.1(0.6-2.2)	7	1.3(0.6-2.8)
Medium	5	0.9(0.4-2.1)	7	0.7(0.3-1.6)
High	6	0.7(0.3-1.5)	6	0.7(0.3-1.7)
		P trend= 0.27		P trend=0.04
Phorate (organophosphate-insecticide)				
None	72	1.0 (ref)	72	1.0 (ref)
low	15	1.0(0.6-1.8)	12	1.3(0.7-2.5)
medium	15	2.3(1.3-4.1)	12	1.2(0.7-2.3)
high	5	0.5(0.2-1.2)	11	0.9(0.5-1.6)
		P for trend=0.53		P for trend=00.86.
Terbufos (organophosphorous-insecticide)				
None	114	1.0 (ref)	114	1.0 (ref)
Low	40	1.4(0.94-1.9)	31-	1.3(0.9-1.9)
Medium	26	1.9(1.2-2.8)	31	1.7(1.2-2.6)
High	26	1.2(0.8-1.9)	30	1.3(0.9-2.0)
		P trend=0.24		P trend=0.16
Chlorinated insecticides				
Aldrin				
None	86	1.0 (ref)	86	1.0 (ref)
Low	9	0.8(0.4-1.6)	9	1.0(0.5-1.9)
Medium	8	0.7(0.4-1.5)	7	0.7(0.3-1.5)
High	6	2.4(1.0-5.4)	7	1.3(0.6-2.9)
		P trend=0.21		P trend=0.86
Chlordane				

None	78	1.0 (ref)	78	1.0 (ref)
Low	10	1.2(0.7-2.0)	10	1.5(0.8-2.9)
Medium	8	1.3(0.7-2.4)	9	1.0(0.4-2.3)
High	10	1.0(0.9-1.1)	9	1.1(0.6-2.1)
		P trend=0.89		P trend=0.77
DDT				
None	71	1.0 (ref)	71	1.0 (ref)
Low	14	0.9(0.5-1.7)	13	1.1(0.6-2.2)
Medium	12	1.4(0.7-2.6)	12	1.0(0.5-1.8)
High	11	1.1(0.6-2.2)	12	1.3(0.7-2.4)
		P trend=0.61		P trend=0.47
Dieldrin				
None	101	1.0 (ref)	101	1.0 (ref)
Low	3	0.9(0.3-2.9)	3	1.9(0.6-5.9)
Medium	3	2.9(0.9-9.2)	2	1.3(0.3-5.2)
High	1	1.1(0.1-7.7)	2	0.9(0.2-3.8)
		P trend=0.47		P trend=0.97
Heptachlor				
None	88	1.0 (ref)	88	1.0 (ref)
Low	8	0.9(0.7-2.6)	7	1.2(0.6-2.4)
Medium	8	1.4(0.7-2.6)	8	1.7(0.7-3.8)
High	5	1.1(0.6-2.2)	6	1.4(0.6-3.3)
		P trend=0.26		P trend=0.42
Lindane				
None	86	1.0 (ref)	86	1.0 (ref)
Low	7	1.0(0.5-2.1)	7	1.1(0.5-2.3)
Medium	8	1.2(0.6-2.4)	7	1.0(0.5-2.2)
High	6	3.7(1.6-8.4)	6	2.8(1.2-6.4)

		P trend=0.0.01		P trend=0.04
Toxaphene				
None	90	1.0 (ref)	90	1.0 (ref)
Low	8	1.2(0.6-2.5)	6	1.6(0.7-3.5)
Medium	4	4.4(1.6-12.1	7	1.3(0.6-3.0)
High	6	0.9(0.4-2.0)	5	0.9(0.4-2.3)
		P trend=0.66		P trend=0.83
Herbicides				
Alachlor **(acetamide-herbicide)**				
None	96	1.0 (ref)	96	1.0 (ref)
Low	39	1.1(0.8-1.6)	38	1.1(0.7-1.6)
Medium	45	0.9(0.6-1.2)	40	0.8 (0.6-1.2)
High	31	1.4(0.9-2.0)	36	1.4(0.96-2.1)
		P trend=0.22		P trend=0.09
Atrazine **(triazine-herbicide)**				
None	59	1.0 (ref)	59	1.0 (ref)
Low	64	1.1(0.8-1.6)	58	1.1(0.8-1.6)
Medium	56	1.3(0.9-1.9)	59	1.2(0.9-1.8)
High	55	1.2(0.8-1.7)	57	1.3(0.9-1.8)
		P trend=0.52		P trend=0.27
Butylate **(thiocarbamate-herbicide)**				
None	75	1.0 (ref)	75	1.0 (ref)
Low	14	0.9 (0.5-1.6)	12	0.9(0.5-1.6)
Medium	15	3.4(1.9-5.9)	11	2.7(1.4-5.0)
High	5	1.1(0.4-2.7)	11	1.6(0.9-3.0)

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		P trend=0.005		P trend=0.049
Chlorimuron-ethyl **(benzoic acid ester-herbicide)**				
None	75	1.0 (ref)	75	1.0 (ref)
low	20	1.1(0.7-1.9)	13	1.1(0.6-2.0)
medium	11	1.5(0.8-2.9)	12	1.3(0.7-2.4))
high	6	0.7(0.3-1.7)	12	1.0(0.5-1.9)
		P for trend=0.73		P for trend=0.94
Cyanazine **(triazine-herbicide)**				
None	114	1.0 (ref)	114	1.0 (ref)
Low	41	1.4(0.95-1.9))	33	1.2(0.8-1.7)
Medium	32	1.3(0.9-1.9)	32	1.3(0.9-1.9)
High	25	1.1(0.7-1.6)	32	1.2(0.8-1.8)
		P for trend=0.0.89		P for trend=0.34
Dicamba **(benzoic-herbicide)**				
None	92	1.0 (ref)	92	1.0 (ref)
Low	39	1.5(1.0-2.2)	38	1.2(0.8-1.8)
Medium	38	1.2(0.8-1.8)	39	1.4(0.9-2.0)
High	38	1.0(0.7-1.5)	37	1.0(0.7-1.5)
		P trend=0.64	.	P trend=0.95
2,4-D **(phenoxy-herbicide)**				
None	53	1.0 (ref)	53	1.0 (ref)
Low	60	0.9(0.6-1.3)	59	0.9(0.6-1.4)
Medium	59	1.0(0.7-1.5)	60	1.0(0.7-1.4)
High	59	0.9(0.6-1.3)	58	0.9(0.6-1.3)

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		P trend=0.61		P trend=0.69
EPTC (thiocarbamate-herbicide)				
None	164	1.0 (ref)	164	1.0 (ref)
Low	21	1.3(0.9-2.1)	15	1.4(0.8-2.4)
Medium	9	1.1(0.6-2.2)	12	1.1(0.6-2.0)
High	10	0.8(0.4-1.5)	13	0.8(0.5-1.5)
		P trend=0.39		P trend=0.61
Glyphosate (phosphinic acid-herbicide)				
None	48	1.0 (ref)	48	1.0 (ref)
Low	72	1.0(0.7-1.4)	61	1.1(0.7-1.6)
Medium	51	0.7(0.5-1.0)	61	0.7(0.5-1.0)
High	60	1.0(0.7-1.4)	60	0.9(0.6-1.4)
		P trend=0.79		P trend=0.0.99
Herbicide Oil				
None	84	1.0 (ref)	84	1.0 (ref)
Low	9	1.0(0.5-1.9)	9	1.2(0.6-2.4)
Medium	10	1.8(0.95-3.6)	10	1.1(0.6-2.1)
High	8	1.1(0.6-2.6)	8	1.5(0.7-3.1)
		P trend=0.62		P trend=0.29
Imazethapyr (imidazolinone-herbicide)				
None	132	1.0 (ref)	132	1.0 (ref)
Low	30	0.9(0.6-1.3)	25	1.0(0.6-1.5)
Medium	20	0.8(0.5-1.2)	25	0.8(0.5-1.3)
High	24	0.9(0.6-1.4)	24	0.8(0.5-1.2)
		P trend=0.50		P trend=0.64

Metolachlor				
None	101	1.0 (ref)	101	1.0(ref)
Low	36	1.2(0.8-1.8)	35	1.1(0.8-1.7)
Medium	36	1.3(0.9-1.9)	36	1.4(0.9-2.0)
High	34	1.1(0.7-1.6)	34	1.1(0.8-1.6)
		P trend=0.73		P trend=0.71
Metribuzin (triazine-herbicide)				
None	70	1.0 (ref)	70	1.0 (ref)
Low	15	0.8 (0.5-1.5)	14	0.9(0.5-1.6)
Medium	20	1.2(0.7-2.0)	14	1.1(0.6-2.0)
High	6	1.1 (0.5-2.5)	13	1.2(0.6-2.1)
		P trend=0.0.59		P trend=0.55
Paraquat				
None	88	1.0 (ref)	88	1.0(ref)
Low	8	2.1(1.0-4.3)	8	4.8(2.3-9.9)
Medium	8	0.8(0.4-1.7)	7	0.7(0.3-1.5)
High	6	1.0(0.4-2.3)	7	0.9(0.4-2.0)
		P trend=0.91		P trend=0.73
Pendimethalin				
None	63	1.0 (ref)	63	1.0(ref)
Low	22	1.3(0.8-2.0)	19	1.5(0.9-2.5)
Medium	17	1.3(0.8-2.3)	19	1.0(0.6-1.7)
High	17	1.1(0.6-1.9)	18	1.3(0.8-2.2)
		P trend=0.68		Ptrend=0.43
Permethrin (Crop)				
None	179	1.0 (ref)	179	1.0 (ref)
Low	12	1.0(0.6-1.9)	9	1.4(0.7-2.7)

Medium	6	2.2(1.0-5.1)	9	1.2(0.6-2.4)
High	8	0.6(0.3-1.2)	8	0.6(0.3-1.2)
		P trend=0.18		P trend=0.15
Trifluralin **(dinitroaniline-herbicide)**				
None	104	1.0 (ref)	104	1.0 (ref)
Low	39	1.0 (0.7-1.5)	37	1.0(0.7-1.4)
Medium	40	1.0(0.7-1.4)	36	1.0(0.7-1.4)
High	29	0.8(0.6-1.3)	34	0.9(0.6-1.3)
		P trend=0.0.36		P trend=0.44
2,4,5 T **(phenoxyacetic acid)**				
None	73	1.0 (ref)	73	1.0 (ref)
low	22	1.9(1.2-3.1)	13	2.0(1.1-3.6)
medium	3	1.3(0.4-4.3)	12	1.8(0.99-3.4)
high	12	1.5(0.8-4.3)	12	1.4(0.7-2.5)
		P for trend=0.0.27		P for trend=0.94

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Carbofuran									
None	1.0(ref)	67	1.0(ref)	58	1.0(ref)	33	1.0(ref)	19
Low	1.4 (0.8-2.5)	15	0.9 (0.4-1.9)	8	0.96(0.4-2.5)	5	1.0(04-2.7)	5
Medium	1.2 (0.6-2.4)	10	0.9 (0.4-1.8)	9	1.6(0.7-3.9)	6	1.4(0.2-10.7)	1
High	1.3 (0.7-2.4)	12	1.1 (0.5-2.9)	5	0.6(0.2-2.0)	3	0.94(0.2-4.1)	2
	P trend=0.36		P trend=0.81		P trend=0.79		P trend=0.99	
Chlorpyrifos								
None	1.0 (ref)	69	1.0 (ref)	55	1.0 (ref)	26	1.0 (ref)	18
Low	0.9(0.5-1.7)	15	1.2(0.6-2.1)	13	1.4(0.7-3.1)	10	0.9(0.3-2.6)	5
Medium	1.1(0.7-2.0)	16	1.0(0.5-1.7)	15	1.2(0.5-2.9)	7	4.2(1.7-10.6)	6
High	1.0(0.5-1.7)	14	0.9(0.6-4.0)	7	1.4(0.6-3.4)	6	0.8(0.3-2.3)	4
	P trend=0.99		P trend=0.66		P trend=0.56		P trend=0.97	
Diazinon								
None	1.0 (ref)	40	1.0 (ref)	33	1.0 (ref)	13	1.0 (ref)	12
Low	1.5(0.7-3.1)	9	1.2(0.4-3.1)	5	1.6(0.4-5.5)	3	xxx	2
Medium	1.2(0.4-3.6)	5	0.9(0.3-2.8)	4	1.6(0.4-7.4)	3	xxx-	1
High	1.2(0.5-3.0)	5	1.2(0.4-3.8)	3	2.0(0.4-10.0)	2	xxx	0
	P trend=0.72		P trend=0.84		P trend=0.35		P trend=xxx	
Permethrin animals								
None	1.0 (ref)	95	1.0 (ref)	78	1.0 (ref)	38	1.0 (ref)	25
Low	1.3(0.5-3.3)	5	Xxx	1	2.8(1.1-7.0)	5	xxx-	1
Medium	0.9(0.2-3.7)	3	xxx	1	2.9(0.7-12.0)	2	-xxx	2
High	0.8(0.3-2.5)	3	-xxx	0	0.8(0.2-3.5)	2	-xxx	0
	P trend=0.75		P trend=xxx		P trend=0.93		P trend=xxx	
Cyanazine								

(triazine)									
None	1.0 (ref)	65	1.0 (ref)	46	1.0 (ref)	24	1.0 (ref)	10
Low	1.2 (0.7-2.2)	15	1.4 (0.8-2.4)	16	1.9(0.9-3.8)	12	3.7(1.4-9.7)	7
Medium	0.9 (0.5-1.6)	16	0.8 (0.4-1.8)	8	1.7(0.8-3.6)	9	2.9 (1.5-7.5)	8
High	1.1(0.6-2.0)	14	1.0 (0.5-2.1)	8	0.8(0.3-2.2)	4	2.6(0.9-7.5)	5
	P trend=0.93		P trend=0.93		P trend=0.87		P trend=0.17	

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Review

Non-Hodgkin Lymphoma and Occupational Exposure to Agricultural Pesticide Chemical Groups and Active Ingredients: A Systematic Review and Meta-Analysis

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Abstract: This paper describes results from a systematic review and a series of meta-analyses of nearly three decades worth of epidemiologic research on the relationship between non-Hodgkin lymphoma (NHL) and occupational exposure to agricultural pesticide active ingredients and chemical groups. Estimates of associations of NHL with 21 pesticide chemical groups and 80 active ingredients were extracted from 44 papers, all of which reported results from analyses of studies conducted in high-income countries. Random effects meta-analyses showed that phenoxy herbicides, carbamate insecticides, organophosphorus insecticides and the active ingredient lindane, an organochlorine insecticide, were positively associated with NHL. In a handful of papers, associations between pesticides and NHL subtypes were reported; B cell lymphoma was positively associated with phenoxy herbicides and the organophosphorus herbicide glyphosate. Diffuse large B-cell lymphoma was positively associated with phenoxy herbicide exposure. Despite compelling evidence that NHL is associated with certain chemicals, this review indicates the need for investigations of a larger variety of pesticides in more geographic areas, especially in low- and middle-income countries, which, despite producing a large portion of the world's agriculture, were missing in the literature that were reviewed.

Keywords: pesticides; insecticides; herbicides; fungicides; lymphoma; non-Hodgkin; occupational; agricultural

1. Introduction

Striking increases in the incidence of non-Hodgkin lymphoma (NHL) cancer have occurred in the last 30 years [1,2], and interest in identifying environmental and occupational exposures associated with this cancer has accompanied this trend. Several environmental exposures have been proposed and investigated as potentially important—pesticides, dioxins, solvents, oils, and viruses, among others [3,4]. Farmers experience low overall mortality but high rates of some cancers; this suggests that some or several agricultural exposures may be key determinants [5,6]. Indeed, positive associations between NHL and farm related exposures, including pesticides, fertilizers, chemicals, animals, viruses, and endotoxin, have been observed previously [3,5,7]. However, the wide variety of chemical and microbial exposures that occur simultaneously in agricultural production makes disentangling the effects of these factors challenging. Of the many exposures experienced in farm settings, pesticides have drawn particular attention, especially since the increased incidence of NHL in the mid- to late-1900s followed widespread use of synthetic organic pesticides [4]. Also, several epidemiologic studies have reported positive associations between NHL and pesticide exposure in occupational manufacturing settings [8,9].

The United States Environmental Protection Agency defines pesticides as substances intended to prevent, destroy, repel, or mitigate a pest [10]. Within this broad category, pesticides are often grouped according to the type of pests that they control; for example, fungicides are used to kill fungi, insecticides to kill insects, and herbicides to kill weeds and plants. In addition to function, pesticides vary in terms of structure, and they are sometimes grouped according to chemical relationships. Furthermore, applicators often use a variety of pesticides simultaneously. These characteristics make designing and conducting epidemiologic studies of their health effects both challenging and expensive.

Because pesticides are thought to have different toxicologic and immunologic effects, identifying the chemicals and chemical groups that are most dangerous to humans and non-target living organisms is important [11]. From a research perspective, the decision about what chemicals to investigate has implications for disease prevention, and it impacts the information that is available to policy makers and the public.

These challenges and needs motivated us to systematically review the published epidemiologic literature of relationships of NHL with occupational exposures to agricultural pesticide chemical groups and active ingredients. The primary objectives of this paper were to investigate the depth of the literature on the relationship between specific pesticide chemicals and NHL, to identify gaps in this area of research, and to elucidate pesticide chemical groups and active ingredients that have shown particularly strong relationships with NHL. To help us to achieve these objectives, we conducted a series of meta-analyses of associations of individual pesticide chemicals with NHL.

2. Methods

2.1. Article Identification

We performed a search of literature on associations between occupational pesticide exposure and NHL. We restricted our search to articles published since 1980. This time period is consistent with that used in previous meta-analyses of farming exposures [5], and it captured the epidemiologic literature

that has not been reviewed by early IARC monograph evaluations of pesticides [12]. The search used combinations of the following words: occupational exposure, pesticides, insecticides, herbicides, fungicides, neoplasms, cancer, lymphomas, non-Hodgkin lymphoma, cancer mortality, agricultural workers' diseases/chemically induced, and humans. We entered combinations of these terms into PubMed and Web of Science. Details of the search are given in Supplementary file S1.

2.2. Article Selection

To identify eligible studies, we reviewed the titles and abstracts of papers. When it was unclear from the abstract and title whether the paper fit these criteria, the full text of the paper was reviewed. We included estimates from papers with the following characteristics:

(1)   Written and published in English;
(2)   Reported results of analyses of case control or cohort epidemiology studies;
(3)   Reported results of studies that used interviews, questionnaires, and/or exposure matrices to assess exposure;
(4)   Reported associations of NHL with occupational, agricultural pesticide exposures;
(5)   Reported quantitative associations of NHL overall and/or NHL subtypes with specific individual active ingredients or chemical groups.

We excluded papers with the following characteristics:

(1)   Written in a language other than English;
(2)   Did not report on associations with NHL;
(3)   Were a commentary, letter to the editor, or monograph;
(4)   Did not report associations with individual pesticide active ingredients or chemical groups; we excluded papers that reported associations with only the broadly defined categories of pesticide, insecticide, herbicide, or fungicide;
(5)   Reported results of analyses of ecologic studies;
(6)   Reported results of analyses of data from studies that were not case control or cohort in design;
(7)   The exposure definition/classification was ambiguous;
(8)   The exposure route was not occupational;
(9)   The exposure route was not agricultural;
(10) Reported only associations within unique subpopulations (e.g., HIV positive patients);
(11) Reported analyses of manufacturing cohorts;
(12) Reported associations with NHL as a second primary;
(13) Reported results of studies in which exposure was assessed using biological markers.

2.3. Data Extraction

We extracted the following information from the full text of each eligible paper:

- author;
- publication year;
- study location;

- study design (case-control or cohort);
- source population for the controls in case-control studies;
- whether case-control studies were matched, and if so, the matching factors;
- diagnosis period if a case-control study or cancer follow-up period if a cohort study;
- number of cohort participants or number of cases and controls;
- cancer definition or ICD codes used to identify the cancers;
- method of assessing exposure;
- exposure metrics and definitions;
- referent categories used in the analysis;
- active ingredient(s) and/or chemical group(s) studied;
- covariates entered into the model to adjust for confounding;
- type of effect estimate reported;
- number of exposed participants;
- effect estimates and confidence interval limits; and
- gender restrictions, if any.

We also identified papers that were related to each other (e.g., pooled analyses that used data that were analyzed and reported on previously, papers that reported on different analyses from the same study, studies that were follow up analyses of the same population). In cases of related papers, we used a specific set of rules to decide which effect estimate to report and use in the meta-analyses; this rule is described in Section 2.5.

2.4. Chemical Group Classification

We reported results for all chemical groups for which there was information from the available literature. We did not consider exposures to chlorophenols in this paper, since much of the exposure to this chemical group comes from non-agricultural settings. We classified pesticide active ingredients into chemical groups based on Alan Wood's classification system [13].

2.5. Reporting of Results for the Systematic Review

From every relevant paper, we extracted an effect estimate for each active ingredient and/or chemical group. We extracted results for associations with NHL, and when available, for associations with subtypes of NHL.

We used the following algorithm to determine which effect estimates to use:

(1) For related papers that examined the same exposure/outcome association, we used the results from the most complete and updated analysis with the greatest number of participants;

(2) If more than one exposure definition was considered and reported, we used the definition that best represented agricultural exposures (e.g., we selected results for farmers who worked with phenoxy herbicides, instead of results for herbicide applicators, gardeners, or landscapers);

(3) The various papers used different confounder adjustment sets, which were selected based on different criteria. In an effort to use the most unbiased estimate, we extracted the most adjusted effect estimate;

(4)   Most papers defined exposure dichotomously. Papers that reported results according to more than two categories used a variety of definitions for the exposure metrics, including duration of use, days/year of use, time since first exposure, and cumulative days of exposure. Because the definitions and metrics used to define categories varied, it was not possible to combine estimates based on multiple categories of exposure in formal meta-analyses. Therefore, for the meta-analyses, we used the result for the dichotomously defined exposure with the greatest number of exposed cases. To assess dose-response relationships, we qualitatively examined results in association with multiple categories;

(5)   Some papers only reported results in association with multiple categories of exposure. We extracted these results for the systematic review, since they can be used to qualitatively evaluate trends in association of NHL with active ingredient or chemical group and are important for identifying dose-response relationships;

(6)   Some studies only reported estimates of association between pesticide exposures and subtypes of NHL. We abstracted these estimates for presentation and analysis of association of pesticide exposures with NHL subtypes.

We present results from the systematic review sorted by chemical group and, within chemical group, by active ingredient.

2.6. Meta Analysis

2.6.1. Grouping

When possible, we conducted separate meta-analyses for each chemical group and active ingredient. We conducted meta-analyses for associations of these pesticides with NHL and NHL subtypes. Although we abstracted results according to dichotomous exposure and multiple levels of exposure, we conducted formal meta-analyses for dichotomously categorized exposures only.

2.6.2. Analytic Methods

Because we identified a variety of sources of heterogeneity between papers, we decided a priori to calculate meta- risk ratio (RR) estimates and 95% confidence intervals (CIs) using random effect models, allowing between study heterogeneity to contribute to the variance [14,15]. We report I^2 values, which represent the percentage of the total variance explained by study heterogeneity and measure inconsistency in results. Larger I^2 values indicate greater inconsistency [15]. We did not perform formal heterogeneity tests; Cochran's Q statistic has been shown to have low power to detect true heterogeneity across studies, especially in meta-analyses that include a small number of papers [15]. Following recommendations for meta-analyses of observational studies, we also identified possible sources of heterogeneity and used sensitivity analyses to evaluate these, as described in Section 2.6.3 [16]. We evaluate the meta- estimates of association based on the magnitude of the point estimate and interpret the associated 95% CIs as indicators of precision. To aid this interpretation, we have calculated and reported confidence limit ratios (CLRs), which are the ratio of the upper to the lower CI limit [17]. We also present forest plots for meta-analyses to which five or more papers contributed.

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2.6.3. Sensitivity Analysis

We conducted sensitivity analyses to evaluate robustness of our results to the following sources of heterogeneity: study design (case-control versus cohort), gender (male only versus both genders), geographic area, decade of cancer diagnosis, and source of the controls in case-control studies (population-based versus hospital).

One paper presented results of analyses of women only [18]. Thus, we were not able to conduct a sensitivity analysis for analyses of women; we were able to conduct sensitivity analyses using papers that reported results for men and for men and women. Only two papers reported estimates of association from studies in which controls were drawn from hospitals, and these two studies reported associations of NHL with different pesticides. Therefore, our sensitivity analysis of the control source in case-control studies was restricted to controls drawn from the population. Data from only one cohort study contributed to our meta-analyses. Therefore, we could not restrict meta-analyses to cohort studies only.

The geographic areas that we investigated separately in sensitivity analyses were North America, the United States, Europe, and Sweden. We selected these because there was more than one study within each area that investigated associations of NHL with a particular pesticide. In addition to maintaining Sweden and the United States in sensitivity analyses of Europe and North America, respectively, we analyzed results from Sweden separately from the rest of Europe, and results from the United States separately from Canada. We conducted these separate analyses because more than one paper reported effect estimates of association with a pesticide from each of these countries, and because we believed effects might be different when separated from the rest of the continent. Although we identified papers from Australia and New Zealand we were not able to analyze these separately because there was not more than one effect estimate of association with an individual pesticide from either country.

We investigated the following diagnosis periods: 1975–1989, 1990–1999, and year 2000 and later. If any part of the diagnosis period overlapped these periods, we included the estimate from the paper in the sensitivity analysis. We selected these periods based on the periods that appeared in the papers that we reviewed and on the different editions of the ICD coding systems [1].

After performing meta-analyses for each active ingredient or chemical group, we repeated analyses, removing studies that differed from the others based on the above-described characteristics. In cases when results from individual studies were also represented in papers that analyzed these data pooled with data from other studies, we performed sensitivity analyses by replacing the results from the pooled analyses with the individual studies, or the individual studies with the results from the pooled analyses.
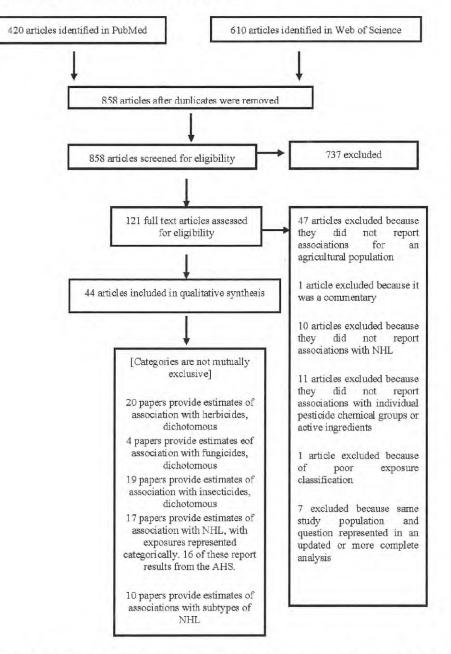
3. Results

3.1. Systematic Review

The PubMed and Web of Science searches yielded 858 unique articles (Figure 1). After screening the abstracts and titles, we excluded 737 articles. Of the remaining 121 articles, 47 were excluded because they reported results within a non-agricultural population. We decided to exclude non-agricultural populations because the nature of exposure they receive is different compared to agricultural groups. Because of contamination and production of multiple chemicals simultaneously, it is difficult to determine the exact chemical to which manufacturing cohort participants have been exposed.

Figure 1. Flow chart showing the articles that were included and excluded in the systematic review, with reasons for the exclusions.

After excluding 27 additional articles because they did not meet one or more of the inclusion criteria described in the methods section, we included 44 papers in our qualitative synthesis. Of these, 20 papers provided estimates of association with herbicide chemical groups or active ingredients, four papers provided estimates of association with fungicides, and 17 with insecticides.

3.2. Summary of Studies from Which Estimates were Extracted

A summary of the 44 papers from which effect estimates were abstracted is presented in Table 1.

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Table 1. Summary of papers from which effect estimates were extracted.

Author, year, location	Design	Source for controls	Matching	Diagnosis or follow-up period (cancer)	No. Participants	Exposure assessment	Referent category for exposure, exposure definition(s)/metric	Men only	Adjustment set	Pesticides	Reported results by subtype
Barry 2012 [19] Iowa and North Carolina, USA	C (AHS)	NA	NA	1993–2007	53,588	Self-administered questionnaire completed during enrollment and interviewer administered follow-up questionnaire	Referent: No exposure Intensity weighted lifetime exposure days, 15 year lag Intensity weighted lifetime exposure days, no lag	No	Age, gender, race, state of residence, applicator type, enrollment year, cigarette smoking, alcohol consumption, education, family history of cancer, 5 most correlated pesticides	Methyl bromide	No
Baris 1998 [20] Iowa, Kansas, Minnesota, Nebraska, USA	Pooled analysis of 3 CC studies	Population	Matched by race, gender, age, and vital status at the time of interview, year of death for controls matched to deceased cases	Dx period [1]: 1979–1983	993 cases/2,918 controls	Telephone interviews (Kansas and Nebraska, USA), In-person interviews (Iowa and Minnesota)	Referent: Non-farmers Used vs. did not use on crops and animals, Used vs. did not use on crops, Used vs did not use on animals Duration of use, in years (1-4, 5-9, ≥10) Days/year of use (≤5, >5)	Yes	Age, state of residence	DDT	Yes
Beane Freeman 2005 [21] Iowa and North Carolina, USA	C (AHS)	NA	NA	1993–2007	23,106	Two self-administered questionnaires	Referent: No exposure Lifetime exposure days Intensity weighted exposure days	Yes	Age, smoking, education, family history of cancer, state of residence, total days of any pesticide application	Diazinon	No
Beane Freeman 2011 [22] Iowa and North Carolina, USA	C (AHS)	NA	NA	1993–2007	36,357	A self-administered questionnaire	Referent 1: No exposure Referent 2: Lowest quartile of exposure Lifetime days of exposure Intensity weighted lifetime days of exposure	No	Age, state, license type, gender, smoking status, alcohol consumption, education, use of most highly correlated pesticides	Atrazine	Yes

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Table 1. *Cont.*

Author, year, location	Design	Source for controls	Matching	Diagnosis or follow-up period (cancer)	No. Participants	Exposure assessment	Referent category for exposure, exposure definition(s)/metric	Men only	Adjustment set	Pesticides	Reported results by subtype
Blair 1998 [23] Iowa, Kansas, Minnesota, Nebraska, USA	CC	Population	Matched by race, gender, age, vital status at the time of interview	Dx period [1]: 1979–1983	987 cases/2,895 controls	Telephone interviews (Kansas and Nebraska, USA), In-person interviews (Iowa and Minnesota)	Referent: nonfarmer Farmers who ever used Days/year of use (<4 days, ≥5 days) First lindane use (≥20 years ago, <20 years ago)	Yes	Age, proxy/direct interview, state of residence	Lindane	Yes
Bonner 2010 [24] Iowa and North Carolina, USA	C (AHS)	NA	NA	1993–2005	44,624	Self-administered questionnaires	Referent 1: Nonexposed Referent 2: Lowest tertile of exposure Intensity weighted lifetime exposure days	No	Age, gender, education, family history of cancer, smoking, alcohol, year of enrollment, state of residence, correlated pesticides	Terbufos	No
Bonner 2005 [25] Iowa and North Carolina, USA	C (AHS)	NA	NA	1993–2001	49,877	Self-administered questionnaire	Referent 1: Nonexposed Referent 2: Lowest tertile of exposure Lifetime exposure days Intensity weighted lifetime exposure days	No	Age, gender, education, family history of cancer, smoking, alcohol, year of enrollment, state of residence, exposure to correlated pesticides	Carbofuran	No
Bonner 2007 [26] Iowa and North Carolina, USA	C (AHS)	NA	NA	1993–2002	19,717	Self-administered questionnaire	Referent 1: Nonexposed Referent 2: Lowest tertile of exposure Lifetime exposure days, Intensity weighted lifetime exposure days	No	Age, gender, smoking, alcohol, education, family history of cancer, year of enrollment, state of residence	Malathion	No

Table 1. *Cont.*

Author, year, location	Design	Source for controls	Matching	Diagnosis or follow-up period (cancer)	No. Participants	Exposure assessment	Referent category for exposure, exposure definition(s)/metric	Men only	Adjustment set	Pesticides	Reported results by subtype
Cantor 1992 [27] Iowa and Minnesota, USA	CC	Population	Matched by 5-year age group, vital status at time of interview, and state of residence	Dx period [1]: 1979–1983	622 cases/1,245 controls	In-person interviews	Referent: Non-farmers Ever handled, Handled prior to 1965 Handled without protective equipment	Yes	Age, vital status, state, cigarette smoking, family history of lymphohematapoeitic cancer, high risk occupations, high risk exposures	2,4-D, 2,4,5-T, alachlor, atrazine, aldrin, bentazon, butylate, carbofuran, carbaryl, chlordane, chloramben, copper acetoarsenate, cyanazine, coumaphos, diazinon, dicamba, dichlorvos, DDT, famphur, Flyspray, fonofos, glyphosate, heptachlor, lindane, malathion, methoxychlor, metribuzen, nicotine, phorate, popachlor, rotenone, toxaphene, trifluralin, turbufos,	No
Cocco 2013 [28] Multicentre, Czech Republic, France, Germany, Italy, Ireland, Spain	CC	Population (German and Italian centers), Hospital (Czech Republic, French, Irish, Spanish centers)	Matched by gender, 5-year age group, and residence area	1998–2004	2,348 cases/2,462 controls	Structured in-person interviews conducted by trained interviewers; jobs were coded by industrial hygienists; industrial hygienists and occupational experts reviewed the questionnaires and job modules to assess exposures to pesticides (with the help of a crop exposure matrix)	Referent: Never exposed Ever exposed, by level of industrial hygienists's degree of confidence that the participant was truly exposed to the agent: Any level of confidence High confidence	No	Age, gender, education, study center	Carbamates, OPs, OC, Triazines and triazoles, phenoxy acids, chlorophenols, mancozeb, methomyl, dimethoate, glyphosate, DDT, endosulfan, 2,4-D, MCPA	Only reported for subtypes
Delancey 2009 [29] Iowa and North Carolina, USA	C (AHS)	NA	NA	1993–2004	23,072	Two self-administered questionnaires	Referent: Lowest tertile of exposure Lifetime exposure days Intensity weighted lifetime exposure days	Yes	Age, smoking, alcohol consumption, education, family history of cancer, state of residence, exposure to all pesticides	Metribuzin	No

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Table 1. *Cont.*

Author, year, location	Design	Source for controls	Matching	Diagnosis or follow-up period (cancer)	No. Participants	Exposure assessment	Referent category for exposure, exposure definition(s)/metric	Men only	Adjustment set	Pesticides	Reported results by subtype
de Roos 2003 [30] Iowa, Kansas, Minnesota, Nebraska, USA	CC	Population	Matched by race, gender, age, vital status at the time of interview	Dx period [1]: 1979–1983	650 cases/1,933 controls	Telephone interviews (Kansas and Nebraska, USA), In-person interviews (Iowa and Minnesota)	Referent: Not exposed Exposed	Yes	Age, study site, use of all other pesticides	Aldrin, bufencarb, carbaryl, carbofuran, chlordane, copper acetoarsenite, coumaphos, DDT, diazinon, dichlorvos, dieldrin, dimethoate, ethoprop, famphur, fly/tick/lice spray, fonofos, heptachlor, lead arsenate, lindane, malathion, methoxychlor, nicotine, phorate, pyrethrins, rotenone, tetrachlorvinphos, toxaphene, terbufos, alachlor, atrazine, bentazon, butylate, chloramben, cyanazine, 2,4-D, dicamba, EPTC, glyphosate, linuron, MCPA, metolachlor, metribuzin, paraquat, propachlor, sodium chlorate, 2,4,5-T, trifluralin	No
de Roos 2005 [31] Iowa and North Carolina, USA	C (AHS)	NA	NA	1993–2001	54,315	Self-administered questionnaire	Referent 1: Never used Referent 2: Lowest tertile of exposure Ever used Cumulative exposure days Intensity weighted exposure days	No	Age at enrollment, education, cigarette smoking, alcohol consumption, family history of cancer, state of residence, other pesticides	Glyphosate	No
Eriksson 2008 [32] Sweden	CC	Population	Matched in 10 year age and gender groups to mirror the age and gender distribution of the cases	Dx period: 1999–2002	1,163 cases/1,016 controls	Telephone interview on life style factors and diseases; Self-administered questionnaire on work history and chemical exposures; follow up telephone interviews to collect incomplete data	Referent: Never exposed Ever exposed, Days of exposure (categorized at the median of the exposure distribution),	No	Age, gender, year of Dx/enrollment	Phenoxyacetic acids, MCPA, 2,4,5-T and/or 2,4-D, glyphosate	Yes

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Table 1. *Cont.*

Author, year, location	Design	Source for controls	Matching	Diagnosis or follow-up period (cancer)	No. Participants	Exposure assessment	Referent category for exposure, exposure definition(s)/metric	Men only	Adjustment set	Pesticides	Reported results by subtype
Hardell 2002 [33] Sweden	CC, pooled analysis of two studies, one of hairy cell lymphoma and one of NHL	Population	Matched by age and county	Dx period: 1987–1990 (NHL); 1987–1992 (hair cell lymphoma)	515 cases/1,141 controls	Self-administered questionnai-re supplement-ed by telephone interviews by a trained interviewer when information was unclear	Referent 1: Not exposed Ever exposure, High exposure (>median number of days for exposed participants) Low exposure (<median number of days for exposed participants) Years between first exposure and diagnosis: Referent 2: 1-10years, >10-20 years, >20-30 years, >30 years Years between last exposure and diagnosis: Referent 3: 1-10 years, >10-20 years, >20-30 years, >30 years Decade of exposure	Yes	Study, study area, vital status, age	Phenoxy acids, MCPA, 2,4-D + 2,4,5-T, glyphosate, DDT, mercurial seed dressing, pyrethrins, arsenic	No
Hoar 1986 [34] Kansas, USA	CC	Population	Matched by age and vital status	Dx period: 1976–1982	170 cases of NHL/948 controls (no. included in NHL analysis unclear)	Telephone interviews, with questions on years living/ working on a farm, and herbicides/insecticides used.	Referent: Non-farmers Ever use, Duration of use (years), Frequency of use (days/year), First year of use	Yes	Age	Phenoxyacetic acids, Triazine herbicides, Amide herbicides, Benzoic herbicides, Carbamate herbicides, Trifluralin herbicides, Uracil herbicides	No

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Table 1. *Cont.*

Author, year, location	Design	Source for controls	Matching	Diagnosis or follow-up period (cancer)	No. Participants	Exposure assessment	Referent category for exposure, exposure definition(s)/metric	Men only	Adjustment set	Pesticides	Reported results by subtype
Kang 2008 [35] Iowa and North Carolina, USA	C (AHS)	NA	NA	1993–2002	50,127	Self-administered questionnai-res completed during enrollment and interviewer administered follow-up questionnaires	Referent 1: Nonexposed Referent 2: Lowest tertile of exposure Lifetime exposure days, Intensity weighted lifetime exposure days	No	Age at enrollment, education, cigarette smoking, alcohol consumption, family history of cancer, state of residence, top five most highly correlated pesticides	Trifluralin	No
Koutros 2009 [36] Iowa and North Carolina, USA	C (AHS)	NA	NA	1993–2004	49,398	Self-administered questionnaire	Referent: Nonexposed Intensity weighted lifetime exposure days	No	Age, year of enrollment, race	Imazethapyr	No
Koutros 2008 [37] Iowa and North Carolina, USA	C (AHS)	NA	NA	1993–2004	49,762	Self-administered questionnaire	NA	No	Not applicable, since an adjusted effect estimate for an association with NHL was not reported	Dichlorvos	No
Lee 2004 [38] Iowa and North Carolina, USA	C (AHS)	NA	NA	1993–2001	54,383	Self-administered questionnaire	Referent 1: Nonexposed Lifetime exposure days, Intensity weighted lifetime exposure days	No	Age, gender, alcohol consumption, smoking history, educational level, family history of cancer, year of enrollment, state of residence, use of 4 correlated pesticides	Chlorpyrifos	No
Lee 2004 [39] Iowa and North Carolina, USA	C (AHS)	NA	NA	1993–2000	49,980	Self-administered questionnaire	Referent 1: Nonexposed Exposed, Referent 2: Lowest quartile of exposure Lifetime exposure days, Intensity weighted lifetime exposure days	No	Age, sex, alcohol, smoking, education, family history of cancer, enrollment year, state of residence, 5 correlated pesticides	Alachlor	No

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Table 1. *Cont.*

Author, year, location	Design	Source for controls	Matching	Diagnosis or follow-up period (cancer)	No. Participants	Exposure assessment	Referent category for exposure, exposure definition(s)/metric	Men only	Adjustment set	Pesticides	Reported results by subtype
Lynch 2009 [40] Iowa and North Carolina, USA	C (AHS)	NA	NA	1993–2004	19,655	Self-administered questionnaire	Referent 1: Nonexposed Referent 2: Lowest tertile of exposure Lifetime exposure days, Intensity weighted lifetime exposure days	No	Age at enrollment, gender, race, smoking status, education, family history of cancer, atrazine, 5 most correlated pesticides	Butylate	No
Lynch 2006 [41] Iowa and North Carolina, USA	C (AHS)	NA	NA	1993–2002	50,800	Self-administered questionnaire	Referent: Lowest tertile of exposure[1] Lifetime exposure days, Intensity weighted lifetime exposure days	No	Age, race, gender, alcohol consumption, smoking status, education level, family history of cancer, state of residence, 5 most correlated pesticides	Cyanazine	No
Mahajan 2007 [42] Iowa and North Carolina, USA	C (AHS)	NA	NA	1993–2003	21,416	Self-administered questionnai-re	Referent 1: Nonexposed Referent 2: Lowest tertile of exposure Lifetime exposure days, Intensity weighted lifetime exposure days	No	Age, smoking, gender, state of residence, use of 4 correlated pesticides	Carbaryl	No
McDuffie 2001 [43] Six Canadian provinces	CC	Population	Frequency matched by age and province of residence	Dx period: 1991–1994	517 cases/1,50 6 controls	Self-administered postal questionnai-re followed by telephone interview with participants who had 10 or more hours of pesticide use in lifetime plus a 15% random sample of those with fewer than 10 hours pesticide use	Referent: Not exposed Exposed, Frequency of exposure (days/year)	Yes	Age, providence of residence	2,4-D, mecoprop, MCPA, DiclofopmethylGlyphosate, phosphonic acids, phenoxy herbicides, thiocarbamates,diallate, dicamba, dinitroaniline, trifluralin, carbaryl, carbofuran, methomyl, carbamate insecticides, organochlorine insecticides, chlordane, lindane, aldrin, methoxychlor, DDT, Captan, vitavax, aldehyde, formaldehyde, mercury dust, mercury liquid, malathion, carbon tetrachloride	

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Table 1. *Cont.*

Author, year, location	Design	Source for controls	Matching	Diagnosis or follow-up period (cancer)	No. Participants	Exposure assessment	Referent category for exposure, exposure definition(s)/metric	Men only	Adjustment set	Pesticides	Reported results by subtype
Miligi 2006 [44] Italy	CC	Population	Stratified by gender and 5-year age groups	Dx period: 1991–1993	1,145 cases/1,232 controls	In-person interviews, including questions on crops grown and whether pesticides were used combined with exposure matrix	Reference: Those who never worked in agriculture. Overall exposure, Probability of use >low and lack of protective equipment	No	Age, gender, area	Phenoxy herbicides, 2,4-D, MCPA	No
Mills 2005 [45] California	CC	Same source as the cases (United Farm Workers of America cohort)	Matched by gender, hispanic ethnicity and +/− one year of birth	Dx period: 1988–2001	60 cases/300 controls	Work histories combined with exposure matrix	Reference: Low use High use	No	Age, gender, length of union affiliation, date of first union affiliation	Methyl bromide, diazinon, malathion, dichloro-propane, captan, simazine, chlrothalonil, mancozeb, methyl parathion, nitrofen, propyzamide, toxaphene, trifluralin, 2,4-D, maneb	No
Orsi 2009 [46] France	CC	Hospital	Matched by center, age +/− 3 year, gender	2000–2004	244 cases/436 controls	Self-administered questionnai-res, followed by face to face interviews with trained staff, and review of interviews by experts to verify logical consistency with pesticide product availability, geographic location, etc.	Reference: Nonexposed Exposed	No	Age, center, socioeconomic characteristic (white collar vs blue collar)	Organochlorine insecticides, organophosphorus insecticides, pyrethrin, carbamate fungicides, imide fungicides, triazole fungicides, phenoline herbicides, phenoxy herbicides, picoline herbicides, triazine herbicides, amide herbicides, urea herbicides, quaternary ammonium herbicides, glyphosate	Yes
Pahwa M 2012 [47] Six Canadian provinces	CC	Population	Frequency matched by age and province of residence	Dx period: 1991–1994	513 cases/ 506 controls	Self-administered postal questionnaire followed by telephone interview with participants who had 10 or more hours of pesticide use in lifetime plus a 15% random sample of those with fewer than 10 hours pesticide use	Reference: No use Use	Yes	Age, province of residence, respondent type (self or proxy), diesel oil exposure	OC insecticides, DDT, OP insecticides, malathion, phenoxy herbicides, MCPA, mecoprop, 2,4-D	No

Table 1. *Cont.*

Author, year, location	Design	Source for controls	Matching	Diagnosis or follow-up period (cancer)	No. Participants	Exposure assessment	Referent category for exposure, exposure definition(s)/metric	Men only	Adjustment set	Pesticides	Reported results by subtype
Pearce 1987 [48] New Zealand	CC	Cancer registry	Matched by year of cancer registration and age (± 2 years)	Dx period: 1977–1981	183 cases/338 controls	Telephone interviews	Reference: Nonexposed Used any agricultural chemical spray in a farming setting	Yes	Decade of birth, type of interview respondent (self or relative)	Phenoxy herbicides	No
Persson 1989 [49] Sweden	CC	Population	Unmatched	Dx period: 1964–1986	106 cases/275 controls	Self-administered questionnaire	Reference: Not exposed Exposed	No	Age, date of Dx, gender, farming, exposure to fresh wood, other exposures associated with at least a doubled risk for hodgkins disease or NHL	Phenoxy herbicides, DDT	No
Persson 1993 [50] Sweden	CC	Population	Unmatched	Dx period: 1975–1984	93 cases/204 controls	Self-administered questionnaires	Reference: Not exposed Exposed	No	Age, other exposures investigated with OR ≥2 or significantly below unity and with at least 5 exposed subjects	Phenoxy herbicides, DDT	No
Purdue 2007 [51] Iowa and North Carolina, USA	C (AHS)	NA	NA	1993–2002	51,011	Self-administered questionnaire	Reference 1: Never use/unexposed Ever use Lifetime days of exposure Intensity weighted lifetime days of exposure	No	Age, sate, gender, education level, smoking status, alcohol use, family history of cancer, lifetime days of total pesticide application	OC insecticides, aldrin, chlordane, DDT, dieldrin, heptachlor, lindane, toxaphene	No
Rafnsson 2006 [52] Iceland	CC	Non-cases from cohort of sheep owners	Unmatched	Dx period: 1966–2003	45 cases/221 controls	Records of sheep owned, used as a proxy measure for dermal exposure from sheep dipping; sheep dipping used as a proxy for exposure to hexa-chlorocyclohexane, which is a mixture of different isomers containing around 15% lindane. <100 sheep owned was used to indicate unexposed	Referent: <100 sheep ≥100 sheep , Categories of number of sheep owned: 100-199 sheep, 200-683 sheep	Yes	Age	Hexachlorocyc-lohexane	No

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Table 1. *Cont.*

Author, year, location	Design	Source for controls	Matching	Diagnosis or follow-up period (cancer)	No. Participants	Exposure assessment	Referent category for exposure, exposure definition(s)/metric	Men only	Adjustment set	Pesticides	Reported results by subtype
Rusiecki 2009 [53] Iowa and North Carolina, USA	C (AHS)	NA	NA	1993–2004	49,093	Self-administered questionnaire	Referent: Nonexposed Lifetime days of exposure Intensity weighted	No	Age, gender, race, family history of cancer, cigarette smoking, state of residence, enrollment year	Permethrin	No
Rusiecki 2006 [54] Iowa and North Carolina, USA	C (AHS)	NA	NA	1993–2002	50,193	Self-administered questionnaire	Referent: Lowest tertile of exposure Lifetime days of exposure Intensity weighted lifetime days of exposure	No	Age, gender, race, smoking, alcohol, applicator status, family history of cancer, sate of residence, most highly correlated pesticides	Metolachlor	No
van Bemmel 2008 [55] Iowa and North Carolina, USA	C (AHS)	NA	NA	1993–2004	48,378	Self-administered questionnaire	Referent: No exposure Lifetime days of exposure Intensity weighted lifetime days of exposure	Yes	Age, race, smoking, alcohol use, applicator type, family history of cancer, state of residence, total days of pesticide use	EPTC	No
Waddell 2001 [56] Iowa, Kansas, Minnesota, Nebraska, USA	Pooled analysis of 3 CC studies	Population	Matched by race, gender, age, and vital status at the time of interview, year of death for controls matched to deceased cases	Dx period [1]: 1979–1983	748 cases/2,236 controls	Telephone interviews (Kansas and Nebraska, USA), In-person interviews (Iowa and Minnesota)	Referent: Non-farmers Ever Used First used Years used Days/year of use Protective gear	Yes	Age, state of residence, respondent type (proxy or direct)	OP insecticides, dichlorvos, trichlorfon, dimethoate, diazinon, disulfoton, ethoprop, malathion, phorate, terbufos, chloropyrifos, coumaphos, crufomate, runnel, tetrachlorvinphos, fensulfothion, famphur, fonofos, parathion	Yes

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Table 1. *Cont.*

Author, year, location	Design	Source for controls	Matching	Diagnosis or follow-up period (cancer)	No. Participants	Exposure assessment	Referent category for exposure, exposure definition(s)/metric	Men only	Adjustment set	Pesticides	Reported results by subtype
Woods 1987 [57] Washington state, USA	CC	Population	Matched by vital status and 5-year age group	Dx period: 1981–1984	746 cases/910 controls	In-person interviews about occupational history and self-reported chemical exposure	Referent: No exposure Farming exposures to phenoxy herbicides Any exposure to DDT Any exposure to chlordane Estimated intensity of occupational exposure to phenoxy herbicides: Low/medium/high	Yes	Age	Phenoxy herbicides, DDT, Chlordane	No
Zahm 1990 [58] Nebraska, USA	CC	Population	Matched by race, gender, vital status, age	Dx period: 1983–1986	201 cases/725 controls	In-person interviews about agricultural pesticide use	Referent: Never lived or worked on a farm Mixed or applied Days/year mixing or applying Years used on a farm First year of use	Yes	Age	2,4-D	No
Zahm 1993 [59] Iowa, Kansas, Minnesota, Nebraska, USA	Pooled analysis of 3 CC studies	Population	Matched by race, gender, age, vital status at the time of interview	Dx period [1]: 1979–1983	993 cases/2,918 controls	Telephone interviews (Kansas and Nebraska, USA), In-person interviews (Iowa and Minnesota)	Referent: Non-farmers Used atrazine [1] Personally handled Used but did not handle Duration of use (years) Days/year handled Year of first use	Yes	Age, state	Atrazine	Yes

Table 1. *Cont.*

Author, year, location	Design	Source for controls	Matching	Diagnosis or follow-up period (cancer)	No. Participants	Exposure assessment	Referent category for exposure, exposure definition(s)/metric	Men only	Adjustment set	Pesticides	Reported results by subtype
Zahm 1993 [18] Nebraska, USA	CC	Population	Matched by race, gender, vital status, and age (5 year age groups)	Dx period: 1983–1986	119 cases/471 controls	In-person interviews about agricultural pesticide use	Referent: women who never lived or worked on a farm Used on farm	No (women only)	Age	Phenoxy herbicides, triazine herbicides, amide herbicides, benzoic acid herbicides, carbamate herbicides, trifluralin herbicides, chlorinated hydrocarbons, carbamate insecticides, OP insecticides	No
Zheng 2001 [60] Nebraska, USA, Iowa and Minnesota, Kansas	Pooled analysis of 3 CC studies	Population	Matched by gender, age, race, vital status, state of residence	Dx period [1]: 1979–1983	985 cases/2,895 controls	In-person interviews about agricultural pesticide use	Referent: Non-farmers Used Personally handled Year since first use Years of use Days/year of use	Yes	Age, type of respondent (proxy or direct), state of residence, first-degree family history of cancer, use of hair dye, use of private wells, tobacco smoking	Carbaryl, carbamate herbicides, carbamate insecticides	Yes

Notes: 2,4-D, 2,4-Dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-Trichlorophenoxyacetic acid; AHS, Agricultural Health Study; C, cohort study; CC, case-control study; DDT, dichlorodiphenyltrichloroethane; DX, Diagnosis; EPTC, s-ethyl dipropylthiocarbamate; MCPA, 2-methyl-4-chlorophenoxyacetic acid; OC, organochlorine; OP, organophosphorus; [1] Diagnosis period varied by state: July 1983–June 1986 (Nebraska, USA), October 1980–September 1982 (Minnesota), March 1981-October 1983 (Iowa), 1979–1981 (Kansas).

3.2.1. Studies Conducted in the United States

Nineteen papers [19,21,22,24–26,29,31,35,36,38–42,51,53–55] report results from analyses of data from the Agricultural Health Study, which is a prospective cohort study of licensed pesticide applicators and their spouses living in Iowa and North Carolina, USA. Enrollment began in 1993 and the study is still ongoing [61]. The number of participants included in the analyses varied due to exclusions and completeness of exposure data. The last year of follow-up was defined by the last date on which the incident cancers were identified. At enrollment, participants completed a questionnaire in which they provided historical data on exposure to pesticides. They were also given a take home questionnaire to complete. Most analyses of the Agricultural Health Study data classified active ingredient exposures using two metrics: (1) lifetime exposure days, defined as number of years of use x number of days used per year; and (2) intensity-weighted lifetime exposure days, which was defined as years of use x number of days used per year x personal protective equipment use x intensity level, which incorporates factors that modify pesticide exposure, such as mixing status, application method, equipment repair status. Four papers [31,38,39,51] also reported associations using ever/never use categories; we used these estimates in the meta-analyses.

Six papers reported results from pooled analyses of three case-control studies that were conducted by the USA National Cancer Institute [20,23,30,56,59,60], in Iowa and Minnesota, Kansas, and Nebraska. Diagnosis periods for NHL ranged from 1979 to 1986, depending upon the study. In all studies, population based controls were frequency matched to cases by race, sex, age, and vital status at the time of the interview, and lifetime exposure to pesticides was assessed via telephone interviews. Using these pooled data, De Roos *et al.* [30] examined associations of NHL with 47 active ingredients. The authors investigated pesticides for which there was exposure data from all three studies and to which at least 20 participants were exposed. They used standard logistic regression to model the association of NHL with the multiple pesticides, simultaneously. These analyses were restricted to participants with complete information on all of the pesticides. Other papers reported results from analyses of these pooled data. Baris *et al.* [20] examined associations with dichlorodiphenyltrichloroethane (DDT), Blair *et al.* [23] with lindane, Zahm *et al.* [59] with atrazine, Waddell *et al.* [56] with organophosphates, and Zheng *et al.* [60] with carbamates. We also extracted results from analyses of the individual studies. Using data from the study in Iowa and Minnesota, Cantor *et al.* [27] examined associations with multiple pesticides. In Kansas, Hoar *et al.* [34] examined associations with exposures to various herbicides. In Nebraska, Zahm *et al.* [58] examined associations with 2,4-Dichlorophenoxyacetic acid (2,4-D).

In a population based case-control study in western Washington State, USA Woods *et al.* [57], examined associations between phenoxy exposure and NHL. Controls were group matched to cases diagnosed 1981–1984, based on vital status and age. Lifetime occupational histories and self-reported pesticide chemical exposures were ascertained using in-person interviews. The authors reported exposure to phenoxy herbicides by occupational type. We extracted the result for farming exposure to phenoxy herbicides. Exposures to DDT and chlordane were reported as ever/never, but they were not stratified by occupation.

We also extracted results from a USA based case-control study nested in a cohort of primarily Hispanic members of the California farm worker labor union [45]. Cases were diagnosed 1988–2001.

Controls were selected from the same cohort as cases and matched on the basis of gender, Hispanic ethnicity, and year of birth. Pesticide exposure was defined as low *versus* high use, with the category cut-points based on the distribution of use of the top 15 pesticides. To estimate exposure, union job history data that described crops farmed in a given month/year and county was combined with data collected by the California Pesticide Databank that describes pesticides used on a crop in a given county and time period.

3.2.2. Canadian Studies

Two papers reported results from the Cross-Canada Study of Pesticides and Health, which was a case control study conducted in six Canadian provinces [43,47]. Population based controls were frequency matched to NHL cases, diagnosed 1991–1994, based on age and province of residence. Detailed information on specific pesticide use was ascertained by telephone interviews. The questionnaires used for this study were based on the one used in the USA National Cancer Institute led case-control studies [20,23,30,56,59,60] in Nebraska [18,58] and Kansas [34]. McDuffie *et al.* [43] and Pahwa *et al.* [47] present results from some of the same analyses with the same population. When the same analysis was reported in both papers we selected the effect estimate from the paper by Pahwa *et al.* [47] because the authors excluded four NHL cases based on pathology review that occurred subsequent to the analyses reported in McDuffie *et al.* [43].

3.2.3. European Studies

Four papers [32,33,49,50] reported results from distinct case-control studies conducted in Sweden. The papers by Eriksson *et al.* [32] and Hardell *et al.* [33] reported analyses from population based case-control studies; case diagnosis periods were 1999–2002 and 1987–1992, respectively. A complete lifetime occupational and chemical exposure history was ascertained using self-administered questionnaires followed by telephone interviews when clarification was needed. The two studies by Persson *et al.* [49,50] report results from unmatched population based case-control studies; the results reported from the paper published in 1993 [50] were performed in an adjacent region of Sweden to the area represented in the earlier paper [49]. They examined the association of NHL with various occupational exposures, including phenoxy herbicides and DDT. Case diagnosis periods were 1964–1986 and 1975–1984, respectively.

We extracted results from papers that report results from analyses of data collected in France [46], Italy [44], Iceland [52], and multiple European centers that form parts of the EPILYMPH study [28]. All of these studies were case-control in design. In France [46], cases (diagnosed 2000–2004) and controls were recruited in the same hospitals. Exposure was assessed using self-administered questionnaires, followed by face-to-face interviews in which participants reported information about farms on which they worked for a minimum of six months; they reported information about location, period, crops and animals farmed, name of pesticides mixed or sprayed, duration and number of pesticide applications. Pesticide exposure was classified as possible or definite; the referent category included people never exposed to the pesticide. In the Italian study [44], cases were diagnosed from 1991 to 1993. Participants were interviewed about agricultural work, crop diseases, pesticides used to treat diseases, frequency of pesticide treatments, period of treatment, protective equipment used,

means of application, and re-entry tasks. Exposure was classified into low, medium, and high probabilities of use. The Icelandic case-control study [52] was nested in a cohort of male sheep owners. The authors included cases diagnosed 1966–2003. Paper records on sheep dipping in hexachlorocyclohexane, an organochlorine insecticide that contains lindane, were used as a proxy measure for exposure; records were available for the period 1962–1980. Number of sheep owned was used as a surrogate measure for exposure. In the EPILYMPH study [28], in-person interviews were conducted to ascertain detailed job histories, including information about farm size, crops farmed, pests treated, types and frequency of pesticides used, protective equipment, and re-entry tasks. Industrial hygienists classified pesticide exposure as possible, probable, or certain. In analysis, contrasts were made between high confidence of ever lifetime exposure *versus* never exposure, and any level of confidence of ever exposure *versus* never exposure.

3.2.4. Studies from Australia and New Zealand

Only two papers reported results from analyses of studies conducted outside of North America and Europe. Pearce *et al.* [48] reported analyses of data from a New Zealand based case-control study of agricultural exposures. Cases were diagnosed 1977–1981. Telephone interviews were used to ascertain lifetime occupational history and work with chemicals (phenoxy herbicides). In analysis, Pearce *et al.* [48] stratified phenoxy herbicide exposure by occupation (farming, forestry, railway work, *etc.*). We extracted the estimate of association with any phenoxy herbicide exposure in farming occupations. In Australia [62], Fritschi *et al.* enrolled incident NHL cases diagnosed between 2000 and 2001. They matched controls to cases based on age, gender, and region of residence. In structured telephone interviews, participants provided occupational histories. Occupational hygienists reviewed the responses to these questions and, with the help of a pesticide crop matrix, assigned likelihood of exposure to pesticides (probable, possible, no exposure), level of exposure, and frequency of exposure. These assignments were combined to classify participants' lifetime amount of exposure (substantial, meaning the person was probably exposed to the substance at a medium or high level for more than five 8-h days per year for a combined total of five years, nonsubstantial, or none).

3.2.5. Gender

Nineteen of the papers reported results from analyses that were restricted to men only [20,21,23,27–30,33,34,43,47,48,52,55–60]. One paper reported results from an analysis that was restricted to women [18]. The other papers reported results from analyses of study populations with men and women; in the analytic models reported in these papers, gender was treated as a confounder.

3.2.6. Covariates

In all papers, age was included in models to adjust for potential confounding. Location (state of residence, study center) was also a common adjustment factor. Other variables that were included in models as covariates were race, smoking status, alcohol consumption, correlated pesticides, education level, year of study enrollment, family history of cancer (all cancers or lympho-hematopoetic),

other environmental risk factors for NHL (e.g., gasoline exposure), and type of respondent to the interview used for exposure assessment (direct or proxy).

3.2.7. Reference Groups

In the majority of papers reviewed, the reference group contained farmers and non-farmers who were not exposed to the pesticide. However, there were exceptions to this, either because of study design or analytic decisions.

By design, all participants in the Agricultural Health Study were either pesticide applicators or spouses of applicators. Most of the analyses from this cohort contrasted exposed participants with two different referent groups: (1) participants with no exposure to the pesticide; and (2) participants in the lowest category of exposure. Similarly, all of the participants in the California based study reported in Mills *et al.* [45] were farm workers. The referent group in this analysis consisted of those with estimated low use of the pesticide being analyzed. Both cases and controls in the Icelandic study on which Rafnsson *et al.* [52] reported were sheep owners; people who owned <100 sheep made up the reference group.

By contrast, in some papers, the authors defined the reference group as those who neither worked nor lived on a farm. Miligi *et al.* [44] defined the referent group as participants who never worked in agriculture. Similarly, in papers reporting analyses of the case-control studies in Iowa, Minnesota, Nebraska, and Kansas, the referent group was defined as participants who never worked or lived on a farm. The exception to this was the paper by De Roos *et al.* [30]; the authors used pooled data from these case-control studies but defined the referent group as farmers and non-farmers who never used the pesticide being considered.

3.2.8. Exposure Period and Definition

Pesticide exposure periods and definitions varied, also. For the most part, papers investigated associations of NHL with ever lifetime pesticide exposure. However, some were more specific in their definition, and not all papers used the ever lifetime exposure metric.

In the cohort of California based union farm workers, Mills *et al.* [45] assessed pesticide exposure in the two to three year decade period prior to cancer diagnosis or enrollment. In Canada, McDuffie *et al.* [43] and Pahwa *et al.* [47] defined pesticide exposure as ever *versus* never lifetime use of pesticides for at least 10 h. In Sweden, Eriksson *et al.* [32] and Hardell *et al.* [33] required participants to have worked with the pesticide for a minimum of eight hours in a day, and the pesticide exposure was required to have occurred at least one year prior to the time of diagnosis or enrollment. Persson *et al.* [49,50] only classified as exposed those participants who were exposed to the chemical for at least one year, five to 45 years prior to case diagnosis. In the Italian study described by Miligi *et al.* [44], an agricultural pesticide questionnaire was only administered to participants who had worked on a farm for at least six months; presumably, therefore, anyone who had worked with pesticides but worked on a farm for less than six months was excluded from the exposed group. In the Icelandic study that Rafnsson *et al.* [52] described, records on sheep ownership, which were used to estimate lindane exposure, were available for the period 1962–1980; however, the cancer diagnosis period was 1966–2003.

3.3. Individual Effect Estimates and Dose Response Relationships

Table 2 presents effect estimates from studies in which chemical exposures were represented using multiple categories. Strong dose response relationships were generally absent; most analyses that examined associations with multiple categories of exposure derived imprecise estimates with wide confidence intervals. McDuffie *et al.* [43] and Eriksson *et al.* [32] observed increased odds of NHL in association with a greater number of days/year of glyphosate exposure. De Roos *et al.* [31] did not observe a similar relationship in analyses of Agricultural Health Study data. McDuffie *et al.* [43] observed elevated effect estimates in association with exposure to 2,4-D; however, they did not observe a dose-response relationship with days/year exposed. In analyses of Agricultural Health Study data, Lynch *et al.* [40] observed a nearly three-fold increase in the rate of NHL among those with ≥26 lifetime- and intensity-weighted exposure days to butylate, although the rate ratio comparing those with one to 25 lifetime exposure days to non-exposed applicators was close to the null.

Table 2. Effect estimates from studies that investigated associations between non-Hodgkin lymphoma and herbicides, insecticide, and fungicide exposures classified using multiple categories.

Author, date	Pesticide	Category of exposure	N exposed	Effect estimate, 95% CI
HERBICIDES				
Amide herbicides				
Lee 2004 [39]	Alachlor	Lifetime exposure days [1]		Rate ratio, 95% CI:
		Quartile 1, 0.1–19.9	5	1.0, Referent
		Quartile 2, 20.0–56.0	4	0.6, 0.1–2.5
		Quartile 3, 56.1–116.0	8	1.5, 0.4–5.4
		Quartile 4, ≥116.1	10	1.1, 0.3–4.4
				P for trend: 0.5
		Intensity weighted exposure days [1]		
		Quartile 1, 0.1–101.9	5	1.0, Referent
		Quartile 2, 102.0–253.1	3	0.6, 0.1–3.4
		Quartile 3, 253.2–710.4	10	2.4, 0.7–8.8
		Quartile 4, ≥710.5	9	1.4, 0.3–6.1
				P for trend: 0.4
Rusiecki 2006 [54]	Metolachlor	Lifetime exposure days [1]		Rate ratio, 95% CI:
		Tertile 1, ≤20	14	1.0, Referent
		Tertile 2, 21–56	11	0.8, 0.3–1.7
		Tertile 3, >56	11	0.7, 0.3–1.7
				P for trend: 0.5
		Intensity-weighted lifetime exposure days [1]		
		Tertile 1, ≤20	13	1.0, Referent
		Tertile 2, 21–56	10	0.7, 0.3–1.7
		Tertile 3, >56	13	1.0, 0.4–2.7
				P for trend: 0.7

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Table 2. *Cont.*

Author, date	Pesticide	Category of exposure	N exposed	Effect estimate, 95% CI
Dinitroaniline herbicides				
Kang 2008 [35]	Trifluralin	Lifetime days of exposure [2]		Rate ratio, 95% CI
		Non-exposed	53	1.0, referent
		Tertile1, 1-24.4	17	0.9, 0.5–1.5
		Tertile 2, 24.5-108.4	23	1.0, 0.6–1.8
		Tertile 3, Lower half, 108.5-224.75	6	0.6, 0.2–1.4
		Tertile 3, Upper half, >224.75	4	0.6, 0.2–1.7
				P for trend: 0.2
		Intensity weighted lifetime days [2]		
		Tertile 1, 0-162.1	15	0.7, 0.4–1.4
		Tertile 2, 162.2-593	20	1.1, 0.8–2.9
		Tertile 3, Lower half, 593.1-1176.0	9	0.9, 0.4–2.0
		Tertile 3, Upper half, >1176.0	4	0.4, 0.1–1.1
				P for trend: 0.1
Glyphosate				
McDuffie 2001 [43] [3]	Glyphosate	Days/year of exposure		OR, 95% CI:
		Unexposed	466 cases/1,373 controls	1.0, Referent
		>0–≤2	28 cases/97 controls	1.0, 0.6–1.6
		>2	23 cases/36 controls	2.1, 1.2–3.7
De Roos 2005 [31] [3]	Glyphosate			
		Lifetime days of exposure [2]		Rate ratio, 95% CI:
		Tertile 1, 1–20	29	1.0, Referent
		Tertile 2, 21–56	15	0.7, 0.4–1.4
		Tertile 3, 57–2678	17	0.9, 0.5–1.6
				P for trend: 0.7
		Intensity weighted exposure days [2]		
		Tertile 1, 0.1–79.5	24	1.0, Referent
		Tertile 2, 79.6–337.1	15	0.6, 0.3–1.1

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Table 2. *Cont.*

Author, date	Pesticide	Category of exposure	N exposed	Effect estimate, 95% CI
		Tertile 3, 337.2–1,824.1	22	0.8, 0.5–1.4
				P for trend: 1.0
Eriksson 2008 [32] [3]	Glyphosate			OR, 95% CI:
		Days of exposure [4]		
		>0–≤10 days	12 cases/9 controls	1.7, 0.7–4.1
		>10 days	17 cases/9 controls	2.4, 1.0–5.4
Imidazolinone herbicides				
Koutros 2009 [36]	Imazethapyr	Intensity weighted exposure days [5]		Rate ratio, 95% CI:
		No exposure:	80	1.0, Referent
		Tertile 1, <54.1	15	1.0, 0.6–1.7
		Tertile 2, 54.1–<152.9	13	0.9, 0.5, 1.6
		Tertile 3, lower half, 152.9–<311.9	7	0.8, 0.3–1.8
		Tertile 3, upper half, ≥311.9	11	1.4, 0.8–2.7
				P for trend: 0.4
Phenoxy herbicides				
Fritschi 2005 [62]	Phenoxy herbicides, group	Degree of pesticide exposure [6]		OR, 95% CI:
		None	679 cases/677 controls	1.0, Referent
		Nonsubstantial	10 cases/14 controls	0.7, 0.3–1.7
		Substantial	5 cases/3 controls	1.8, 0.4–7.4
Eriksson 2008 [32] [3]	Phenoxy herbicides, group	Days of exposure [4]		
		>0–≤45 days	32 cases/13 controls	2.8, 1.5–5.5
		>45 days	15 cases/13 controls	1.3, 0.6–2.7
Hardell 2002 [33] [3]	Phenoxy herbicides, group			OR, 95% CI:
		Number of days of exposure		
		Not exposed	NR	1.0, Referent
		Low	NR	1.7, 1.0–2.7
		High	NR	1.7, 1.0–2.7

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Table 2. *Cont.*

Author, date	Pesticide	Category of exposure	N exposed	Effect estimate, 95% CI
		Years between first exposure and diagnosis		
		1–10	NR	-
		>10–20	NR	2.9, 1.1–7.7
		>20–30	NR	1.5, 0.9–2.8
		>30	NR	1.5, 0.9–2.4
		Years between last exposure and diagnosis		
		1–10	NR	3.2, 1.6–6.7
		>10–20	NR	2.1, 1.0–4.1
		>20–30	NR	1.0, 0.5–1.8
		>30	NR	1.3, 0.6–2.6
		Decade of exposure		
		1940s	4 cases/6 controls	1.5, 0.4–5.2
		1950s	35 cases/53 controls	1.4, 0.9–2.3
		1960s	43 cases/58 controls	1.7, 1.1–2.6
		1970s	32 cases/33 controls	2.4, 1.4–4.0
		1980s	16 cases/33 controls	3.3, 1.5–7.1
Eriksson 2008 [32] [3]	MCPA	Days exposed [4]		
		≤32	15 cases/5 controls	3.8, 1.4–10.5
		>32	6 cases/4 controls	1.7, 0.5–6.0
Hardell 2002 [33] [3]	MCPA			OR, 95% CI:
		Number of days of exposure		
		Not exposed	NR	1.0, Referent
		Low	NR	1.9, 0.8–4.6
		High	NR	3.6, 1.5–9.1
		Years between first exposure and diagnosis		
		1–10	NR	-
		>10–20	NR	5.4, 1.6–21

Table 2. *Cont.*

Author, date	Pesticide	Category of exposure	N exposed	Effect estimate, 95% CI
		>20–30	NR	0.9, 0.2–3.0
		>30	NR	3.8, 1.5–10.0
		Years between last exposure and diagnosis		
		1–10	NR	3.5, 1.6–8.0
		>10–20	NR	2.3, 0.6–9.1
		>20–30	NR	0.9, 0.1–4.4
		>30	NR	-
McDuffie 2001 [43] [3]	Mecoprop	Days/year exposed		
		Unexposed	464 cases/1,425 controls	1.0, Referent
		>0–≤2	31 cases/48 controls	2.3, 1.4–3.7
		≥2	22 cases/33 controls	2.1, 1.2–3.6
Hardell 2002 [33] [3]	2,4-D + 2,4,5-T			OR, 95% CI:
		Number of days of exposure		
		Low	NR	1.9, 1.1–3.2
		High	NR	1.2, 0.7–2.1
		Years between first exposure and diagnosis		
		1–10	NR	-
		>10–20	NR	2.9, 0.8–11.0
		>20–30	NR	1.9, 1.0–3.5
		>30	NR	1.2, 0.7–1.9
		Years between last exposure and diagnosis		
		1–10	NR	4.3, 1.1–21.0
		>10–20	NR	1.9, 0.9–3.8
		>20–30	NR	0.9, 0.1–4.4
		>30	NR	1.4, 0.7–2.9
Eriksson 2008 [32] [3]	2,4,5-T and/or 2,4-D	Days exposed [4]		OR, 95% CI:
		Non-exposed		1.0, Referent

Table 2. *Cont.*

Author, date	Pesticide	Category of exposure	N exposed	Effect estimate, 95% CI
		≤29	21 cases/11 controls	2.1, 1.0–4.4
		>29	12 cases/10 controls	1.3, 0.6–3.1
Zahm 1990 [58] [3]	2,4-D			OR, 95% CI:
		Never lived/worked on a farm	54 cases/184 controls	1.0, Referent
		Days/year mixing or applying		
		1–5	16 cases/44 controls	1.2, 0.6–2.4
		6–20	12 cases/25 controls	1.6, 0.7–3.6
		21+	3 cases/4 controls	3.3, 0.5–22.1
		Unknown	12 cases/25 controls	-
				P for trend: 0.1
		Years used on farm		
		1–5	3 cases/12 controls	0.9, 0.2–3.6
		6–15	11 cases/15 controls	2.8, 1.1–7.1
		16–20	3 cases/18 controls	0.6, 0.1–2.1
		21+	13 cases/33 controls	1.3, 0.6–2.7
		Unknown	15 cases/29 controls	-
				P for trend: 0.3
		First year of use		
		Prior to 1945	8 cases/21 controls	1.4, 0.5–3.5
		1946–1955	13 cases/39 controls	1.1, 0.5–2.3
		1956–1965	5 cases/8 controls	2.1, 0.6–7.7
		1965–1986	4 cases/12 controls	1.3, 0.3–4.9
		Unknown year	13 cases/18 controls	-
				P for trend: 0.2
McDuffie 2001 [43] [3]	2,4-D	Days/yr exposed		OR, 95% CI:
		Unexposed	406 cases/1,213 controls	1.0, Referent
		>0–≤2	55 cases/160 controls	1.2, 0.8–1.6
		>2–≤5	36 cases/82 controls	1.4, 0.9–2.1

Table 2. *Cont.*

Author, date	Pesticide	Category of exposure	N exposed	Effect estimate, 95% CI
		>5–≤7	9 cases/20 controls	1.4, 0.6–3.2
		>7	11 cases/31 controls	1.2, 0.6–2.5
Thiocarbamate herbicides				
Zheng 2001 [60] [3]	Butylate			OR, 95% CI
		Non-farmers	243 cases/775 controls	1.0, Referent
		Years since first use		
		<20	34 cases/56 controls	1.5, 0.9–2.4
		≥20	4 cases/10 controls	1.1, 0.3–3.7
		Years of use		
		<7	21 cases/35 controls	1.5, 0.9–2.8
		≥7	20 cases/37 controls	1.5, 0.8–2.7
		Days/year of use		
		<5	3 cases/5 controls	2.6, 0.6–11.1
		≥5	2 cases/2 controls	4.7, 0.6–34.5
Lynch 2009 [40]	Butylate	Lifetime exposure days [5]		Rate ratio, 95% CI:
		No exposure	27	1.0, Referent
		Low exposure, 1–25	6	0.9, 0.4–2.0
		High exposure, ≥26	12	2.9, 1.5–5.8
				P for trend: 0.0
		Intensity weighted exposure days [5]		
		No exposure	27	1.0, Referent
		Low exposure, 1–157	5	0.8, 0.3–2.0
		High exposure, ≥158	13	2.9, 1.5–5.5
				P for trend: 0.0
Van Bemmel 2008 [55]	EPTC	Lifetime exposure days [5]		Rate ratio, 95% CI:
		No exposure	83	1.0, Referent
		Tertile 1, 1–9	10	1.2, 0.6–2.3
		Tertile 2, 10–49	7	1.5, 0.7–3.2

Table 2. *Cont.*

Author, date	Pesticide	Category of exposure	N exposed	Effect estimate, 95% CI
		Tertile 3, 50+	5	0.8, 0.3–2.0
				P for trend:0.7
		Intensity-weighted lifetime exposure days [5]		Rate ratio, 95% CI:
		No exposure	83	1.0, Referent
		Tertile 1, 1–47	8	1.4, 0.7–2.8
		Tertile 2, 48–111	4	0.9, 0.3–2.5
		Tertile 3, 112+	10	1.1, 0.6–2.1
				P for trend:0.9
Zheng 2001 [60] [3]	EPTC + Protectant			OR, 95% CI:
		Non-farmers:		1.0, Referent
		Years since first use		
		<20	19 cases/34 controls	1.7, 0.9–3.1
		≥20	0 cases/1 control	-
		Years of use		
		<7	15 cases/20 controls	2.2, 1.1–4.4
		≥7	7 cases/26 controls	1.0. 0.4–2.4
		Days/year of use		
		<5	7 cases/12 controls	2.2, 0.8–5.8
		≥5	1 case/5 controls	0.9, 0.1–7.7
Triazine herbicides				
Lynch 2006 [41]	Cyanazine	Lifetime exposure days [5]		Rate ratio, 95% CI
		Tertile 1, 1–16	9	1.0, Referent
		Tertile 2, 17–56	18	1.6, 0.7–3.5
		Tertile 3, ≥57	9	1.3, 0.5–3.4
				P for trend: 1.0
		Intensity-weighted exposure days [5]		
		Tertile 1, 1–83	10	1.0, Referent
		Tertile 2, 84–314.35	12	1.3, 0.6–3.0

Table 2. *Cont.*

Author, date	Pesticide	Category of exposure	N exposed	Effect estimate, 95% CI
		Tertile 3, ≥315.35	13	1.4, 0.6–3.4
				P for trend: 0.5
Zahm 1993 [59] [3]	Atrazine			OR (95% CI not presented)
		No use	445 cases/1507 controls	1.0, Referent
		Years of use		
		1–5	4 cases/14 controls	0.4
		6–15	5 cases/20 controls	0.5
		16–20	5 cases/8 controls	0.6
		≥21	7 cases/11 controls	0.8
		Days/year personally handled		
		1–5	7 cases/20 controls	0.6
		6–20	8 cases/17 controls	0.7
		≥21	1 cases/1 control	1.4
		Year of first use		
		1965 or prior	10 cases/35 controls	0.4
		1966 or later	10 cases/18 controls	1.0
Beane Freeman 2011 [22]	Atrazine	Lifetime days of exposure [5]		Rate ratio, 95% CI
		Quartile 1, >0–20	41	1.0, Referent
		Quartile 2, 21–56	41	1.1, 0.7–1.7
		Quartile 3, >56–178.5	38	0.9, 0.6–1.5
		Quartile 4, >178.5	32	1.0, 0.6–1.6
				P for trend: 0.7
		Intensity weighted lifetime days of exposure [5]		
		Quartile 1, >0–20	38	1.0, Referent
		Quartile 2, 21–56	45	1.2, 0.8–1.9
		Quartile 3, >56–178.5	34	0.9, 0.6–1.5
		Quartile 4, >178.5	34	0.9, 0.6–1.5
				P for trend: 0.5

Table 2. *Cont.*

Author, date	Pesticide	Category of exposure	N exposed	Effect estimate, 95% CI
Triazinone herbicides				
Delancey 2009 [29]	Metribuzin	Lifetime days of exposure [5]		Rate ratio, 95% CI
		No exposure	39	
		Tertile 1, >0–8.75	5	1.0, Referent
		Tertile 2, 8.76–24.5	6	2.3, 0.6–8.6
		Tertile 3, >24.5	8	2.6, 0.8–9.1
				P for trend: 0.1
		Intensity weighted lifetime exposure days [5]		
		No exposure: 0	39	
		Tertile 1, >0–58.3	4	1.0, Referent
		Tertile 2, >58.3–174.4	6	1.4, 0.3–5.8
		Tertile 3, >174.5	9	2.5, 0.7–9.6
				P for trend: 0.1
FUNGICIDES				
McDuffie 2001 [43] [3]	Captan	Days/year exposed		OR, 95% CI:
		Unexposed	497 cases/1,482 controls	1.0, Referent
		>0–≤2	11 cases/12 controls	2.7, 1.2–6.2
		>2	9 cases/12 controls	2.8, 1.1–6.9
INSECTICIDES				
Carbamate insecticides				
Zheng 2001 [60] [3]	Carbaryl			OR, 95% CI:
		Non-farmers	243 cases/775 controls	1.0, Referent
		Years since first use		
		<20	19 cases/44 controls	1.1, 0.6–2.0
		≥20	14 cases/21 controls	1.8, 0.9–3.7
		Years of use		
		<7	16 cases/36 controls	1.1, 0.6–2.1
		≥7	15 cases/26 controls	1.5, 0.8–3.0

Table 2. *Cont.*

Author, date	Pesticide	Category of exposure	N exposed	Effect estimate, 95% CI
		Days/year of use		
		<5	9 cases/14 controls	2.4, 1.0–5.9
		≥5	2 cases/4 controls	1.8, 0.3–10.0
Mahajan 2007 [42]	Carbaryl	Lifetime days of exposure [2]		Rate ratio, 95% CI
		No exposure	23	1.0, Referent
		Tertile 1, 1–9	5	0.7, 0.2–1.8
		Tertile 2, 10–56	8	1.2, 0.5–3.0
		Tertile 3, >56	10	1.7, 0.6–4.5
				P for trend: 0.3
Zheng 2001 [60] [3]	Carbofuran			OR, 95% CI:
		Nonfarmers	243 cases/775 controls	1.0, Referent
		Years since first use		
		<20	32 cases/63 controls	1.3, 0.8–2.1
		≥20	15 cases/30 controls	1.6, 0.8–3.1
		Years of use		
		<7	30 cases/48 controls	1.7, 1.0–2.9
		≥7	24 cases/47 controls	1.4, 0.8–2.4
		Days/year of use		
		<5	9 cases/15 controls	2.7, 1.1–6.4
		≥5	12 cases/16 controls	3.1, 1.4–6.8
Bonner 2005 [25]	Carbofuran	Lifetime days of exposure [2]		Rate ratio, 95% CI
		No exposure	44	1.0, Referent
		Tertile 1, 1–9	6	0.8, 0.3–1.9
		Tertile 2, 10–56	7	1.3, 0.6–2.9
		Tertile 3, >56	7	1.4, 0.6–3.3
				P for trend: 0.4

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Table 2. *Cont.*

Author, date	Pesticide	Category of exposure	N exposed	Effect estimate, 95% CI
Organophosphorus insecticides				
Fritschi 2005 [62]	Organophosphorus insecticides, group	Degree of exposure [6]		OR, 95% CI:
		No exposure	662 cases/660 controls	1.0, Referent
		Nonsubstantial exposure	20 cases/28 controls	0.7, 0.4–1.3
		Substantial exposure	12 cases/6 controls	2.1, 0.8–5.7
Waddell 2001 [56] [3]	Organophosphorus pesticides, group			OR, 95% CI:
		Non-farmers	243 cases/775 controls	1.0, Referent
		Years since first use		
		<20	44 cases/94 controls	1.0, 0.7–1.5
		≥20	79 cases/188 controls	1.6, 1.1–2.2
		Years used		
		<10	34 cases/69 controls	1.1, 0.7–1.7
		10–19	44 cases/71 controls	1.4, 0.9–2.1
		20+	39 cases/59 controls	1.5, 1.0–2.4
Lee 2004 [38]	Chlorpyrifos	Lifetime days of exposure [1]		Rate ratio, 95% CI:
		Nonexposed	53	1.0, Referent
		Quartile 1, 0.1–8.8	10	0.6, 0.2–1.5
		Quartile 2, 8.9–24.5	13	1.8, 0.9–3.5
		Quartile 3, 24.6–56.0	5	0.9, 0.4–2.4
		Quartile 4, ≥56.1	9	1.0, 0.4–2.4
				P for trend: 0.7
		Intensity-weighted lifetime days of exposure [1]		
		Nonexposed	53	1.0, Referent
		Quartile 1, 0.1–48.9	6	0.9, 0.3–2.2
		Quartile 2, 49.0–135.9	6	0.6, 0.2–1.8
		Quartile 3, 136.0–417.6	10	1.2, 0.6–2.7
		Quartile 4, ≥417.7	10	1.6, 0.7–3.5
				P for trend: 0.4

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<div align="center">Table 2. <i>Cont.</i></div>

Author, date	Pesticide	Category of exposure	N exposed	Effect estimate, 95% CI
Beane Freeman 2005 [21]	Diazinon			Rate ratio, 95% CI:
		No exposure	26	1.0, Referent
		Lifetime days of exposure [2]		
		Tertile 1, <20	6	1.8, 0.7–4.4
		Tertile 2, 20–38.8	3	1.4, 0.4–4.6
		Tertile 3, >38.8	2	0.9, 0.2–4.1
				P for trend: 1.0
		Intensity-weighted lifetime days of exposure [2]		
		Tertile 1	5	1.9, 0.7–5.1
		Tertile 2	2	0.7, 0.2–3.1
		Tertile 3	4	1.7, 0.6–5.2
				P for trend: 0.4
Waddell 2001 [56] [3]	Diazinon			OR, 95% CI:
		Non-farmers	243 cases/775 controls	1.0, Referent
		Years since first use		
		<20	20 cases/34 controls	1.1, 0.6–2.0
		>20	16 cases/24 controls	1.4, 0.7–2.7
		Years used		
		<10	20 cases/40 controls	0.9, 0.5–1.7
		10–19	10 cases/11 controls	1.8, 0.7–4.4
		20+	1 cases/1 controls	1.9, 0.1–31.6
		Days/year of use		
		<5	6 cases/11 controls	1.3, 0.5–3.9
		≥5	6 cases/6 controls	2.4, 0.7–8.0

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Table 2. *Cont.*

Author, date	Pesticide	Category of exposure	N exposed	Effect estimate, 95% CI
Waddell 2001 [56] [3]	Fonofos			OR, 95% CI:
		Non-farmers	243 cases/775 controls	1.0, Referent
		Years since first use		
		<20	20 cases/36 controls	1.0, 0.6–1.9
		≥20	5 cases/6 controls	1.6, 0.5–5.5
		Years used		
		<10	16 cases/25 controls	1.2, 0.6–2.4
		10–19	7 cases/9 controls	1.5, 0.5–4.1
		20+	2 cases/1 control	4.2, 0.4–47.2
		Days/year of use		
		<5	2 cases/6 controls	0.7, 0.1–3.8
		≥5	9 cases/6 controls	3.4, 1.1–10.3
McDuffie 2001 [43] [3]	Malathion	Days/year of exposure		OR, 95% CI:
		Unexposed	445 cases/1,379 controls	1.0, Referent
		>0–≤2	50 cases/88 controls	1.8, 1.3–2.7
		≥2	22 cases/39 controls	1.8, 1.0–3.0
Waddell 2001 [56] [3]	Malathion			OR, 95% CI:
		Non-farmers	243 cases/775 controls	1.0, Referent
		Years since first use		
		<20	22 cases/46 controls	0.9, 0.5–1.6
		≥20	35 cases/39 controls	1.7, 1.1–2.9
		Years used		
		<10	22 cases/39 controls	1.1, 0.6–1.9
		10–19	23 cases/23 controls	1.9, 1.0–3.5
		20+	10 cases/18 controls	1.1, 0.5–2.4
		Days/year of use		
		<5	7 cases/8 controls	2.1, 0.7–6.1
		≥5	5 cases/7 controls	1.5, 0.5–5.2

Table 2. *Cont.*

Author, date	Pesticide	Category of exposure	N exposed	Effect estimate, 95% CI
Bonner 2007 [26]	Malathion	Lifetime days of exposure [5]		Rate ratio, 95% CI
		No exposure	1.0 Referent	
		Tertile 1, >0–9	0.6, 0.2–1.6	
		Tertile 2, 10–39	0.7, 0.3–1.8	
		Tertile 3, >39	0.8, 0.3–2.0	
		Intensity-weighted lifetime days of exposure [2]		Rate ratio, 95% CI
		No exposure	14	1.0, Referent
		Tertile 1, >0–58	5	0.5, 0.2–1.5
		Tertile 2, 59–245	9	0.7, 0.3–1.8
		Tertile 3, >245	9	0.8, 0.3–2.0
				P for trend: 0.9
Waddell 2001 [56] [3]	Phorate			OR, 95% CI:
		Non-farmers	243 cases/775 controls	1.0, Referent
		Years since first use		
		<20	19 cases/43 controls	0.8, 0.4–1.5
		≥20	14 cases/23 controls	1.3, 0.6–2.6
		Years used		
		<10	20 cases/33 controls	1.2, 0.6–2.1
		10–19	9 cases/19 controls	0.9, 0.4–2.1
		20+	4 cases/5 controls	1.5, 0.4–5.9
		Days/year of use		
		<5 days	5 cases/9 controls	1.3, 0.4–4.0
		≥5 days	7 cases/8 controls	2.0, 0.7–5.9
Waddell 2001 [56] [3]	Terbufos			OR, 95% CI:
		Non-farmers	243 cases/775 controls	1.0, Referent
		Years since first use		
		<20	23 cases/51 controls	0.9, 0.5-1.5
		≥20	0 cases/1 control	-

Table 2. *Cont.*

Author, date	Pesticide	Category of exposure	N exposed	Effect estimate, 95% CI
		Years used		
		<10	13 cases/38 controls	0.6, 0.3–1.3
		10–19	6 cases/8 controls	1.5, 0.5–4.4
		20+	0 cases/1 control	-
		<20	23 cases/51 controls	0.9, 0.5–1.5
		≥20	0 cases/1 control	-
		Days/year of use		
		<5	3 cases/8 controls	0.8, 0.2–3.4
		≥5	7 cases/4 controls	4.0, 1.1–14.5
Bonner 2010 [24]	Terbufos	Intensity weighted lifetime exposure days [5]		Hazard ratio, 95% CI
		No exposure	69	1.0, referent
		Tertile 1, >0–107	17	1.3, 0.7–2.3
		Tertile 2, >107–352	24	1.9, 1.2–3.2
		Tertile 3, >352	15	1.2, 0.7–2.2
				P for trend: 0.6
Organochlorine insecticides				
Fritschi 2005 [62]	Organochlorines, group	Degree of exposure [6]		OR, 95% CI:
		None	674 cases/679 controls	1.0, Referent
		Nonsubstantial	14 cases/13 controls	1.1, 0.5–2.3
		Substantial	6 cases/2 controls	3.3, 0.7–16.4
Purdue 2007 [51] [3]	Organochlorines, group	Lifetime days of exposure [5]		Rate ratio, 95% CI:
		Unexposed	16	1.0, Referent
		Tertile 1, 1–110	8	1.2, 0.5–2.8
		Tertile 2, 111–450	10	1.5, 0.6–3.5
		Tertile 3, >450	11	1.5, 0.6–3.8
				P for trend: 0.3

Table 2. *Cont.*

Author, date	Pesticide	Category of exposure	N exposed	Effect estimate, 95% CI
		Intensity weighted lifetime days of exposure [5]		
		Unexposed	16	1.0, Referent
		Tertile 1, 1–110	9	1.3, 0.6–3.1
		Tertile 2, 111–450	7	1.1, 0.4–2.9
		Tertile 3, >450	13	1.7, 0.7–4.2
				P for trend: 0.3
Purdue 2007 [51] [3]	Aldrin	Lifetime days of exposure [5]		Rate ratio, 95% CI:
		Unexposed	38	1.0, Referent
		1–20	5	0.8, 0.3–2.1
		>20	4	0.4, 0.1–1.5
				P for trend: 0.2
		Intensity weighted lifetime days of exposure [5]		
		Unexposed	38	1.0, Referent
		1–20	4	0.6, 0.2–1.9
		>20	5	0.6, 0.2–1.8
				P for trend: 0.4
Purdue 2007 [51] [3]	Chlordane	Lifetime days of exposure [5]		Rate ratio, 95% CI:
		Unexposed	32	1.0, Referent
		1–9	9	1.6, 0.8–3.6
		>9	6	1.8, 0.7–4.6
				P for trend: 0.2
		Intensity weighted lifetime days of exposure [5]		
		Unexposed	32	1.0, Referent
		1–9	8	1.8, 0.8–4.0
		>9	7	1.6, 0.7–3.9
				P for trend: 0.3
Baris 1998 [20] [3]	DDT			OR, 95% CI:
		Non-farmers	243 cases/775 controls	1.0, Referent

Table 2. *Cont.*

Author, date	Pesticide	Category of exposure	N exposed	Effect estimate, 95% CI
		Days/year of use		
		≤5	12 cases/35 controls	1.0, 0.5–2.1
		>5	11 cases/15 controls	2.1, 0.9–4.9
		Duration of use in years		
		1–4	36 cases/79 controls	1.0, 0.7–1.6
		5–9	31 cases/53 controls	1.4, 0.8–2.2
		≥15	39 cases/64 controls	1.5, 0.9–2.3
McDuffie 2001 [43] [3]	DDT	Days/year of exposure		OR, 95% CI:
		Unexposed	485 cases/1,447 controls	1.0, Referent
		>0–≤2	18 cases/32 controls	1.8, 1.0–3.2
		≥2	14 cases/27 controls	1.5, 0.8–2.9
Hardell 2002 [33] [3]	DDT			OR, 95% CI:
		Never exposed	NR	1.0, Referent
		Years between first exposure and diagnosis		
		1–10	NR	-
		>10–20	NR	2.6, 0.6–11.0
		>20–30	NR	1.6, 0.8–3.3
		>30	NR	1.2, 0.8–1.7
		Years between last exposure and diagnosis		
		1–10	NR	1.5, 0.7–3.1
		>10–20	NR	1.1, 0.6–2.0
		>20–30	NR	1.5, 0.8–2.5
		>30	NR	1.2, 0.7–2.0

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Table 2. *Cont.*

Author, date	Pesticide	Category of exposure	N exposed	Effect estimate, 95% CI
Purdue 2007 [51] [3]	DDT			
		Lifetime days of exposure [5]		Rate ratio, 95% CI:
		Unexposed	32	1.0, Referent
		1–20	5	0.7, 0.3–1.9
		>20	9	1.2, 0.5–2.8
				P for trend: 0.6
		Intensity weighted lifetime days of exposure [5]		
		Unexposed	32	1.0, Referent
		1–20	6	0.9, 0.3–2.2
		>20	8	1.0, 0.4–2.5
				P for trend: 0.9
Eriksson 2008 [32] [3]	DDT	Days of exposure [4]		
		≤37 days	20 cases/19 controls	1.2, 0.6–2.2
		>37 days	30 cases/18 controls	1.8, 1.0–3.2
Purdue 2007 [51] [3]	Dieldrin			
		Lifetime days of exposure [5]		Rate ratio, 95% CI:
		Unexposed	46	1.0, Referent
		1–20	1	0.6, 0.1–4.2
		>20	1	0.9, 0.1–6.9
				P for trend: 0.8
		Intensity weighted lifetime days of exposure [5]		
		Unexposed	46	1.0, Referent
		1–20	1	0.7, 0.1–5.0
		>20	1	0.7, 0.1–5.5
				P for trend: 0.7

Table 2. *Cont.*

Author, date	Pesticide	Category of exposure	N exposed	Effect estimate, 95% CI
Purdue 2007 [51] [3]	Heptachlor	Lifetime days of exposure		Rate ratio, 95% CI:
		Unexposed	38	1.0, Referent
		1–9	6	1.5, 0.6–4.1
		>9	4	1.1, 0.4–3.2
				P for trend: 0.8
		Intensity weighted lifetime days of exposure		
		Unexposed	38	1.0, Referent
		1–9	4	1.2, 0.4–3.6
		>9	6	1.4, 0.5–3.7
				P for trend:0.6
Blair 1998 [23] [3]	Lindane			OR, 95% CI:
		Nonfarmer	243 cases/775 controls	1.0, Referent
		Years since first use		
		≥20	59 cases/83 controls	1.7, 1.1–2.5
		<20	18 cases/30 controls	1.3, 0.7–2.4
		Days/ year of use		
		<4	8 cases/16 controls	1.6, 0.6–4.0
		≥5	5 cases/8 controls	2.0, 0.6–6.4
Rafnsson 2006 [52] [3]	Lindane	Number of sheep owned		OR, 95% CI:
		100–199 sheep	22 cases/71 controls	3.8, 1.6–9.3
		200–683 sheep	15 cases/62 controls	3.4, 1.3–9.0
Purdue 2007 [51] [3]	Lindane	Lifetime days exposed [5]		Rate ratio, 95% CI:
		Unexposed	34	1.0, Referent
		1–22 days	6	1.9, 0.8–4.7
		>22 days	7	2.1, 0.8–5.5
				P for trend: 0.1

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Table 2. *Cont.*

Author, date	Pesticide	Category of exposure	N exposed	Effect estimate, 95% CI
		Intensity-weighted lifetime days of exposure [5]		
		Unexposed	34	1.0, Referent
		1–22	5	0.9, 0.3–3.0
		>22	8	2.6, 1.1–6.4
				P for trend: 0.04
Purdue 2007 [51] [3]	Toxaphene	Lifetime days exposed [5]		Rate ratio, 95% CI:
		Unexposed	35	1.0, Referent
		1–25 days	10	2.3, 1.1–5.0
		>25 days	2	1.3, 0.3–5.5
				P for trend: 0.8
		Intensity-weighted lifetime days of exposure [5]		
		Unexposed	35	1.0, Referent
		1–25	7	2.3, 1.0–5.4
		>25	5	1.6, 0.5–4.8
				P for trend:0.4
Pyrethroid insecticides				
Rusiecki 2009 [53]	Permethrin	Lifetime days of exposure [5]		Relative rate, 95% CI:
		Nonexposed	94	1.0, Referent
		Tertile 1, ≤8.74	8	0.8, 0.4–1.7
		Tertile 2, 8.75–50.75	5	0.6, 0.3–1.7
		Tertile 3, >50.75	5	0.7, 0.3–1.7
				P for trend: 0.2
		Intensity-weighted lifetime days of exposure [5]		
		Nonexposed	94	1.0, Referent
		Tertile 1, ≤8.74	7	0.8, 0.4–1.8
		Tertile 2, 8.75–50.75	7	0.9, 0.4–2.0
		Tertile 3, >50.75	4	0.5, 0.2–1.3
				P for trend: 0.2

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Table 2. *Cont.*

Author, date	Pesticide	Category of exposure	N exposed	Effect estimate, 95% CI
Other insecticides				
Eriksson 2008 [32] [3]	Pyretrine	Days of exposure [4]		OR, 95% CI:
		≤25	8 cases/5 controls	1.9, 0.6–5.8
		>25	6 cases/5 controls	1.4, 0.4–4.5
	Mercurial seed dressing	Days of exposure [4]		
		≤12	7 cases/6 controls	1.3, 0.4–3.8
		>12	14 cases/5 controls	2.9, 1.0–8.3
	Fumigant fungicides			
Barry 2012 [19]	Methyl Bromide	Intensity weighted lifetime days of exposure [5]		Rate ratio, 95% CI:
		Nonexposed	166	1.0, Referent
		Tertile 1, >0–310	21	2.3, 1.4–3.9
		Tertile 2, 311–1519	8	0.7, 0.3–1.6
		Tertile 3, >1519	6	0.6, 0.3–1.5
				P for trend: 0.1
		Intensity weighted lifetime days of exposure, 15 year lag [5]		
		Nonexposed	174	1.0, Referent
		Tertile 1, >0–310	13	1.7, 0.9–3.1
		Tertile 2, 311–1519	6	0.6, 0.3–1.5
		Tertile 3, >1519	8	1.0, 0.5–2.1
				P for trend: 0.7

Notes: CI, confidence interval; EPTC, s-ethyl dipropylthiocarbamate; MCPA, 2-methyl-4-chlorophenoxyacetic acid; NHL, non-Hodgkin lymphoma; OR, odds ratio; CI, confidence interval; [1] Categories based on mid-points of the questionnaire category; [2] Categories based on distribution among users; [3] Effect estimates in association with dichotomous exposure were also reported; [4] Categories based on the number of days of exposure among controls; [5] Categories based on the distribution of exposure among cancer cases; [6] Substantial indicates the person was exposed to the substance at a medium or high level for more than five 8-hour days per year for a combined total of more than 5 years. Non-substantial indicates any other combination of exposures; estimates derive from a case-control study.

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Table 3. Associations of subtypes of non-Hodgkin lymphoma with herbicides and insecticides.

	Chemical	Number of exposed cases	Risk ratio, 95% CI
B cell lymphoma			
HERBICIDES			
Organophosphorus herbicides			
Eriksson 2008 [32]	Glyphosate (OP herbicide)	NR	1.9, 1.0–3.5
Phenoxy herbicides			
Cocco 2012 [28]	Phenoxy herbicides	12 cases	1.4, 0.6–3.1
Eriksson 2008 [32]	Phenoxy herbicides	NR	2.0, 1.2–3.3
Fritschi 2005 [62] [1]	Phenoxy herbicides	NR	No exposure: 1.0, Referent
			Non-substantial exposure: 0.6, 0.3–1.5
			Substantial exposure: 1.5, 0.3–6.6
Eriksson 2008 [32]	2,4,5-T and/or 2,4-D (Phenoxy herbicide)	NR	1.7, 0.9–3.0
Cocco 2012 [28]	2,4-D (Phenoxy herbicide)	2 cases	0.6, 0.1–3.5
Cocco 2012 [28]	MCPA (Phenoxy herbicide)	4 cases	Infinity (zero exposed controls)
Eriksson 2008 [32]	MCPA (Phenoxy herbicide)	NR	2.6, 1.1–5.9
Thiocarbamate herbicides			
Zheng 2001 [60]	Butylate (Thiocarbamate herbicides)	4 cases (small lymphocytic)	1.1, 0.3–3.4
Zheng 2001 [60]	EPTC + Protectant (Thiocarbamate herbicides)	2 cases (small lymphocytic)	1.5, 0.3–7.1
Cocco 2012 [28]	Triazines and triazoles	6 cases	0.7, 0.2–1.7
INSECTICIDES			
Carbamate insecticides			
Zheng 2001 [60]	Carbaryl (Carbamate insecticide)	9 cases(small lymphocytic)	2.9, 1.2–7.0
Zheng 2001 [60]	Carbofuran (Carbamate insecticide)	7 cases (small lymphocytic)	1.5, 0.6–3.8
Cocco 2012 [28]	Methomyl (Carbamate insecticide)	0 cases	NR(zero exposed cases)
Cocco 2012 [28]	Mancozeb (Dithiocarbate fungicide)	2 cases	0.6, 0.1–3.5
Cocco 2012 [28]	Glyphosate (OP herbicide)	4 cases	3.1, 0.6–17.1

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Table 3. *Cont.*

Author, date	Chemical	Number of exposed cases	Risk ratio, 95% CI
Organochlorine (OC) insecticides			
Cocco 2012 [28]	Organochlorines	27 cases	0.9, 0.5–1.4
Fritschi 2005 [62] [1]	Organochlorines	NR	No exposure: 1.0, Referent
			Nonsubstantial: 1.1, 0.5–2.5
			Substantial: 3.5, 0.7–17.3
Baris 1998 [20] [2]	DDT (OC insecticides)	22 cases	1.6, 0.8–2.9
Eriksson 2008 [32]	DDT (OC insecticide)	NR	1.3, 0.8–2.1
Cocco 2012 [28]	DDT (OC insecticide)	3 cases	1.2, 0.2–5.9
Cocco 2012 [28]	Endosulfan (OC insecticide)	0 cases	NR, zero exposed cases
Organophosphorus insecticides			
Cocco 2012 [28]	Organophosphates	23 cases	1.4, 0.8, 2.6
Zheng 2001 [60] [2]	Organophosphates	18 cases	1.6, 0.8–3.2
Fritschi 2005 [62] [1]	Organophosphates	NR	No exposure [1]: 1.0, Referent
			Non-substantial: 0.6, 0.3–1.2
			Substantial: 2.1, 0.8–5.7
Cocco 2012 [28]	Dimethoate (OP insecticide)	3 cases	1.8, 0.3–10.6
Waddell 2001 [56] [2]	Fonofos (OP insecticide)	5 cases	2.6, 0.8–8.5
Waddell 2001 [56] [2]	Malathion (OP insecticide)	10 cases	1.9, 0.8–4.7
Waddell 2001 [56] [2]	Diazinon (OP insecticide)	9 cases	2.8, 1.1–7.3
Waddell 2001 [56] [2]	Phorate (OP insecticides)	8 cases	2.3, 0.9–6.0
Waddell 2001 [56] [2]	Terbufos (OP insecticides)	5 cases	2.2, 0.7–7.4
Other insecticides			
Eriksson 2008 [32]	Pyrethrine (Botanical insecticide)	NR	1.7, 0.7–3.9
Eriksson 2008 [32]	Mercurial seed dressing	NR	1.8, 0.8–3.9

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Table 3. *Cont.*

Author, date	Chemical	Number of exposed cases	Risk ratio, 95% CI
Mature B cell lymphoma			
Beane Freeman 2011 [22]	Atrazine (Triazine herbicide)	Lifetime days of exposure:	
		Quartile 1, >0–20: 36	1.0, Referent
		Quartile 2, 21–56: 34	1.0, 0.7–1.7
		Quartile 3, >56–178.5: 31	0.9, 0.5–1.4
		Quartile 4, >178.5: 28	0.9, 0.6–1.6
			P for trend: 0.8
		Intensity weighted lifetime days of exposure:	
		Quartile 1, >0–20: 34	1.0, Referent
		Quartile 2, 21–56: 38	1.1, 0.7–1.8
		Quartile 3, >56–178.5: 25	0.8, 0.5–1.3
		Quartile 4, >178.5: 31	0.9, 0.6, 1.5
			P for trend: 0.7
Diffuse large B cell lymphoma			
HERBICIDES			
Organophosphorus herbicides			
Eriksson 2008 [32]	Glyphosate (OP herbicides)	NR	1.2, 0.4–3.4
Phenoxy herbicides			
Cocco 2012 [28]	Phenoxy herbicides	4 cases	1.7, 0.5–5.2
Eriksson 2008 [32]	Phenoxy herbicides	NR	2.2, 1.1–4.3
Fritschi 2005 [62] [1]	Phenoxy herbicides	NR	No exposure [1]: 1.0, Referent
			Nonsubstantial exposure: 0.5, 0.1–2.0
			Substantial exposure: 2.2, 0.4–13.1
Eriksson 2008 [32]	MCPA (Phenoxy herbicide)	NR	3.9, 1.5–10.5
Eriksson 2008 [32]	2,4,5-T and/or 2,4-D (Phenoxy herbicide)	NR	1.7, 0.7–3.8

Table 3. *Cont.*

Author, date	Chemical	Number of exposed cases	Risk ratio, 95% CI
Thiocarbamate herbicides			
Zheng 2001 [60]	Butylate (Thiocarbamate herbicides)	15 cases	1.6, 0.9–3.1
Zheng 2001 [60]	EPTC + Protectant (Thiocarbamate herbicides)	10 cases	1.8, 0.8–3.7
Triazine herbicides			
Cocco 2012 [28]	Triazines and triazoles	2 cases	0.8, 0.2–3.4
Beane Freeman 2011 [22]	Atrazine (Triazine herbicides)	Lifetime exposure days:	
		Quartile 1, >0–20: 20	1.0, Referent
		Quartile 2, 21–56: 14	0.8, 0.4–1.6
		Quartile 3, >56–178.5: 14	0.7, 0.4–1.5
		Quartile 4, >178.5: 11	0.7, 0.3–1.6
			p for trend:0.5
		Intensity-weighted lifetime exposure days:	
		Quartile 1, >0–20: 15	1.0, Referent
		Quartile 2, 21–56: 18	1.2, 0.6–2.5
		Quartile 3, >56–178.5: 11	0.8, 0.4–1.7
		Quartile 4, >178.5: 15	1.1, 0.5–2.3
			p for trend:0.96
Zahm 1993 [59]	Atrazine (Triazine herbicides)	66 cases	1.6, 1.1–2.2
INSECTICIDES			
Carbamate insecticides			
Zheng 2001 [60]	Carbaryl (Carbamate insecticides)	15 cases	1.5, 0.8–2.8
Zheng 2001 [60]	Carbofuran (Carbamate insecticides)	24 cases	1.6, 1.0–2.7

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Table 3. *Cont.*

Author, date	Chemical	Number of exposed cases	Risk ratio, 95% CI
Organochlorine insecticides			
Cocco 2012 [28]	Organochlorines	5 cases	0.6, 0.2–1.6
	Organochlorines	NR	No exposure [1]: 1.0, Referent
Fritschi 2005 [62] [1]			Non-substantial exposure: 1.2, 0.4–3.4
			Substantial exposure: 1.6, 0.2–18.1
Eriksson 2008 [32]	DDT (OC insecticide)	NR	1.2, 0.6–2.5
Baris 1998 [20]	DDT (OC insecticide)	53 cases	1.2, 0.8–1.7
Organophosphorus insecticides			
Cocco 2012 [28]	Organophosphates	5 cases	1.1, 0.4–2.9
Waddell 2001 [56]	Organophosphates	63 cases	1.8, 1.2–2.6
Fritschi 2005 [62]	Organophosphates	NR	No exposure [1]: 1.0, Referent
			Non-substantial exposure: 0.6, 0.3–1.6
			Substantial exposure: 2.1, 0.6–7.7
Waddell 2001 [56]	Fonofos (OP insecticide)	10 cases	1.3, 0.6–2.7
Waddell 2001 [56]	Malathion (OP insecticide)	19 cases	1.1, 0.6–1.9
Waddell 2001 [56]	Diazinon (OP insecticide)	13 cases	1.2, 0.6–2.4
Waddell 2001 [56]	Phorate (OP insecticide)	10 cases	0.8, 0.4–1.8
Waddell 2001 [56]	Terbufos (OP insecticide)	7 cases	0.8, 0.4–2.0
Other insecticides			
Cocco 2012 [28]	Arsenicals	2 cases	0.4, 0.1–1.6
Eriksson 2008 [32]	Pyrethrine (Botanical insecticide)	NR	1.3, 0.3–4.6
Eriksson 2008 [32]	Mercurial seed dressing	NR	2.2, 0.8–6.1
Chronic lymphocytic leukemia			
HERBICIDES			
Cocco 2012 [28]	Phenoxy acids	Ever *vs.* never exposed	
		2 cases ever exposed	0.9, 0.2–4.1
		Intensity of exposure	
		Unexposed: 362 cases	1.0, Referent

Table 3. *Cont.*

Author, date	Chemical	Number of exposed cases	Risk ratio, 95% CI
		Low: 0 cases	
		Medium/high: 2 cases	2.4, 0.4–13.8
Cocco 2012 [28]	Triazines and triazoles	2 cases	0.9, 0.2–4.1
INSECTICIDES			
Cocco 2012 [28]	Arsenicals	15 cases	1.6, 0.8–2.9
Cocco 2012 [28]	Carbamates		
Cocco 2012 [28]	Organochlorines	Ever *vs* never exposed	
		10 cases ever exposed	1.2, 0.6–2.5
		Intensity of exposure	
		Unexposed: 362 cases	1.0, Referent
		Low: 5 cases	1.8, 0.6–5.0
		Medium/high: 5 cases	1.0, 0.4–2.8
Cocco 2012 [28]	Organophosphates	Ever *vs* never exposed	
		9 cases ever exposed	2.7, 1.2–6.0
		Intensity of exposure	
		Unexposed: 362 cases	1.0, Referent
		Low: 5 cases	2.7, 0.9–7.8
		Medium/high: 4 cases	2.6, 0.7–9.2
Lymphocytic lymphoma			
HERBICIDES			
Organophosphorus herbicides			
Eriksson 2008 [32]	Glyphosate (OP herbicide)	NR	3.4, 1.4–7.9
Phenoxy herbicides			
Eriksson 2008 [32]	Phenoxy herbicides	NR	2.1, 1.0–4.5
Cocco 2013 [28]	Phenoxy herbicides	NR	0.9, 0.2–4.1

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Table 3. *Cont.*

Author, date	Chemical	Number of exposed cases	Risk ratio, 95% CI
Eriksson 2008 [32]	2,4,5-T and/or 2,4-D (Phenoxy herbicides)	NR	1.9, 0.9–4.4
Eriksson 2008 [32]	MCPA (Phenoxy herbicides)	NR	2.6, 0.7–9.0
INSECTICIDES			
Organochlorine insecticides			
Eriksson 2008 [32]	DDT (OC insecticides)	NR	1.4, 0.7–2.8
Organophosphorus insecticides			
Fritschi 2005 [62][1]	Organophosphates	NR	No exposure: 1.0, Referent
			Non-substantial exposure: 1.1, 0.5–2.3
			Substantial exposure: 4.3, 1.4–13.0
Other insecticides			
Eriksson 2008 [32]	Pyrethrine (Botanical insecticide)	NR	2.4, 0.7–7.9
Eriksson 2008 [32]	Mercurial seed dressing	NR	2.9, 1.0–8.3
Follicular lymphoma			
HERBICIDES			
Organophosphorus herbicides			
Eriksson 2008 [32]	Glyphosate (OP herbicide)	NR	1.9, 0.6–5.8
Phenoxy herbicides			
Eriksson 2008 [32]	Phenoxy herbicides	NR	1.3, 0.4–3.8
Fritschi 2005 [62][1]	Phenoxy herbicides	NR	No exposure: 1.0, Referent
			Non-substantial exposure: 0.5, 0.1–2.0
			Substantial exposure: 1.2, 0.1–11.2
Eriksson 2008 [32]	2,4,5-T and/or 2,4-D (Phenoxy herbicide)	NR	1.2, 0.4–4.2
Eriksson 2008 [32]	MCPA (Phenoxy herbicide)	NR	No exposed cases
Thiocarbamate herbicides			
Zheng 2001 [60]	Butylate (Thiocarbamate herbicides)	17 cases	1.5, 0.8–2.8
Zheng 2001 [60]	EPTC + Protectant use (Thiocarbamate herbicides)	10 cases	1.7, 0.8–3.8

Table 3. *Cont.*

Author, date	Chemical	Number of exposed cases	Risk ratio, 95% CI
Triazine herbicides			
Zahm 1993 [59]	Atrazine (Triazine herbicide)	40 cases	1.3, 0.9–1.9
Beane Freeman 2011 [22]	Atrazine (Triazine herbicide)	Lifetime exposure days, by quartile:	
		Quartile 1, >0–20: 10	1.0, Referent
		Quartile 2, 21–56: 8	0.9, 0.3–2.2
		Quartile 3, >56–178.5: 6	0.6, 0.2–1.7
		Quartile 4, >178.5: 8	1.0, 0.4–2.6
			p for trend: 0.9
		Intensity-weighted exposure days:	
		Quartile 1, >0–20: 10	1.0, Referent
		Quartile 2, 21–56: 10	1.0, 0.4–2.4
		Quartile 3, >56–178.5: 8	0.8, 0.3–2.1
		Quartile 4, >178.5: 4	0.4, 0.1–1.3
			p for trend: 0.07
INSECTICIDES			
Carbamate insecticides			
Zheng 2001 [60]	Carbaryl (Carbamate insecticides)	14 cases	1.3, 0.6–2.4
Zheng 2001 [60]	Carbofuran (Carbamate insecticides)	22 cases	1.4, 0.8–2.4
Organochlorine insecticides			
Fritschi 2005 [62][1]	Organochlorines	NR	No exposure: 1.0, Referent
			Non-substantial exposure: 1.8, 0.7–4.8
			Substantial exposure: 3.5, 0.5–25.2
Eriksson 2008 [32]	DDT (OC insecticide)	NR	2.1, 1.1–4.4
Baris 1998 [20]	DDT (OC insecticide)	47 cases	1.3, 0.8–1.9
Organophosphorus insecticides			
Waddell 2001 [56]	OP pesticides, group	50 cases	1.3, 0.9–2.0
Waddell 2001 [56]	Fonofos (OP insecticide)	14 cases	1.2, 0.6–2.4
Waddell 2001 [56]	Malathion (OP insecticide)	29 cases	1.3, 0.8–2.2

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Table 3. *Cont.*

Author, date	Chemical	Number of exposed cases	Risk ratio, 95% CI
Waddell 2001 [56]	Diazinon (OP insecticide)	17 cases	1.3, 0.7–2.3
Waddell 2001 [56]	Phorate (OP insecticide)	10 cases	0.7, 0.3–1.4
Waddell 2001 [56]	Terbufos (OP insecticide)	9 cases	0.7, 0.3–1.6
Eriksson 2008 [32]	Mercurial seed dressing	NR	3.6, 1.2–10.9
Eriksson 2008 [32]	Pyrethrine (Botanical insecticide)	NR	2.6, 0.8–8.5
T cell lymphoma			
HERBICIDES			
Organophosphorus herbicides			
Eriksson 2008 [32]	Glyphosate (OP insecticide)	NR	2.3, 0.5–10.4
Phenoxy herbicides			
Eriksson 2008 [32]	Phenoxy herbicides	NR	1.6, 0.4–7.3
Eriksson 2008 [32]	2,4,5-T and/or 2,4-D (Phenoxy herbicides)	NR	1.0, 0.1–8.0
Eriksson 2008 [32]	MCPA (Phenoxy herbicides)	NR	2.4, 0.3–20.0
INSECTICIDES			
Eriksson 2008 [32]	DDT (OC insecticide)	NR	2.9, 1.1–8.0
Eriksson 2008 [32]	Mercurial seed dressing	NR	2.1, 0.3–17.1
Eriksson 2008 [32]	Pyrethrine (Botanical insecticide)	NR	2.2, 0.3–17.8
Unspecified NHL			
HERBICIDES			
Organophosphorus herbicides			
Eriksson 2008 [32]	Glyphosate (OP insecticide)	NR	5.6, 1.4–22.0
Phenoxy herbicides			
Eriksson 2009 [32]	Phenoxy herbicides	NR	3.8, 1.2–12.1
Eriksson 2008 [32]	2,4,5-T and/or 2,4-D (Phenoxy herbicide)	NR	3.2, 0.9–12.1
Eriksson 2008 [32]	MCPA (Phenoxy herbicide)	NR	9.3, 2.1–41.2
INSECTICIDES			
Eriksson 2008 [32]	DDT (OC insecticide)	NR	2.4, 0.8–7.4
Eriksson 2008 [32]	Mercurial seed dressing	NR	5.4, 1.3–22.0

Table 3. *Cont.*

Author, date	Chemical	Number of exposed cases	Risk ratio, 95% CI
Eriksson 2008 [32]	Pyrethrine (Botanical insecticide)	NR	3.1, 0.4–26.3
Other specified B cell lymphoma			
HERBICIDES			
Organophosphorus herbicides			
Eriksson 2008 [32]	Glyphosate (OP herbicide)	NR	1.6, 0.5–5.0
Phenoxy herbicides			
Eriksson 2008 [32]	Phenoxy herbicides	NR	2.6, 1.2–5.6
Eriksson 2008 [32]	2,4,5-T and/or 2,4-D (Phenoxy herbicide)	NR	2.2, 0.9–5.4
Eriksson 2008 [32]	MCPA (Phenoxy herbicide)	NR	3.2, 1.0–10.7
INSECTICIDES			
Eriksson 2008 [32]	DDT (OC insecticide)	NR	1.3, 0.6–3.1
Eriksson 2008 [32]	Mercurial seed dressing	NR	2.4, 0.7–7.8
Eriksson 2008 [32]	Pyretrine	NR	1.5, 0.3–6.9
Unspecified B cell lymphoma			
HERBICIDES			
Organophosphorus herbicides			
Eriksson 2008 [32]	Glyphosate (OP herbicide)	NR	1.5, 0.3–6.6
Phenoxy herbicides			
Eriksson 2008 [32]	Phenoxy herbicides	NR	1.1, 0.3–4.0
Eriksson 2008 [32]	2,4,5-T and/or 2,4-D (Phenoxy herbicide)	NR	0.9, 0.2–3.9
Eriksson 2008 [32]	MCPA (Phenoxy herbicide)	NR	1.4, 0.2–11.2
INSECTICIDES			
Eriksson 2008 [32]	DDT (OC insecticide)	NR	0.2, 0.0–1.8
Eriksson 2008 [32]	Mercurial seed dressing	NR	No exposed cases

Notes: 2,4-D, 2,4-Dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-Trichlorophenoxyacetic acid; DDT, dichlorodiphenyltrichloroethane; EPTC, s-ethyl dipropylthiocarbamate; MCPA, 2-methyl-4-chlorophenoxyacetic acid; NHL, non-Hodgkin lymphoma; NR, Not reported; OC, Organochlorine; OP, Organophosphorus; [1] Substantial indicates the person was exposed to the substance at a medium or high level for more than five 8-hour days per year for a combined total of more than 5 years. Nonsubstantial indicates any other combination of exposures; estimates derive from a case-control study; [2] NHL subtype is labeled small lymphocytic in the paper.

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In the Agricultural Health Study, Delancey *et al.* [29] observed a fairly strong dose response relationship between exposure to metribuzin, a triazinone herbicide, and NHL (P for trend: 0.13). Waddell *et al.* [56] observed a dose-response relationship between years of use of the organophosphorus insecticide fonofos and NHL. These authors also observed a strong positive relationship between days/year of exposure to another organophosphorus insecticide, terbufos, and NHL (OR, 95% CI for ≥5 days *vs.* non-farmers: 4.0, 1.1–14.5).

Table 3 shows estimates of association between subtypes of NHL and chemical groups or active ingredients. Table 4 shows the individual effect estimates of associations with herbicides, fungicides, and insecticides, coded dichotomously.

Table 4. Effect estimates from papers that investigated associations between non-Hodgkin lymphoma and herbicide, fungicide, and insecticide exposures, categorized dichotomously.

Author, date	N exposed	Risk ratio, 95% CI
HERBICIDES		
Amide herbicides		
Amide herbicides, group		
Hoar 1986 [34]	8 cases/22 controls	2.9, 1.1–7.6
Cantor 1992 [27]	58 cases/114 controls	1.2, 0.8–1.7
Zahm 1993 [18] [1]	8 cases/34 controls	0.9, 0.4–2.2
Orsi 2009 [46]	5 cases/12 controls	0.9, 0.3–2.8
Alachlor		
De Roos 2003 [30]	68 cases/152 controls	1.1, 0.7–1.7
Lee 2004 [39] [2]	29 cases	0.7, 0.5–1.1
Metolachlor		
De Roos 2003 [30]	13 cases/37 controls	0.7, 0.3–1.6
Propachlor		
De Roos 2003 [30]	20 cases/50 controls	1.0, 0.5–2.0
Propyzamide		
Mills 2005 [45]	NR	0.7, 0.3–1.4
Organophosphorus herbicides		
Glyphosate		
McDuffie 2001 [43]	51 cases/133 controls	1.2, 0.8–1.7
Hardell 2002 [33]	8 cases/8 controls	3.0, 1.1–8.5
De Roos 2003 [30]	36 cases/61 controls	2.1, 1.1–4.0
De Roos 2005 [31] [2]	71 cases	1.1, 0.7–1.9
Eriksson 2008 [32]	29 cases/18 controls	2.0, 1.1–3.7
Orsi 2009 [46]	12 cases/24controls	1.0, 0.5–2.2
Phosphonic acid		
McDuffie 2001 [43]	63 cases/147 controls	1.4, 0.9–1.9
Phenoxy herbicides		
Phenoxy herbicides, group		
Hoar 1986 [34]	24 cases/78 controls	2.2, 1.2–4.1
Pearce 1987 [48]	81 cases/143 controls	1.0, 0.8–1.4
Woods 1987 [57]	NR	1.3, 0.9–2.0
Persson 1989 [49]	6 cases/6 controls	4.9, 1.0–23.5

Table 4. *Cont.*

Author, date	N exposed	Risk ratio, 95% CI
Cantor 1992 [27]	118 cases/231 controls	1.2, 0.9–1.6
Persson 1993 [50]	10 cases/14 controls	2.3, 0.2–2.8
Zahm 1993 [18] [1]	14 cases/63 controls	0.9, 0.4–1.7
Hardell 2002 [33]	64 cases/90 controls	1.7, 1.2–2.3
Miligi 2006 [44]	32 cases/28 controls	1.1, 0.6–1.8
Eriksson 2008 [32]	47 cases/26 controls	2.0, 1.2–3.4
Orsi 2009 [46]	11 cases/25 controls	0.9, 0.4–1.9
Pahwa 2012 [47]	129 cases/138 controls	1.5, 1.1–1.9
2,4-D		
Zahm 1990 [58]	43 cases/98 controls	1.5, 0.9–2.5
Cantor 1992 [27]	Ever handled: 115 cases/227 controls	1.2, 0.9–1.6
Cantor 1992 [27] [3]	Handled prior to 1965: 86 cases/153 controls	1.3, 0.9–1.8
Mills 2005 [45]	NR	3.8, 1.9–7.8
Miligi 2006 [44]	17 cases/18 controls	0.9, 0.5–1.8
Pahwa 2012 [47]	110 cases/293 controls	1.3, 1.0–1.7
2,4,5-T		
De Roos 2003 [30]	Ever handled: 25 cases/63 controls	1.0, 0.5–1.9
Cantor 1992 [27] [3]	Handled prior to 1965: 13 cases/18 controls	1.7, 0.8–3.6
2,4,5-T and/or 2,4-D		
Eriksson 2008 [32]	33 cases/21 controls	1.6, 0.9–3.0
Diclofop-methyl		
McDuffie 2001 [43]	9 cases/25 controls	1.0, 0.4–2.2
MCPA		
Hardell 2002 [33]	21 cases/23 controls	2.6, 1.4–4.9
De Roos 2003 [30] [1]	8 cases/16 controls	1.0, 0.4–2.6
Miligi 2006 [44]	18 cases/19 controls	0.9, 0.4–1.8
Eriksson 2008 [32]	21 cases/9 controls	2.8, 1.3–6.2
Pahwa 2012 [47]	17 cases/46 controls	1.1, 0.6–2.0
Carbamate/Thiocarbamate herbicides		
Carbamate/Thiocarbamate herbicides, group		
Zahm 1993 [18] [1]	2 cases/14 controls	0.6, 0.1–2.8
McDuffie 2001 [43]	21 cases/49 controls	1.5, 0.8–2.6
Zheng 2001 [60]	60 cases/108 controls	1.5, 1.1–2.3
Butylate		
Cantor 1992 [27] [3]	Handled prior to 1965: 1 case/6 controls	0.5, 0.1–4.3
Zheng 2001 [60]	45 cases/76 controls	1.6, 1.0–2.4
Diallate		
McDuffie 2001 [43]	11 cases/29 controls	1.5, 0.7–3.1
EPTC + Protectant		
Zheng 2001 [60]	23 cases/49 controls	1.6, 0.9–2.7

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Table 4. *Cont.*

Author, date	N exposed	Risk ratio, 95% CI
Aromatic acid herbicides		
Benzoic acid herbicides		
Hoar 1986 [34]	1 case/2 controls	4.0, 0.1–62.6
Cantor 1992 [27]	53 cases/98 controls	1.3, 0.9–1.9
Zahm 1993 [18] [1]	4 cases/12 controls	1.2, 0.3–4.4
Chloramben		
Cantor 1992 [27] [3]	Handled prior to 1965: 16 cases/19 controls	2.0, 1.0–4.0
De Roos 2003 [30]	34 cases/81 controls	0.9, 0.5–1.6
Dicamba		
Cantor 1992 [27] [3]	Handled prior to 1965: 7 cases/7 controls	2.8, 1.0–8.1
McDuffie 2001 [43]	26 cases/50 controls	1.6, 1.0–2.6
De Roos 2003 [30]	39 cases/79 controls	1.2, 0.6–2.3
Dinitroaniline herbicides		
Dinitroanilines, group		
Cantor 1992 [27]	46 cases/88 controls	1.2, 0.8–1.8
McDuffie 2001 [43]	11 cases/31 controls	1.2, 0.6–2.4
Trifluralin		
Cantor 1992 [27] [3]	Handled prior to 1965: 14 cases/23 controls	1.5, 0.8–3.1
Zahm 1993 [18] [1]	3 cases/24 controls	0.5, 0.1–1.7
McDuffie 2001 [43]	11 cases/31 controls	1.1, 0.5–2.2
De Roos 2003 [30]	52 cases/120 controls	0.9, 0.5–1.6
Mills 2005 [43,45]	NR	0.9, 0.4–1.8
Triazine herbicides		
Triazine herbicides, group		
Hoar 1986 [34]	14 cases/43 controls	2.5, 1.2–5.4
Cantor 1992 [27]	64 cases/133 controls	1.1, 0.8–1.6
Zahm 1993 [18] [1]	12 cases/38 controls	1.2, 0.6–2.6
Orsi 2009 [46]	17 cases /20 controls	1.9, 0.9–3.8
Atrazine		
Zahm 1993 [59]	130 cases/249 controls	1.4, 1.1–1.8
Cyanazine		
De Roos 2003 [30]	37 cases/96 controls	0.6, 0.3–1.0
Metribuzin		
De Roos 2003 [30]	20 cases/53 controls	0.8, 0.4–1.7
Simazine		
Mills 2005 [45]	NR	1.7, 0.9–3.0
Urea herbicides		
Urea herbicides		
Cantor 1992 [27]	5 cases/18 controls	0.6, 0.2–1.6
Orsi 2009 [46]	5 cases/7 controls	1.8, 0.5–6.0
Linuron		
De Roos 2003 [30]	5 cases/22 controls	0.3, 0.1–1.2

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Table 4. *Cont.*

Author, date	N exposed	Risk ratio, 95% CI
Other herbicides		
Bentazon		
Cantor 1992 [27]	22 cases/58 controls	0.7, 0.3–1.5
Nitrofen		
Mills 2005 [45]	NR	1.2, 0.6–2.5
Paraquat		
De Roos 2003 [30]	2 cases/15 controls	0.1, 0.2–0.7
Quaternary ammonium compounds, group		
Orsi 2009 [46]	4 cases/12 controls	0.7, 0.2–2.3
Sodium chlorate		
De Roos 2003 [30]	8 cases/7 controls	4.1, 1.3–13.6
Uracil herbicides		
Hoar 1986 [34]	19 cases/114 controls	1.3, 0.7–2.5
FUNGICIDES		
Aldehyde fungicides		
Aldehyde fungicides, group		
McDuffie 2001 [43]	7 cases/25 controls	0.9, 0.4–2.3
Formaldehyde		
McDuffie 2001 [43]	7 cases/25 controls	0.9, 0.4–2.3
Amide fungicides		
Amide fungicides, group		
McDuffie 2001 [43]	30 cases/58 controls	1.7, 1.0–2.8
Captan		
McDuffie 2001 [43]	20 cases/24 controls	2.5, 1.3–4.8
Mills 2005 [45]	NR	0.9, 0.5–1.6
Vitavax		
McDuffie 2001 [43]	10 cases/39 controls	0.8, 0.4–1.9
Carbamate and dithiocarbamate fungicides		
Carbamate fungicides		
Orsi 2009 [46]	15 cases/17 controls	1.8, 0.9–3.7
Maneb		
Mills 2005 [45]	NR	1.1, 0.6–2.1
Mancozeb		
Mills 2005 [45]	NR	0.9, 0.5–1.9
Triazole fungicides		
Triazole fungicides, group		
Orsi 2009 [46]	8 cases/9 controls	1.9, 0.7–5.3
Mecoprop		
Pahwa 2012 [47]	51 cases/81 controls	2.3, 1.5–3.3
Mercury containing fungicides		
Mercury fungicides, group		
McDuffie 2001 [43]	18 cases/48 controls	1.3, 0.7–2.3
Mercury dust		
McDuffie 2001 [43]	15 cases/39 controls	1.2, 0.6–2.4

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Table 4. *Cont.*

Author, date	N exposed	Risk ratio, 95% CI
Mercury liquid		
McDuffie 2001 [43]	8 cases/22 controls	1.4, 0.7–3.2
Fumigant fungicides		
Methyl bromide		
Mills 2005 [45]	NR	1.5, 0.8–2.7
Dichloro-propane		
Mills 2005 [45]	NR	0.9, 0.5–1.7
Other fungicides		
Chlorothalonil		
Mills 2005 [45]	NR	1.2, 0.6–2.2
Sulfur compounds		
McDuffie 2001 [43]	17 cases/21 controls	2.8, 1.4–5.6
INSECTICIDES		
Arsenicals		
Acetoarcenate		
De Roos 2003 [30]	41 cases/68 controls	1.4, 0.9–2.3
Arsenic		
Hardell 2002 [33]	8 cases/10 controls	1.8, 0.7–4.5
Eriksson 2008 [32]	7 cases/5 controls	1.6, 0.5–5.2
Lead arsenate		
De Roos 2003 [30]	9 cases/25 controls	0.5, 0.2–1.2
Botanical insecticides		
Nicotine		
Cantor 1992 [27]	31 cases/47 controls	1.5, 0.9–2.5
Cantor 1992 [27] [3]	Handled prior to 1965: 28 cases/36 controls	1.8, 1.0–3.0
Pyrethrine		
De Roos 2003 [30]	6 cases/12 controls	1.0, 0.3–3.2
Eriksson 2008 [32]	15 cases/10 controls	1.7, 0.8–3.9
Rotenone		
Cantor 1992 [27]	12 cases/23 controls	0.5, 2.2–1.0
Carbamate insecticides		
Carbamate insecticides, group		
McDuffie 2001 [43]	37 cases/60 controls	1.9, 1.2–3.0
Zahm 1993 [18] [1]	7 cases/17 controls	1.6, 0.6–4.4
Zheng 2001 [60]	89 cases/172 controls	1.6, 1.0–2.4
Bufencarb		
De Roos 2003 [30]	6 cases/12 controls	1.1, 0.3–3.7
Carbaryl		
Cantor 1992 [27] [3]	Handled prior to 1965: 7 cases/4 controls	3.8, 1.1–13.6
De Roos 2003 [30]	30 cases/57 controls	1.0, 0.5–1.9
McDuffie 2001 [43]	25 cases/34 controls	2.1, 1.2–3.7
Carbofuran		
Cantor 1992 [27] [3]	Handled prior to 1965: 28 cases/63 controls	1.0, 0.6–1.7
McDuffie 2001 [43]	9 cases/18 controls	1.6, 0.7–3.9
Zheng 2001 [60]	66 cases/131 controls	1.6, 1.1–2.3

Table 4. *Cont.*

Author, date	N exposed	Risk ratio, 95% CI
Methomyl		
McDuffie 2001 [43]	37 cases/60 controls	2.1, 1.2–3.7
Fly spray		
Cantor 1992 [27]	185 cases/394 controls	1.1, 0.9–1.4
Cantor 1992 [27] [3]	Handled prior to 1965: 173 cases/368 controls	1.1, 0.9–1.4
Organochlorine insecticides		
Organochlorine insecticides, group		
Cantor 1992 [27]	150 cases/162 controls	1.3, 1.0–1.7
Zahm 1993 [18] [1]	20 cases/46 controls	1.6, 0.8–3.1
Orsi 2009 [46]	15 cases/17 controls	1.8, 0.9–3.8
Purdue 2007 [51]	58 cases/44 non cases	0.8, 0.5–1.3
Pahwa 2012 [47]	106 cases/276 controls	1.3, 1.0–1.7
Aldrin		
Cantor 1992 [27] [3]	Handled prior to 1965: 34 cases/59 controls	1.3, 0.8–2.1
McDuffie 2001 [43]	10 cases/6 controls	4.2, 1.5–12.0
De Roos 2003 [30]	47 cases/97 controls	1.1, 0.7–1.7
Purdue 2007 [51]	21 cases/79 non-cases	0.6, 0.3–1.0
Chlordane		
Woods 1987 [57]	NR	1.6, 0.7–3.8
Cantor 1992 [27] [3]	Handled prior to 1965: 22 cases/22 controls	2.2, 1.2–4.2
McDuffie 2001 [43]	36 cases/105 controls	1.1, 0.7–1.7
De Roos 2003 [30]	21 cases/26 controls	1.7, 0.9–3.2
Purdue 2007 [51]	27 cases/73 non-cases	0.7, 0.4–1.2
DDT		
Woods 1987 [57]	Not reported	1.8, 1.0–3.2
Cantor 1992 [27] [3]	Handled prior to 1965: 68 cases/123 controls	1.3, 0.9–1.8
Persson 1993 [50]	4 case/3 controls	2.0, 0.2–18.9
Baris 1998 [20]	161 cases/340 controls	1.2, 1.0–1.6
Hardell 2002 [33]	77 cases/138controls	1.2, 0.9–1.7
De Roos 2003 [30]	98 cases/226 controls	1.0, 0.7–1.3
Purdue 2007 [51]	37 cases/63 noncases	0.9, 0.6–1.5
Eriksson 2008 [32]	50 cases/37 controls	1.5, 0.9–2.3
Pahwa 2012 [47]	33 cases/59 controls	1.7, 1.1–2.7
Dieldrin		
Cantor 1992 [27] [3]	Handled prior to 1965: 10 cases/13 controls	1.9, 0.8–4.4
De Roos 2003 [30]	21 cases/39 controls	1.8, 0.8–3.9
Purdue 2007 [51]	7 cases/92 controls	0.6, 0.2–1.3
Heptachlor		
Cantor 1992 [27] [3]	Handled prior to 1965: 14 cases/25 controls	1.3, 0.6–2.6
De Roos 2003 [30]	25 cases/43 controls	1.3, 0.7–2.2
Purdue 2007 [51] [2]	18 cases/82 noncases	0.8, 0.4–1.4
Lindane		
Cantor 1992 [27] [3]	Handled prior to 1965: 14 cases/25 controls	2.2, 1.0–4.7
Blair 1998 [23]	93 cases/151 controls	1.5, 1.1–2.0

Table 4. *Cont.*

Author, date	N exposed	Risk ratio, 95% CI
McDuffie 2001 [43]	15 cases/23 controls	2.1, 1.0–4.2
Rafnsson 2006 [52]	37 cases/133 controls	3.5, 1.4–9.0
Purdue 2007 [51] [2]	24 cases/76 controls	1.3, 0.8–2.1
Methoxychlor		
McDuffie 2001 [43]	65 cases/201 controls	1.0, 0.7–1.4
De Roos 2003 [30]	9 cases/16 controls	1.2, 0.5–2.7
Toxaphene		
Cantor 1992 [27] [3]	Handled prior to 1965: 6 cases/5 controls	2.4, 0.7–8.2
De Roos 2003 [30]	10 cases/13 controls	1.5, 0.6–3.5
Purdue 2007 [51] [2]	24 cases/75 controls	1.5, 0.9–2.5
Organophosphorus insecticides		
Organophosphorus insecticides		
Zahm 1993 [18] [1]	14 cases/43 controls	1.2, 0.6–2.5
Waddell 2001 [56]	158 cases/279 controls	1.5, 1.2–1.9
Orsi 2009 [46]	20 cases/24 controls	1.7, 0.9–3.3
Pahwa 2012 [47]	92 cases/169 controls	1.9, 1.4–2.6
Chlorpyrifos		
Waddell 2001 [56]	7 cases/8 controls	3.2, 1.1–9.2
Lee 2004 [38] [2]	37 participants	1.0, 0.6–1.7
Coumaphos		
Cantor 1992 [27] [3]	Handled prior to 1965: 3 cases/5 controls	1.5, 0.3–6.3
Waddell 2001 [56]	23 cases/37 controls	1.7, 1.0–2.9
Crufomate		
Waddell 2001 [56]	5 cases/8 controls	1.6, 0.5–4.9
Diazinon		
Cantor 1992 [27] [3]	Handled prior to 1965: 14 cases/12 controls	2.6, 1.2–5.9
McDuffie 2001 [43]	18 cases/28 controls	1.7, 0.9–3.2
Waddell 2001 [56]	60 cases/93 controls	1.7, 1.2–2.5
Mills 2005 [45]	NR	1.4, 0.8–2.5
Dichlorvos		
Cantor 1992 [27] [3]	Handled prior to 1965: 12 cases/17 controls	1.8, 0.8–3.9
Waddell 2001 [56]	23 cases/51 controls	1.0, 0.6–1.7
Koutros 2008 [37] [2]	6 exposed cases	NR
Dimethoate		
McDuffie 2001 [43]	22 cases/50 controls	1.2, 0.7–2.1
Waddell 2001 [56]	12 cases/22 controls	1.8, 0.9–3.8
Disulfoton		
Waddell 2001 [56]	7 cases/13 controls	2.0, 0.8–5.3
Ethoprop		
Waddell 2001 [56]	7 cases/17 controls	0.9, 0.4–2.3
Famphur		
Waddell 2001[56]	18 cases/47 controls	1.0, 0.5–1.8
Fensulfothion		
Waddell 2001 [56]	4 cases/4 controls	2.0, 0.5–8.2

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Table 4. *Cont.*

Author, date	N exposed	Risk ratio, 95% CI
Fonofos		
Waddell 2001 [56]	43 cases/67 controls	1.7, 1.1–2.6
Malathion		
Cantor 1992 [27] [3]	Handled prior to 1965: 11 cases/9 controls	2.9, 1.1–7.4
Waddell 2001 [56]	91 cases/147 controls	1.6, 1.2–2.2
Mills 2005 [45]	NR	1.8, 1.0–3.2
Pahwa 2012 [47]	72 cases/127 controls	2.0, 1.4–2.7
Methyl parathion		
Mills 2005 [45]	NR	0.6, 0.3–1.2
Parathion		
Waddell 2001 [56]	5 cases/8 controls	2.9, 0.9–9.7
Phorate		
Cantor 1992 [27] [3]	Handled prior to 1965: 9 cases/12 controls	1.8, 0.7–4.5
Waddell 2001 [56]	44 cases/97 controls	1.1, 0.8–1.7
Ronnel		
Waddell 2001 [56]	6 cases/11 controls	1.3, 0.5–3.6
Terbufos		
Waddell 2001 [56]	32 cases/97 controls	1.1, 0.7–1.8
Tetrachlorvinphos		
Waddell 2001 [56]	9 cases/17 controls	1.8, 0.7–4.7
Toxaphene		
Mills 2005 [45]	NR	0.9, 0.5–1.9
Trichlorfon		
Cantor 1992 [27] [3]	Handled prior to 1965: 6 cases/5 controls	2.4, 0.7–8.2
Waddell 2001 [56]	7 cases/11 controls	1.8, 0.7–4.7

Notes: 2,4-D, 2,4-Dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-Trichlorophenoxyacetic acid; EPTC, S-Ethyl dipropylthiocarbamate; MCPA, 2-methyl-4-chlorophenoxyacetic acid; DDT, dichlorodiphenyltrichloroethane; NHL, non-Hodgkin lymphoma; NR, Not reported; [1] Only women included in analysis; [2] Cohort study; [3] Effect estimate not included in the meta-analysis; another estimate from the same paper with a larger number of exposed cases was used..

3.4. Meta Analyses

When there was more than one effect estimate for a chemical group or active ingredient, the estimates shown in Tables 3 and 4 were combined to produce meta-analytic summary estimates and 95% CIs (Table 5).

The strongest meta RR estimates were associated with subtypes of NHL. There was a positive association between exposure to organophosphorus herbicide, glyphosate, and B cell lymphoma (2.0, 95% CI: 1.1–3.6, CLR: 3.2). Phenoxy herbicide exposures were associated with B cell lymphoma (1.8, 95% CI: 1.2–2.8, CLR: 2.4), lymphocytic lymphoma (1.8, 95% CI: 0.9–3.5, CLR: 3.8), and diffuse large B-cell lymphoma (DLBCL; 2.0, 95% CI: 1.1–3.7, CLR: 3.3). All these effect estimates were relatively precise, with CLRs < 4.

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Table 5. Meta analytic summary estimates of association between herbicides and insecticides with non-Hodgkin lymphoma.

Chemical group or active ingredient	Meta Risk Ratio estimate, 95% CI	I^2	Papers contributing
HERBICIDES			
Amide herbicides			
Amide herbicides	1.3, 0.8–1.9	22.2%	[18,27,34,46]
Alachlor	0.9, 0.6–1.3	43.0%	[30,39]
Aromatic acid herbicides			
Benzoic acid herbicides	1.3, 0.9–1.9	0.0%	[18,27,34,46]
Dicamba	1.4, 1.0-2.1	0.0%	[30,43]
Carbamate/thiocarbamate herbicides			
Carbamate/thiocarbamate herbicides	1.4, 1.1–2.0	0.0%	[18,43,60]
Dinitroanilines			
Dinitroanilines	1.2, 0.8–1.7	0.0%	[27,43]
Trifluralin	0.9, 0.6–1.3	0.0%	[18,30,43,45]
Organophosphorus herbicides			
Glyphosate	1.5, 1.1–2.0	32.7%	[30–33,43,46]
Glyphosate-association with B cell lymphoma	2.0, 1.1–3.6	0.0%	[32,63]
Phenoxy herbicides			
Phenoxy herbicides	1.4, 1.2–1.6	37.7%	[27,32–34,44, 46–50,57,59]
Phenoxy herbicides, association with B cell lymphoma	1.8, 1.2–2.8	0.0%	[32,63]
Phenoxy herbicides, association with DLBCL	2.0, 1.1–3.7	0.0%	[32,63]
Phenoxy herbicides, association with lymphocytic lymphoma	1.8, 0.9–3.5	0.0%	[32,63]
2,4-D	1.4, 1.0–1.9	61.5%	[27,44,45,47,58]
MCPA	1.5, 0.9–2.5	54.4%	[30,32,33,44,47]
Triazine herbicides			
Triazine herbicides	1.5, 1.0, 2.1	38.5%	[18,27,34,46]
Urea herbicides			
Urea herbicides, group	1.0, 0.3–2.9	43.4%	[27,46]
INSECTICIDES			
Arsenicals			
Arsenic	1.7, 0.8–3.6	0.0%	[32,33]
Botanical insecticides			
Pyrethrine	1.4, 0.8–2.8	0.0%	[30,32]
Carbamate insecticides			
Carbamate insecticides, group	1.7, 1.3–2.3	0.0%	[18,43,60]
Carbaryl	1.7, 1.3–2.3	0.0%	[43,60]
Carbofuran	1.6, 1.2–2.3	0.0%	[43,60]
Organophosphorus insecticides			
Organophosphorus insecticides, group	1.6, 1.4–1.9	0.0%	[18,46,47,56]
Chlorpyrifos	1.6, 0.6–4.9	72.0%	[38,56]
Diazinon	1.6, 1.2–2.2	0.0%	[43,45,56]
Dimethoate	1.4, 0.9–2.1	0.0%	[43,56]
Malathion	1.8, 1.4–2.2	0.0%	[45,47,56]

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Table 5. *Cont.*

Chemical group or active ingredient	Meta Risk Ratio estimate, 95% CI	I^2	Papers contributing
Organochlorine insecticides			
Organochlorine insecticides, group	1.3, 1.0–1.5	19.6%	[18,27,46,47,51]
DDT	1.3, 1.1–1.5	0.0%	[20,32,33,47,50,51,57]
DDT-association with B cell lymphoma	1.4, 1.0–2.0	0.0%	[20,32,63]
DDT-association with DLBCL	1.2, 0.9–1.7	0.0%	[20,32]
DDT-association with follicular lymphoma	1.5, 1.0–2.4	26.6%	[20,32]
Methoxychlor	1.0, 0.7–1.4	0.0%	[30,43]
Aldrin	1.0, 0.4–2.7	84.6%	[30,43,51]
Chlordane	1.1, 0.8–1.6	32.5%	[30,43,51,57]
Dieldrin	1.1, 0.4–3.1	67.6%	[30,51]
Heptachlor	0.9, 0.6–1.5	0.0%	[30,51]
Lindane	1.6, 1.2–2.2	26.0%	[23,43,51,52]
Toxaphene	1.4, 0.9–2.1	0.0%	[30,45,51]
Amide fungicides			
Captan	1.5, 0.5–4.2	82.5%	[43,45]

Notes: 2,4-D, 2,4-Dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-Trichlorophenoxyacetic acid; DDT, dichlorodiphenyltrichloroethane; EPTC, s-ethyl dipropylthiocarbamate; MCPA, 2-methyl-4-chlorophenoxyacetic acid; NHL, non-Hodgkin lymphoma; DLBCL, diffuse large B cell lymphoma; OC, Organochlorine; OP; Organophosphorus.

The meta RR estimates (95% CI) of association between phenoxy herbicide exposure and NHL subtypes were more positive than those for NHL overall, although the estimate of association with NHL overall was more precise (meta RR, 95% CI: 1.4, 1.2–1.6, CLR: 1.4). Only two papers contributed to each of the estimates of association between phenoxy herbicide exposures and NHL subtypes, and 12 papers contributed to the meta RR estimates for the relationship between phenoxy herbicide exposure and NHL overall.

There was a positive and relatively precise association between NHL and the phenoxy herbicide 2-methyl-4-chlorophenoxyacetic acid (MCPA) (meta RR, 95% CI: 1.5, 0.9–2.5, CLR: 2.6). Five estimates contributed to this summary estimate; an I^2 value of 54.4% indicates some inconsistency in the effect estimates. The forest plot for the meta-analysis of MCPA, along with plots for meta-analyses of phenoxy herbicides as a group, the phenoxy herbicide 2,4-D, glyphosate, organochlorine insecticides as a group, and the organochlorine insecticide DDT, are presented in Supplementary Figure S1.

In addition to assessing the association of ever exposure to MCPA with NHL, Hardell *et al.* [33] investigated dose-response relationships between number of days of exposure; they observed increasing odds in association with increased number of days of MCPA exposure (Table 2). In similar analyses, Eriksson *et al.* [32] and Mcduffie *et al.* [43] did not observe dose-response relationship between days/year of MCPA exposure and NHL.

There was a positive but less precise estimate of association between arsenic and NHL (meta RR, 95% CI: 1.7, 0.8–3.6, CLR: 4.4). Meta estimates of association between NHL and carbamate insecticides and carbaryl, a carbamate insecticide, were nearly identical (meta RR, 95% CI: 1.7, 1.3–2.3,

CLR: 1.8) and both were positive and precise. Estimates from three papers contributed to the meta analysis of carbamate insecticides. The I^2 value was 0%, indicating consistency in effect estimates. Carbofuran, another carabamate insecticide, was positively associated with NHL (meta RR, 95% CI: 1.6, 1.2–2.3, CLR: 2.0). However, in two investigations from the Agricultural Health Study that reported estimates of association with tertiles of lifetime days of exposure to carbofuran [25] and carbaryl [42], the relationships were imprecise and there was a lack of a dose-response relationship (Table 2).

There were positive and precise estimates of association between NHL and organophosphorus insecticides (meta RR, 95% CI: 1.6, 1.4–1.9, CLR: 1.4), and the organophosphorus insecticides diazinon (meta RR, 95% CI: 1.6, 1.2–2.2, CLR: 1.8), and malathion (meta RR, 95% CI: 1.8, 1.4–2.2, CLR: 1.5). Although Fritschi *et al.* [62] studied the relationship between organophosphorus insecticides and NHL, we did not include the estimate from their paper in the meta analysis because they investigated the association with exposure in three categories (no exposure, non-substantial exposure, substantial exposure). Fritschi *et al.* [62] reported a positive but imprecise estimate for substantial exposure *versus* no exposure (odds ratio, 95% CI: 2.1, 0.8–5.7, CLR: 7.3). The meta RR estimate of association between NHL and the organophosphorus insecticide chlorpyrifos was positive but imprecise (meta RR, 95% CI: 1.6, 0.6–4.9, CLR: 8.9). There was a positive and precise association with lindane, an organochlorine insecticide (meta RR, 95% CI: 1.6, 1.2–2.2, CLR: 1.8); estimates of association with other organochlorine insecticides were closer to the null.

3.5. Sensitivity Analyses

We conducted sensitivity analyses to examine the effect of gender (Supplementary Table S1), study design (Supplementary Table S2), diagnosis period (Supplementary Table S3), geographic region (Supplementary Table S4), source for controls in case-control studies (Supplementary Table S5) and/or the effect of using alternative papers that represent the same study population (Supplementary Table S6). For the most part, meta-estimates were robust.

3.5.1. Gender

When we subset the analyses of associations between NHL and amide herbicides to the two studies that included men only, the association became more positive but less precise (meta RR, 95% CI: moved from 1.3, 0.8–1.9, CLR: 2.3 to 1.7, 0.7–3.8, CLR: 5.3). Restricting to all male studies moved the summary estimate of the relationship with aldrin up and across the null; however, the estimate in the sensitivity analysis was too unstable to interpret (meta RR, 95% CI: moved from 1.0, 0.4–2.7, CLR: 7.8 to 1.4, 0.2–11.1, CLR: 65.0). Restricting the analysis to studies that included men and women caused the meta RR estimate of association between NHL and 2,4-D to become more positive but less precise; it moved from 1.4, 1.0–1.9, CLR: 1.9 to 1.8, 0.5–7.5, CLR: 16.7. We were not able to conduct sensitivity analyses for female only studies, since only one paper reported results for women only [18].

3.5.2. Study Design

Nearly all of the studies that contribute to the meta estimates were case control in design. The only cohort study was the Agricultural Health Study. In nearly all of the analyses of data from the

Agricultural Health Study, exposure was defined using multiple categories. However, in the papers on glyphosate [31], chlorpyrifos [38], organochlorine insecticides, aldrin, chlordane, dieldrin, lindane, and toxaphene [51], the association with ever/never use of exposure was analyzed. For the most part, restricting analyses to case control studies did not cause the meta estimate to change substantially (Supplementary Table S2). However, the magnitude of the meta RR for aldrin moved up and away from the null, but became more imprecise (it moved from 1.0, 0.4–2.7, CLR: 6.8 to 1.4, 0.2–11.1, CLR: 55.5). For lindane it changed from 1.6, 1.2–2.2, CLR: 1.8 to 1.9, 1.2–2.9, CLR: 2.4.

3.5.3. Diagnosis Period

We also investigated the sensitivity of the meta-analytic estimates to decade of cancer diagnosis (Supplementary Table S3). For the most part, estimates were robust. However, when we subset the meta-analysis of glyphosate to the two papers in which cases were diagnosed from 1975–1989, the meta RR, 95% CI changed from 1.5, 1.1–2.0, CLR: 1.8 to 2.3, 1.4–4.0, CLR: 3.0. Similarly, for the phenoxy herbicide 2,4-D, when we included estimates from the three papers with diagnosis periods from 1975 to 1989, the summary estimate was more positive but less precise (meta RR, 95% CI: 1.8, 1.0–3.1, CLR: 3.2) compared to the full meta-analysis estimate (1.4, 95% CI: 1.0–1.9; CLR: 1.9).

3.5.4. Geographic Area

We investigated the impact of geographic area on the meta-analytic RR estimates (Supplementary Table S4). For glyphosate exposure, including estimates from papers that reported results from Swedish studies caused the estimate to become more positive; it moved from 1.5, 95% CI: 1.1–2.0, CLR: 1.8 to 2.2, 95% CI: 1.3–3.8, CLR: 2.9. Similarly, restricting estimates of the relationship between NHL and phenoxy herbicide exposure to Sweden caused the estimate to become more positive; it changed from 1.4, 95% CI: 1.2–1.6, CLR: 1.4 to 1.9, 1.4–2.4, CLR: 1.7. When we restricted estimates of association with MCPA to those that came from North American studies, the meta RR moved towards the null, from 1.5, 0.9–2.5, CLR: 2.6 to 1.1, 0.7–1.8, CLR: 2.7. In contrast, restricting to European and Swedish studies caused the estimate of association with MCPA to become more positive (meta RR, 95% CI: 1.9, 0.9–3.8, CLR: 4.1 and 2.7, 1.6–4.4, CLR: 2.7 respectively). When we included estimates of association with aldrin that came from studies conducted in the USA, the estimate became more precise but moved down and away from the null (meta RR, 95% CI: 1.0, 95% CI: 0.4–2.7, CLR: 7.8 changed to 0.5, 95% CI: 0.4–0.8, CLR: 2.3).

3.5.5. Source of Controls in Case Control Studies

Only two papers reported results from case control studies in which controls were selected from the hospital [46,48]. The meta-analytic RR estimates remained robust when we restricted the estimates to those resulting from population-based case-control studies (Supplementary Table S5).

3.5.6. Alternative Papers

In several cases, analyses of the same study populations were represented in multiple papers. For the meta-analyses, we included the result(s) that represented the largest number of participants.

In some cases, we selected the result from a pooled analysis instead of the individual, original studies. In other cases, use of effect estimates from the individual studies was preferable because it represented more people. We performed sensitivity analyses to evaluate the impact of replacing results from pooled analyses of multiple studies [23,30,59,60] with the original ones [27,34,58], or the original ones with the pooled analyses (Supplementary Table S6).

When we replaced the estimate of a relationship between carbofuran exposure and NHL reported in Zheng *et al.* [60] by that reported in Cantor *et al.* [27] the relationship became weaker and less precise; the meta RR and 95% CI changed from 1.6, 1.2–2.3, CLR: 2.0 to 1.1, 0.7–1.8, CLR: 2.4. Using the estimate reported in De Roos *et al.* [30] yielded a similar result (meta RR, 95% CI changed to 1.1, 0.6–2.0, CLR: 3.1). For the relationship between aldrin and NHL, we replaced the estimate reported in De Roos *et al.* [30] by that reported by Cantor *et al.* [27]; the estimate moved from a null relationship to a positive one (meta RR, 95% CI changed from 1.0, 0.4–2.7 to 1.3, 0.5–2.9).

4. Discussion

This systematic review and series of meta-analyses show that there is consistent evidence of positive associations between NHL and carbamate insecticides, organophosphorus insecticides, lindane, an organochlorine insecticide, and MCPA, a phenoxy herbicide. Our results represent an important contribution to a growing body of literature on agricultural exposures associated with cancer. Past review papers and meta-analyses have identified positive associations between NHL and farming related exposures, including fertilizers, chemicals, and animals [5], and occupational exposures to pesticides [6].

We extracted estimates of association of NHL with individual pesticide chemical groups or active ingredients from 44 papers that reported analyses of results from 17 independent studies. The studies represented data collected in 12 countries, the majority of which were located in either Europe or North America. Several of the papers that we identified were related to one another; many used data from the same cohort study, the Agricultural Health Study, and several others pooled the same data from individual studies. Thus, although this review identified 44 papers, it also highlights the need for additional epidemiologic studies in a larger variety of geographic locations.

In the papers from which we extracted information, estimates of associations with NHL were reported with 13 herbicide chemical groups and 28 herbicide active ingredients, five fungicide groups and 12 fungicide active ingredients, and three insecticide groups and 40 insecticide active ingredients. More than 1,700 active ingredients are listed in Alan Wood's compendium of pesticide common names, although not all of these are necessarily used in agriculture or currently registered for use in any or all countries [13]. Many chemicals remain for consideration in future epidemiologic analyses of associations between NHL and pesticides. It would be useful to identify pesticides to investigate by ranking, by country, the most commonly used chemicals.

The positive and precise estimate of associations of NHL with carbamate insecticides, organophosphorus insecticides, and lindane were robust to sensitivity analyses of gender, geographic area, and cancer diagnosis period. The positive association between MCPA and NHL was robust to a sensitivity analysis of diagnosis period, but when we restricted the meta-analysis to estimates from studies conducted in North America, the estimate moved to the null.

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Consistent with the results from the meta-analysis of lindane exposure, analyses of data from the American cohort, the Agricultural Health Study, revealed a positive dose-response relationship between NHL and intensity weighted lifetime days of lindane exposure, where the referent group consisted of applicators never exposed to pesticide products containing the active ingredient [51]. In this same paper, however, the estimate of association with dichotomously coded exposure to lindane was close to the null and imprecise. This difference in results within the Agricultural Health Study suggests that dichotomous classification of exposure might be too crude; the binary categories could lead to exposure misclassification and attenuated effect estimates. Because of variability in definitions and cut-points across papers, we were unable to conduct formal meta-analyses of exposures classified using multiple categories. When they were available, we reviewed estimates of dose-response relationships from the individual papers. We found that, in most of the papers in which dose-response relationships were investigated, effect estimates were imprecise due to small numbers of exposed cases within categories.

There were positive meta RR estimates of association of NHL with two carbamate insecticides, carbaryl and carbofuran, and the organophosphorus insecticide active ingredients diazinon and malathion. However, results from analyses of Agricultural Health Study data, which were not included in the meta-analyses, did not show dose response relationships between NHL and lifetime days of exposure to carbofuran [25], carbaryl [42], diazinon [29] or malathion [21,26].

Some discrepancies in findings from the Agricultural Health Study compared to the other studies could be due to differences in design (cohort *versus* case-control). Differences could also be the result of different referent category compositions. All participants of the Agricultural Health Study were pesticide applicators; therefore, the referent group generally consisted of applicators who were not exposed to the pesticide active ingredient of interest. In contrast, in the papers contributing to the meta-RR estimate for carbaryl [30,43] and carbofuran [43,60], the referent groups consisted of farmers and non-farmers [30,43], or only of non-farmers [60]. In the papers contributing to the meta-analyses of malathion and diazinon, the referent categories consisted of non-farmers [56], farmers and non-farmers [43,47], and only farm-workers [45]. It is possible that, in studies that included non-farmers in the referent group, confounding by other agricultural exposures, not adjusted for in analysis, caused estimates of association to be higher than results from Agricultural Health Study analyses.

Only a handful of papers reported associations of pesticides with NHL subtypes; this is probably due to small sample sizes. Our meta-analyses of these relationships suggested the need for further studies of this kind, especially since some of the strongest relationships were seen with the most common subtype of NHL, B cell lymphoma and, more specifically, with DLBCL. NHL are a heterogeneous group of malignancies that include multiple subtypes with varied characteristics and possibly diverse etiologies [4]. Consequently, the overall group of neoplasms represented by NHL might be too diverse as a study endpoint to adequately detect associations with pesticide exposures in epidemiologic analyses. Some but not all specific subtypes of lymphoma might be associated with pesticides, and these relationships would only be revealed by analyses of the subtypes. Pooling projects that include cases of the NHL subtypes that have been classified according to the more recent and etiologically specific definitions (B-cell, T-cell, and within these, more refined subtypes of T- and B-cell neoplasms) [65] present the opportunity to perform more sensitive

epidemiologic analyses and identify important relationships that may have been undetected if the cancer outcome was defined broadly as NHL overall. Such projects are particularly attractive for studying rarer subtypes (*i.e.*, T-cell). To this end, a pooling project within the AGRICOH consortium [64] is currently underway to investigate these associations.

There are various sources of heterogeneity across the studies that contributed to these meta-analyses; these include gender, region, cancer diagnosis period, exposure assessment methods, exposure definitions, referent groups, study populations, and/or analysis adjustment sets. Different activity patterns, which might cause differences in exposure, combined with different biological mechanisms, could result in between-gender differences in chemical exposure and disease risk associations. Pesticide use, application, and handling patterns, regulations and legislation, demographics and genetics differ by region, which could contribute to area-specific differences in associations. In the papers that contributed to the meta analyses, a variety of exposure assessment methods were used; these included self-reported chemical exposures, exposure matrices, and approximations based on number of animals raised. Differences in exposure assessment methods could influence the magnitude of effects observed, especially since some methods might be superior to others in terms of reducing the potential for exposure misclassification. Study design (case-control *versus* cohort) and source of controls in case-control studies (hospital *versus* population) could also influence the magnitude of the exposure estimates observed. In case-control studies, exposure is assessed retrospectively, which could lead to recall bias. In contrast, in the Agricultural Health Study, the only cohort included in this review, exposure was assessed when participants were cancer-free. Finally, NHL classification systems have changed over time, reflecting changes in disease definitions [1]. Recently (after year 2000), the definition of NHL has become more comprehensive. The definition now includes disease entities that were excluded from earlier definitions, such as plasma cell neoplasms (*i.e.*, multiple myeloma) and chronic lymphocytic leukemia. These malignancies are also among the most frequently reported sub-types within NHL [65]. Thus, estimates of association between pesticides and overall NHL from studies conducted in earlier periods may not be entirely comparable to estimates from research conducted since the year 2000 that used the updated NHL definition.

We did not conduct a formal test of publication bias; it is unclear if asymmetry tests with funnel plots are useful in meta-analyses of observational studies, and it has been recommended that these tests not be used when fewer than 10 studies contribute to a meta-analysis [66]. For the most part, we believe that our review was systematic and comprehensive.

Nevertheless, we did not identify papers that published results of studies conducted in middle- and low-income countries. It is possible that, in such regions where cancer-follow and exposure ascertainment may be particularly challenging, no studies have investigated the relationship of NHL with pesticide exposures. Restricting our literature search to articles published in English could be another reason that we did not identify studies in lower-income countries. A lack of studies in these areas is potentially alarming, since these regions are responsible for much of the world's agricultural production [67]. Also, lympho-hematopoetic malignancies represent a substantial proportion of cancers in low- and middle-income countries. For example, based on estimates from the World Health Organization's GLOBOCAN 2012, NHL accounted for 37.7% of the estimated prevalent cancer cases diagnosed in the past 5 years, among adults in less-developed regions (Africa, Asia excluding Japan, Latin America and the Caribbean, Melanesia, Micronesia, and Polynesia) [68]. Nevertheless, research results

from higher-income countries could be transferable and have important implications for pesticide regulation and legislation world-wide, especially in low-income countries where protective equipment may be less available and/or used.

There are several mechanisms by which pesticide exposure might be associated with NHL. First, pesticides might cause chromosomal aberrations and genetic mutations. An often studied chromosomal abnormality is the t(14;18) translocation, which is particularly common among cases of follicular lymphoma and diffuse large B-cell lymphoma [69]. In a paper that used data from the Iowa/Minnesota case-control study that contributed to several of the pooled and individual analyses that we reviewed [23,30,59], Schroeder *et al.* [70] investigated the relationship between pesticide exposures and the t(14;18) translocation. Compared with controls, t(14;18) positive NHL cases but not t(14;18) negative cases had a higher odds of exposure to dieldrin, toxaphene, lindane, and atrazine. Chiu *et al.* [69,71] performed a similar analysis using data from the Nebraska-based case-control study and reported positive associations between t(14;18) positive NHL and dieldrin, toxapehen, and lindane. A second mechanism by which pesticide exposure may cause NHL is by altering cell mediated immune function. Indeed, immunological changes have been observed following short-term exposure to phenoxy herbicides (2,4-D and MCPA) among farmers [72].

The IARC Monographs have evaluated the carcinogenicity of a handful of pesticides. Of these, only arsenic and inorganic arsenic compounds have been given a Group 1 rating (carcinogenic to humans) [73]. The fumigant insecticide ethylene dibromide was classified as a group 2A carcinogen based on inadequate evidence for carcinogenicity in humans but sufficient evidence in experimental animals; the overall evaluation was upgraded to 2A (probably carcinogenic to humans) with supporting evidence from other relevant data [74]. In Volume 53 (1991) [75], the fungicide captafol was also classified as a group 2A carcinogen based on sufficient evidence in experimental animals but no available data from human studies. In this same volume, several other pesticides were classified as either group 2B (possibly carcinogenic to humans) or group 3 carcinogens (not classifiable as to its carcinogenicity)—aldicarb chlordane/heptachlor, DDT, deltamethrin, dichlorvos, fenvalerate, permethrin, thiram, ziram, atrazine, monuron, picloram, simazine, and trifluralin. The IARC monographs have classified other pesticides, including heptachlor, chlordane, and toxaphene [76], as group 2B carcinogens; in each of these cases, the 2B classification was based on inadequate evidence in humans but sufficient evidence in experimental animals. Chlorophenoxy herbicides were classified as group 2B carcinogens based on limited evidence for carcinogenicity in humans, and inadequate evidence for carcinogenicity of 2,4-D and 2,4,5-T in animals [77].Similarly, hexachlorocyclohexanes were evaluated as group 2B carcinogens due to inadequate evidence for carcinogenicity to humans, sufficient evidence for carcinogenicity to animals for the technical-grade and the alpha isomers but limited for the beta and gamma (lindane) isomers [77]. Several other pesticides, including malathion and maneb [77] have been classified as group 3 carcinogens. These evaluations took place several decades ago and there is now more epidemiologic literature that can provide information. There also remains a need for further epidemiologic research of certain chemicals, which could help to inform future evaluations. In the current systematic review, we did not observe entirely consistent trends in association for all of the active ingredients within chemical groups. Furthermore, classification of active ingredients into groups is subjective and there is not a consistent and established scheme for doing so. Therefore, evaluations of individual active ingredients rather than chemical groups might be more useful.

Limitations and Strengths

Because of variability in definitions and metrics that were used in published papers, we were not able to consider additional exposure definitions, such as exposure lags, duration of exposure (e.g., number of days/year exposed), or routes of exposure (e.g., application *versus* mixing of pesticides). In an effort to use similar exposure definitions from the various papers, we only included dichotomous definitions in the meta-analyses. Since dose-response relationships could not be summarized, this restricted the strength of our conclusions from an etiologic perspective. Furthermore, we were not able to conduct analyses of certain active ingredients or chemical groups due to a lack of published literature. In other cases, very few papers contributed to the meta-analyses. The largest number of papers contributing to any meta-analysis was 12 for phenoxy herbicides, followed by eight for DDT. Most meta-analyses included estimates from only two to three studies. In most papers, associations with NHL overall, rather than with subtypes of NHL, were investigated. Thus, most of our meta-analyses were of associations with NHL rather than with its subtypes, which are probably more homogeneous disease entities for assessing the relationship with pesticides. It is possible that this led to a dilution of effects, since the various NHL subtypes have diverse etiologies and some might be more strongly associated with certain pesticides than others.

Nevertheless, this systematic review represents a novel contribution to the literature on NHL and pesticide exposure. We identified trends in the relationship of NHL and NHL subtypes with chemical groups and active ingredient groups. To our knowledge, this is the most comprehensive systematic review and meta-analysis to investigate associations with specific agricultural pesticide active ingredients. We observed fairly consistent results for certain pesticide groups and active ingredients. We evaluated the robustness of our meta-analyses by examining the sensitivity of the estimates to gender, study design, region, diagnosis period, control source in case-control studies, and paper that provided the effect estimate.

5. Conclusions

We systematically reviewed more than 25 years' worth of epidemiologic literature on the relationship between pesticide chemical groups and active ingredients with NHL. This review indicated positive associations between NHL and carbamate insecticides, OP insecticides, the phenoxy herbicide MCPA, and lindane. Few papers reported associations with subtypes of NHL; however, based on the few that did, there were strong associations between certain chemicals and B cell lymphomas. Our results show that there is consistent evidence that pesticide exposures experienced in occupational agricultural settings may be important determinants of NHL. This review also revealed clear research needs, including further investigation of some already studied pesticide active ingredients, of additional pesticides that have not yet been investigated in epidemiologic analyses, of the strength of association of pesticide exposures with subtypes of NHL, and of the relationship between NHL and pesticides in middle- and low- income areas.

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Acknowledgments

Author Contributions

Leah Schinasi conducted the literature search, screened the papers from the search, abstracted data from the papers, conducted the meta-analyses, and led the writing of the manuscript. Maria E. Leon co-defined the scope of the review, the search strategy for the literature search and contributed to the writing of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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