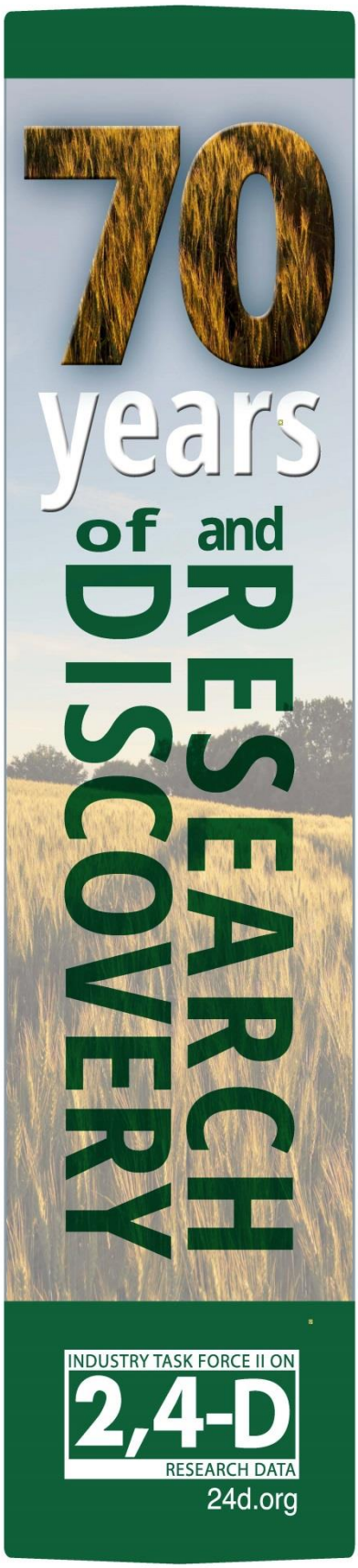

2,4-Dichlorophenoxyacetic Acid and Non-Hodgkin's Lymphoma: Results from the Agricultural Health Study and an Updated Meta-analysis

With the continuing approval of regulatory agencies worldwide and a wealth of experimental evidence showing it does not cause cancer, the herbicide 2,4-D is one of the most well studied chemicals in the world. This study adds to that body of evidence, concluding that there is no scientific evidence of a link between 2,4-D and Non-Hodgkin's Lymphoma (NHL).

The authors conducted a meta-analysis of the literature on 2,4-D and NHL. Scientific meta-analyses involve examining and weighing the results of multiple studies together, because collectively those studies can tell us things they cannot tell us individually. This is the first meta-analysis conducted on 2,4-D and NHL to include data from the Agricultural Health Study (AHS). The AHS is an ongoing research project that has been studying the effects of pesticide exposure on the health of agricultural workers in Iowa and North Carolina. The AHS has several strengths; notably its large cohort of over 55,000 participants and the wide variety of ways in which it examines exposure.

This study first examines data from the AHS to see if there is an association between 2,4-D and NHL. The authors adjusted for external factors like tobacco smoking, alcohol consumption, and family history of cancer; they also adjusted for other pesticides to which the participants may have been exposed. The results of their analysis of the AHS data showed that a person exposed to 2,4-D is not at any greater risk of developing NHL than a person not exposed to 2,4-D. The authors then compared this result with the results of 9 other studies on 2,4-D and NHL that they assessed in their previous meta-analysis. They verified the results of those studies by performing their own statistical analysis of the data. They assessed the quality of each study and weighted them to account for their strengths or shortcomings. The results of this analysis also demonstrated that exposure to 2,4-D does not increase the risk of developing NHL.

These results contribute to the ever growing weight of evidence showing 2,4-D does not cause cancer.

Reference: http://www.annalsofepidemiology.org/article/S1047-2797(16)30490-2/abstract

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2,4-Dichlorophenoxyacetic Acid and Non-Hodgkin's Lymphoma: Results from the Agricultural Health Study and an Updated Meta-analysis

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Keywords:
2,4-dichlorophenoxyacetic acid, non-Hodgkin's lymphoma, cancer, Agricultural Health Study, meta-analysis, epidemiology

List of Abbreviations

2,4-D – 2,4-Dichlorophenoxyacetic Acid; AHS – Agricultural Health Study; CI – Confidence Interval; IRB – Institutional Review Board; NHL – Non-Hodgkin's Lymphoma; RR – Relative Risk

Introduction

Despite evidence from experimental studies indicating that the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) is not carcinogenic (*e.g.*, see EFSA [1]), several epidemiology studies have evaluated 2,4-D and non-Hodgkin's lymphoma (NHL). Meta-analyses of this literature, including one we conducted, have arrived at mixed conclusions [2, 3, 4]. Notably, none of these studies incorporated results from the Agricultural Health Study (AHS), which is a large-scale prospective cohort study of pesticide applicators in North Carolina and Iowa designed to investigate associations between agricultural exposures and various health outcomes, with a focus on cancer [5]. Because of its prospective study design and large study population, results from the AHS could have contributed considerable weight to the synthesis of epidemiology evidence on 2,4-D and NHL. However, to date, no analyses of 2,4-D exposure and NHL in the AHS cohort have been published. Thus, we evaluated associations between NHL and 2,4-D among AHS pesticide applicators and updated our previous meta-analysis [2] to include AHS results.

Materials and Methods

The AHS datasets and our statistical analyses are described in the Supplemental Material. Briefly, we estimated the relative risks (RRs) of NHL associated with dichotomous 2,4-D exposures, as well as three categories of exposure duration, using Poisson regression with adjustment for a variety of potential confounders, including other pesticide exposures. For dose-response analyses, we tested for linear trends across the three categories of 2,4-D exposure duration. Our analyses of the AHS datasets were approved by the Chesapeake Institutional Review Board (IRB; protocol # 00015772; December 22, 2015).

Our literature search strategy and meta-analysis are described in detail elsewhere [2]. For the updated meta-analysis, we repeated the literature search on December 28, 2015, for new publications satisfying our inclusion criteria but did not identify any.

We pooled studies identified in our previous meta-analysis and the results from the AHS cohort to obtain summary RRs and 95% confidence intervals (CIs) for NHL associated with ever being exposed to 2,4-D, using random effects models. We calculated the I-squared statistic (I^2) and obtained a p-value from the chi-square test to assess between-study heterogeneity. We also constructed a funnel plot of the log RR *vs.* its standard error and conducted an Egger's test to evaluate potential publication bias. All analyses were conducted using Stata, version 13.1 (StataCorp LP, College Station, Texas).

Results

In the AHS cohort, we found no increased risk of NHL associated with reported ever use of 2,4-D (RR = 1.02, 95% CI: 0.54-1.90) when adjusting for age, smoking, drinking, family history of cancer, education, and exposure to 10 other pesticides. Risk of NHL was also not elevated in any category of exposure duration (measured as intensity-weighted lifetime days of 2,4-D exposure) and there was no trend across exposure categories (p = 0.77). Detailed results from the AHS cohort are presented in the Supplemental Material.

We updated our original meta-analysis with the results from the AHS cohort, using the risk estimate above with adjustment for pesticide co-exposures. We estimated a meta-RR of 0.97 (95% CI: 0.79-1.18), indicating that 2,4-D exposure is not associated with an increased risk of NHL (Figure 1). There was no significant heterogeneity across underlying studies (I^2 = 20.4%, p = 0.255). However, there appeared to be a publication bias, with smaller studies reporting positive associations (p = 0.011 for Egger's test).

Discussion

Our analysis indicates that there is no increased risk of NHL from 2,4-D exposure in the AHS cohort. Our updated meta-analysis, with inclusion of the results from the AHS cohort, also had null findings, confirming our previous conclusion that 2,4-D is not associated with NHL.

The omission of the AHS results from previous meta-analyses of 2,4-D and NHL is an important limitation, because, although the AHS has some shortcomings (*e.g.*, low and variable response rates and limited understanding of the reliability and validity of self-reported exposures; [15]), it has several methodological advantages over other studies. It is a large cohort, with over 55,000 applicators enrolled who had relatively high exposures to 2,4-D and other pesticides. Follow-up for cancer began at the time of enrollment (1993-1997) and continues today. Exposure was assessed prospectively, so case status could not have influenced the subjects' estimated exposure to 2,4-D. Various exposure metrics related to the duration and intensity of pesticide use were evaluated, including dichotomous (ever *vs*. never used), lifetime exposure-days, and intensity-weighted lifetime exposure-days. The AHS exposure surveys assessed 50 different pesticides, allowing adjustment for other pesticides when evaluating the associations between 2,4-D and cancer. This is notable because prior meta-results were sensitive to whether risk estimates from individual studies were adjusted for other pesticides.

Strengths of our meta-analysis are that it includes a thorough evaluation of study quality and has several subgroup and sensitivity analyses. We also preferentially selected risk estimates adjusted for other pesticides, whenever possible. In addition, while most available epidemiology studies of 2,4-D and cancer are relatively low in quality and were likely affected by uncertainty and multiple biases, the risk estimates we calculated using the secondary AHS dataset may be less biased because of its prospective cohort study design.

Follow-up of subjects in the AHS dataset available to us continued through the end of 2001, at which point 2,088 cancers had been diagnosed. An analysis of an updated AHS dataset would include more NHL cases, but at the time of this report, no analyses of 2,4-D and cancer have been published, aside from a conference abstract [16]. Based on this abstract, however, there is no reason to conclude that using the updated dataset would materially change results.

Conclusion

Our analysis contributes to a growing body of epidemiology, toxicology, and mechanistic evidence indicating that 2,4-D does not cause cancer in humans.

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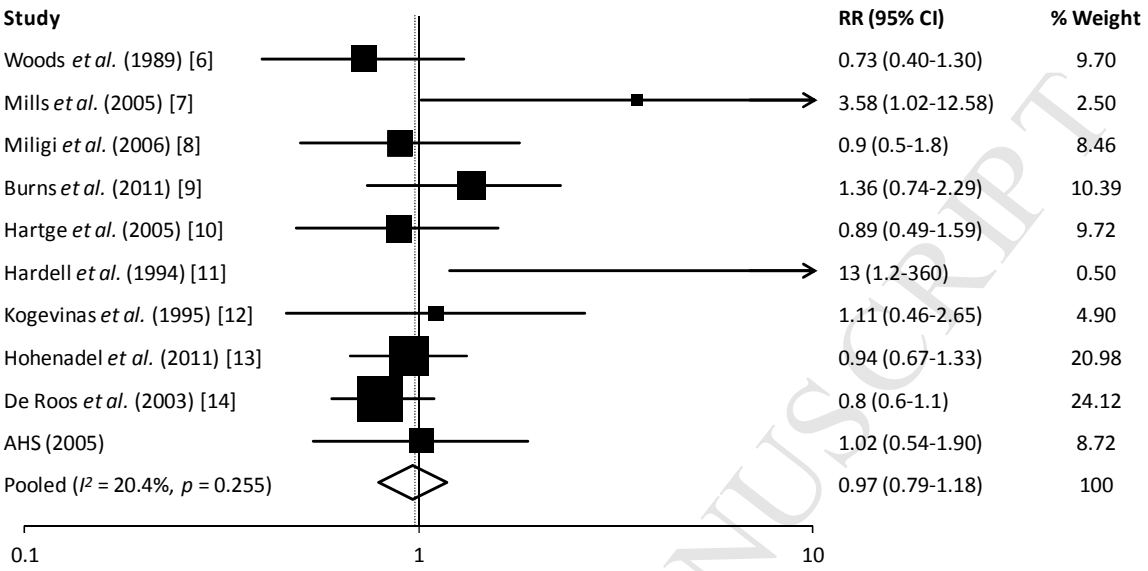
Figure Legend

Figure 1: Study-specific and summary relative risks (RRs) and 95% confidence intervals (CIs) for 2,4-dichlorophenoxyacetic acid (2,4-D) and non-Hodgkin's lymphoma (NHL). Studies were pooled using a random effects model. Squares represent study-specific risk estimates and the size of each square is proportional to the study-specific statistical weight. The horizontal lines show 95% CIs for study-specific estimates. The diamond represents the summary risk estimate and its corresponding 95% CI. AHS (2005) refers to our analysis of 2,4-D and NHL in the AHS cohort based on the analytical dataset of De Roos *et al*. [17].

Figure



2,4-Dichlorophenoxyacetic Acid and Non-Hodgkin's Lymphoma: Results from the Agricultural Health Study and an Updated Meta-analysis

Julie E. Goodman, Ph.D., DABT; Christine T. Loftus, Ph.D., M.S., MPH; Ke Zu, Ph.D., Sc.D., M.P.H.

Supplemental Material

We evaluated the association between 2,4-dichlorophenoxyacetic acid (2,4-D) exposure and non-Hodgkin's lymphoma (NHL) in the Agricultural Health Study (AHS) cohort. We then updated our previous meta-analysis (Goodman *et al*., 2015) with the inclusion of the AHS results. The main paper briefly describes our methods and summarizes our results. Below, we describe the AHS datasets and present our analyses and results in more detail.

Statistical Analyses of the AHS Data

Secondary AHS data files were obtained by CropLife America by a Freedom of Information Act (FOIA) request, which was focused on several AHS publications (Alavanja *et al*., 2003, 2004; Rusiecki *et al*., 2004; De Roos *et al*., 2005). In response to the FOIA request, AHS researchers constructed one dataset specific to each publication, with individual-level data on participants and sufficient covariates necessary to replicate the results presented in each paper. To protect the confidentiality of research subjects, no identifying information from the master AHS dataset (*i.e.*, name, address, date of birth, social security number, race, applicator type, and state of residence) was included in secondary data files provided to CropLife America.

AHS research participants gave informed consent upon enrollment in the AHS, and all AHS research activities were approved and monitored by the Institutional Review Board (IRB) of the National Institutes of Health. Our analysis of secondary AHS data files was approved by a private IRB prior to receipt of the data from CropLife America (Chesapeake IRB protocol # 00015772; December 22, 2015).

We calculated associations between 2,4-D exposure and NHL incidence using the secondary data file specific to De Roos *et al*. (2005), a study of associations between glyphosate exposure and various cancer endpoints (including NHL) among AHS applicators. Subjects in this dataset enrolled between 1993 and 1997, and case ascertainment occurred between enrollment and December 31, 2001. The median follow-up time was 6.7 years. Information on 2,4-D exposure was included in this dataset because De Roos *et al*. (2005) evaluated it as a potential confounder in analyses of glyphosate and cancer. An analysis of missing data in this dataset and potential implications for associations between glyphosate and multiple myeloma has been published (Sorahan, 2015).

In our analyses, we adhered as closely as possible to the approach of De Roos *et al*. (2005); our approach differed slightly because some covariates used for adjustment by the AHS investigators were not included in the secondary dataset available to us, including state of residence and type of applicator. In the same manner as De Roos *et al*. (2005), we excluded participants with missing data on person-years of follow-up or age, as well as participants with a prevalent cancer at the time of enrollment in the AHS.

We first calculated the relative risks (RRs) of NHL associated with dichotomized glyphosate exposure using Poisson regression so that we could compare our methods and results to those reported by De Roos

et al. (2005). Using the same method described by De Roos *et al*. (2005), we calculated associations between NHL and glyphosate adjusted only for age, and then adjusted for age (by category), education (dichotomized as greater than a high school diploma or General Educational Development certificate *vs*. high school education or less), alcohol consumption in the last year, reported smoking in the past year, and family history of any cancer in a first-degree relative. (De Roos *et al*. [2005] also adjusted for state of residence, but we did not have access to information on this variable.) After confirming our methodology, we estimated associations between 2,4-D exposure and NHL using the same methods.

We calculated RRs of NHL associated with dichotomous 2,4-D exposure (ever *vs*. never sprayed or applied 2,4-D), as well as across three categories of exposure (never-users, intensity-weighted lifetime days at or below the median, and intensity-weighted lifetime days above the median). For the dose-response analysis, we calculated a p-value for a linear test of trend across these three categories.

In sensitivity analyses, we used the Poisson regression model with several variations on the covariates included for adjustment. This included years of education as a continuous variable instead of dichotomized, adding current smoking status in addition to past smoking frequency, and removing covariates one at a time (family history of cancer, alcohol consumption, smoking status). We also added variables pertaining to other pesticide exposures: first, one at a time, and then all 10 other pesticides at once.

All analyses were conducted using Stata, version 13.1 (StataCorp LP, College Station, TX).

Characteristics of the AHS Cohort

We included 55,941 pesticide applicators in our final analysis, with 93 cases of NHL identified during follow-up. We excluded subjects with prevalent cancer upon enrollment in the AHS (n = 1,074) and subjects with missing age (n = 7) or person-years of follow-up (n = 298). Supplemental Table 1 summarizes the characteristics of the cohort and the numbers of subjects who reported ever personally mixing or applying 2,4-D or several other pesticides. Overall, the characteristics and reported pesticide exposures of subjects diagnosed with NHL were similar to those of the subjects who did not have NHL. Statistically significant differences between the two groups included age (participants with NHL were more likely to be older), drinking (more participants with NHL were non-drinkers), and paraquat exposure (participants with NHL were more likely to have reported paraquat use).

Associations Between NHL and Pesticides in the AHS Cohort

We first repeated the analysis of NHL and dichotomized glyphosate exposure as described by De Roos *et al*. (2005), except that we were unable to control for state of residence. Our results were the same as those of De Roos *et al*. (2005) when adjusted only for age (RR = 1.2, 95% CI: 0.7-1.9) and were nearly identical when fully adjusted (RR = 1.1, 95% CI: 0.7-1.9 *vs*. RR = 1.1, 95% CI: 0.7-1.8, as reported by De Roos *et al*. [2005]).

We found no association between NHL incidence and reported use of 2,4-D, dichotomized as ever *vs*. never sprayed or applied (RR = 1.18, 95% CI: 0.71-1.95), when adjusting for age, smoking, drinking, a family history of cancer, and education (Supplemental Table 2). Additional adjustment for any one other pesticide resulted in attenuation of the RR up to 15% (with the exception of adjustment for maneb, which effectively did not change the result), and simultaneous adjustment for all 10 other pesticides resulted in an RR of 1.02 (95% CI: 0.54-1.90). Other changes in the statistical model did not change the RR by more than 10%.

The results of our dose-response analysis of 2,4-D exposure and NHL incidence in the AHS cohort were also null (Supplemental Table 3). Risk of NHL was not elevated in any category of exposure (measured as intensity-weighted lifetime days of 2,4-D exposure) relative to subjects who reported never being exposed to 2,4-D, and the test of trend was not significant (p = 0.77).

Previous Meta-analyses Updated with the AHS Results

There have been three previous meta-analyses of 2,4-D and NHL, including ours (Goodman *et al*., 2015). Schinasi and Leon (2014) conducted an analysis of agricultural 2,4-D exposure and NHL and reported a slightly increased risk of NHL associated with 2,4-D exposure (meta-relative risk [meta-RR] = 1.34, 95% CI: 1.03-1.91); however, this analysis was restricted to agricultural exposures and was affected by a high degree of unexplained heterogeneity (I^2 = 61.5%). We conducted a systematic review and meta-analysis of 2,4-D exposure and NHL, in addition to two other cancer endpoints (*i.e.*, prostate and gastric cancers) (Goodman *et al*., 2015). In contrast to the analysis of Schinasi and Leon (2014), we found the association between 2,4-D and NHL to be null overall (meta-RR = 0.97, 95% CI: 0.77-1.22; I^2 = 28.8%). In sensitivity analyses, we found the results to be sensitive to whether risk estimates were adjusted for other pesticides, potentially explaining the discrepancy with Schinasi and Leon (2014). More recently, an International Agency for Research on Cancer (IARC) Working Group reviewed 2,4-D as a potential human carcinogen, and, during its review of the epidemiology evidence, conducted a meta-analysis of 2,4-D and NHL (IARC, 2016). The IARC Working Group meta-analysis differed from the other two in the selection of studies for inclusion, but its results were similar to those of Goodman *et al*. (2015). Incorporating the results of nine individual studies in its analysis of NHL, the IARC Working Group calculated a meta-RR of 1.06 (95% CI: 0.80-1.40; I^2 = 36.3%).

The Schinasi and Leon (2014) meta-analysis was similar to ours in some ways, but it was restricted to studies of 2,4-D exposure in agricultural occupational settings, such as the exposures experienced by farm workers and pesticide applicators (n = 5 studies). Also, Schinasi and Leon (2014) did not preferentially select effect estimates adjusted for other pesticides, when available.

The IARC meta-analysis had only minor differences from ours in how effect estimates were selected from individual studies (*e.g.*, selecting the results from logistic rather than hierarchical regression in De Roos *et al*. [2005]) and the exclusion of Hartge *et al*. (2005), which used measurements of 2,4-D in carpet dust for estimating exposure. While the IARC Working Group included studies of NHL subtypes in its primary analysis, here, we focus on its meta-analysis that was restricted to NHL only, so that we could directly compare it to the two other systematic reviews.

We replicated the results of Schinasi and Leon (2014) exactly, and those of the IARC Working Group (IARC, 2016) very closely (*i.e.*, within less than 1%). When we updated the meta-analysis of Schinasi and Leon (2014) to include the risk estimate from the AHS data, we calculated a meta-RR of 1.34 (95% CI: 1.02-1.76) and an I^2 of 54.5%. The Egger's test indicated no evidence of publication bias (p = 0.54). As discussed above, Schinasi and Leon (2014) only included studies of agricultural exposures and did not preferentially select study-specific effect estimates that were adjusted for other pesticides. This is likely why results are statistically significant, even when AHS data are included.

Our update of the IARC Working Group (IARC, 2016) meta-analysis produced a meta-RR of 1.03 (95% CI: 0.81-1.31) and an I^2 of 27.6%. The Egger's test of publication bias indicated weak statistical evidence of bias (p = 0.084).

As discussed in the main paper, when we repeated our meta-analysis with the addition of the AHS 2,4-D and NHL risk estimate calculated using the strongest adjustment for pesticide co-exposures (*i.e.*, the risk

estimate calculated when all 10 other pesticides were included in the model, in addition to other covariates), we estimated a meta-RR of 0.97 (95% CI: 0.79-1.18) and an I^2 of 20.4%. There is evidence of publication bias with smaller studies reporting positive associations (p = 0.011 for the Egger's test).

In all three cases, the results of the updated analyses were slightly attenuated; the differences between the updated results and the original meta-estimates (*i.e.*, prior to the inclusion of the AHS results) were minimal (Supplemental Table 4). These findings strengthen the evidence base that 2,4-D is not causally associated with NHL.

Supplemental Table 1 Characteristics of AHS Study Subjects Stratified by NHL Status

Characteristic	Entire Cohort n = 55,941 n (%)	NHL Diagnosed Following Enrollment n = 93 n (%)	No NHL Diagnosis n = 55,848 n (%)	p-Value
Sex				
Male	54,407 (97.3)	91 (97.8)	54,316 (97.3)	0.97
Female	1,534 (2.7)	2 (2.2)	1,532 (2.7)	
Missing	0 (0)	0 (0)	0 (0)	
Age				
<40 years old	9,009 (16.1)	5 (5.4)	9,004 (16.1)	<0.001
40-49 years old	16,054 (28.7)	12 (12.9)	16,042 (28.8)	
50-59 years old	13,441 (24.0)	17 (18.3)	13,424 (24.0)	
60-69 years old	10,476 (18.7)	34 (36.6)	10,442 (18.7)	
70+ years old	6,954 (12.4)	25 (26.9)	6,929 (12.4)	
Missing	7 (0)	0 (0)	7 (0)	
Smoking				
Non-smoker	28,717 (51.3)	47 (50.5)	28,670 (51.3)	0.32
Pack-years at/below median	12,209 (21.8)	16 (17.2)	12 193 (21.8)	
Pack-years above median	11,907 (21.2)	25 (26.9)	11,882 (21.3)	
Missing	3,108 (5.6)	5 (5.4)	3,103 (5.6)	
Current Smoking Status				
Smoker	9,191 (16.4)	11 (11.8)	9,180 (16.4)	0.29
Non-smoker	44,886 (80.2)	79 (85.0)	44,807 (80.2)	
Missing	1,864 (3.3)	3 (3.2)	1,861 (3.3)	
Drinking				
No drinking	16,957 (30.3)	41 (44.1)	16,916 (30.3)	0.003
Drinks per year at/below median	18,123 (32.4)	28 (30.1)	18,095 (32.4)	
Drinks per year above median	16,936 (30.3)	16 (17.2)	16,920 (30.3)	
Missing	3,925 (7.0)	8 (8.6)	3,917 (7.0)	
Family History of Any Cancer				
Yes	21,099 (37.7)	39 (41.9)	21,060 (37.7)	0.46
No	34,842 (62.3)	54 (58.1)	34,788 (62.3)	
Missing	0 (0)	0 (0)	0 (0)	
Education				
At least high school	22,799 (40.8)	35 (37.6)	22,764 (40.8)	0.5382
Less than high school	30,656 (54.8)	55 (59.1)	30,601 (54.8)	
Missing	2,486 (4.4)	3 (3.2)	2,483 (4.4)	
2,4-D Exposure				
Ever mixed or applied	40,082 (71.7)	71 (76.3)	40,011 (71.6)	0.58
Never mixed or applied	13,985 (25.0)	21 (22.6)	13,964 (25.0)	
Missing	1,874 (3.3)	1 (1.1)	1,873 (3.4)	

Characteristic	Entire Cohort n = 55,941 n (%)	NHL Diagnosed Following Enrollment n = 93 n (%)	No NHL Diagnosis n = 55,848 n (%)	p-Value
Atrazine				
Ever mixed or applied	36,965 (66.1)	69 (74.2)	36,896 (66.1)	0.14
Never mixed or applied	17,303 (30.9)	22 (23.7)	17,281 (30.9)	
Missing	1,673 (3.0)	2 (2.2)	1,671 (3.0)	
Metolachlor				
Ever mixed or applied	23,297 (41.6)	36 (38.7)	23,261 (41.7)	0.77
Never mixed or applied	27,229 (48.7)	46 (49.5)	27,183 (48.7)	
Missing	5,415 (9.7)	11 (11.8)	5,404 (9.7)	
Alachlor				
Ever mixed or applied	26,380 (47.2)	39 (42.0)	26,341 (47.2)	0.41
Never mixed or applied	24,267 (43.4)	44 (47.3)	24,223 (43.4)	
Missing	5,294 (9.5)	10 (10.8)	5,284 (9.5)	
Glyphosate				
Ever mixed or applied	41,039 (73.4)	71 (76.3)	40,968 (73.4)	0.81
Never mixed or applied	13,281 (23.7)	21 (22.6)	13,260 (23.7)	
Missing	1,621 (2.9)	1 (1.1)	1,620 (2.9)	
Triflurin				
Ever mixed or applied	26,316 (47.0)	41 (44.1)	26,275 (47.0)	0.63
Never mixed or applied	24,259 (43.4)	43 (46.2)	24,216 (43.4)	
Missing	5,366 (9.6)	9 (9.7)	5,357 (9.6)	
Carbaryl				
Ever mixed or applied	28,227 (50.5)	53 (57.0)	28,174 (50.4)	0.23
Never mixed or applied	22,814 (40.8)	32 (34.4)	22,782 (40.8)	
Missing	4,900 (8.8)	8 (8.6)	4,892 (8.6)	
Diazinon				
Ever mixed or applied	15,856 (28.3)	29 (31.2)	15,827 (28.3)	0.53
Never mixed or applied	33,837 (60.5)	52 (55.9)	33,785 (60.5)	
Missing	6,248 (11.2)	12 (12.9)	6,236 (11.2)	
Paraquat				
Ever mixed or applied	12,334 (22.0)	28 (30.1)	12,306 (22.0)	0.06
Never mixed or applied	37,331 (66.7)	53 (57.0)	37,278 (66.7)	
Missing	6,276 (11.2)	12 (12.9)	6,264 (11.2)	
Benomyl				
Ever mixed or applied	5,427 (9.7)	9 (9.7)	5,418 (9.7)	1
Never mixed or applied	44,517 (79.6)	70 (75.3)	44,447 (79.6)	
Missing	5,997 (10.7)	14 (15.1)	5,983 (10.7)	
Maneb				
Ever mixed or applied	4,924 (8.8)	10 (10.8)	4,914 (8.8)	0.53
Never mixed or applied	44,772 (80.0)	69 (74.2)	44,703 (80.0)	
Missing	6,245 (11.2)	14 (15.1)	6,231 (11.2)	

Note:
2,4-D = 2,4-Dichlorophenoxyacetic Acid; AHS = Agricultural Health Study; NHL = Non-Hodgkin's Lymphoma.

Supplemental Table 2 Risk of NHL Associated with 2,4-D Exposure (Ever *vs.* Never) Among AHS Pesticide Applicators

Statistical Model	RR	95% CI	p-Value
Primary Model: Adjusted for age, alcohol consumption, smoking, education, and family history of cancer	1.18	0.71, 1.95	0.53
Sensitivity Analyses (Variations on Primary Model):			
Years of education as a continuous variable	1.19	0.72, 1.98	0.49
Additional smoking variables	1.29	0.75, 2.21	0.35
No adjustment for family history	1.18	0.71, 1.94	0.53
No adjustment for smoking	1.17	0.71, 1.94	0.53
No adjustment for alcohol consumption	1.15	0.69, 1.89	0.60
Adjustment for atrazine use	1.03	0.60, 1.74	0.93
Adjustment for metolachlor use	1.03	0.60, 1.77	0.91
Adjustment for alachlor use	1.08	0.64, 1.84	0.77
Adjustment for glyphosate use	1.16	0.69, 1.94	0.58
Adjustment for trifluralin use	1.06	0.62, 1.81	0.84
Adjustment for paraquat use	1.09	0.63, 1.89	0.75
Adjustment for diazinon use	1.08	0.63, 1.84	0.79
Adjustment for carbaryl use	1.08	0.64, 1.82	0.76
Adjustment for benomyl use	1.19	0.98, 2.09	0.53
Adjustment for maneb use	1.11	0.64, 1.92	0.71
Adjustment for use of all 10 pesticides simultaneously	1.02	0.54, 1.90	0.96

Note:
2,4-D = 2,4-Dichlorophenoxyacetic Acid; AHS = Agricultural Health Study; CI = Confidence Interval; NHL = Non-Hodgkin's Lymphoma; RR = Relative Risk.

Supplemental Table 3 Risk of NHL Associated with Categories of 2,4-D Exposure Among AHS Pesticide Applicators

2,4-D Exposure	Number of NHL Cases	RR	95% CI	p-Value
Never used	21	1	--	--
Intensity-weighted lifetime days at or below median	36	1.15	0.66, 2.00	0.61
Intensity-weighted lifetime days above median	31	1.10	0.62, 1.96	0.73
Trend test				0.77

Note:
2,4-D = 2,4-Dichlorophenoxyacetic Acid; AHS = Agricultural Health Study; CI = Confidence Interval; NHL = Non-Hodgkin's Lymphoma; RR = Relative Risk.

Supplemental Table 4 Summary of Meta-analyses of 2,4-D and NHL

Citation and Description of Analysis	Inclusion of AHS Results	# of Studies	Meta-RR	95% CI	I-Squared	p-Value for Heterogeneity	p-Value for Publication Bias
Goodman *et al.* (2015) primary analysis	No	9	0.97	0.77, 1.22	28.80%	0.19	0.018
	Yes	10	0.97	0.79, 1.19	20.40%	0.26	0.011
Schinasi and Leon (2014)	No	5	1.40	1.03, 1.91	61.50%	0.034	0.41
	Yes	6	1.34	1.02, 1.74	54.50%	0.052	0.54
IARC (2016) primary NHL analysis	No	8	1.05	0.80, 1.38	36.60%	0.14	0.064
	Yes	9	1.03	0.81, 1.31	27.60%	0.20	0.084

Note:
2,4-D = 2,4-Dichlorophenoxyacetic Acid; AHS = Agricultural Health Study; CI = Confidence Interval; NHL = Non-Hodgkin's Lymphoma; RR = Relative Risk.

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