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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.

#### 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].

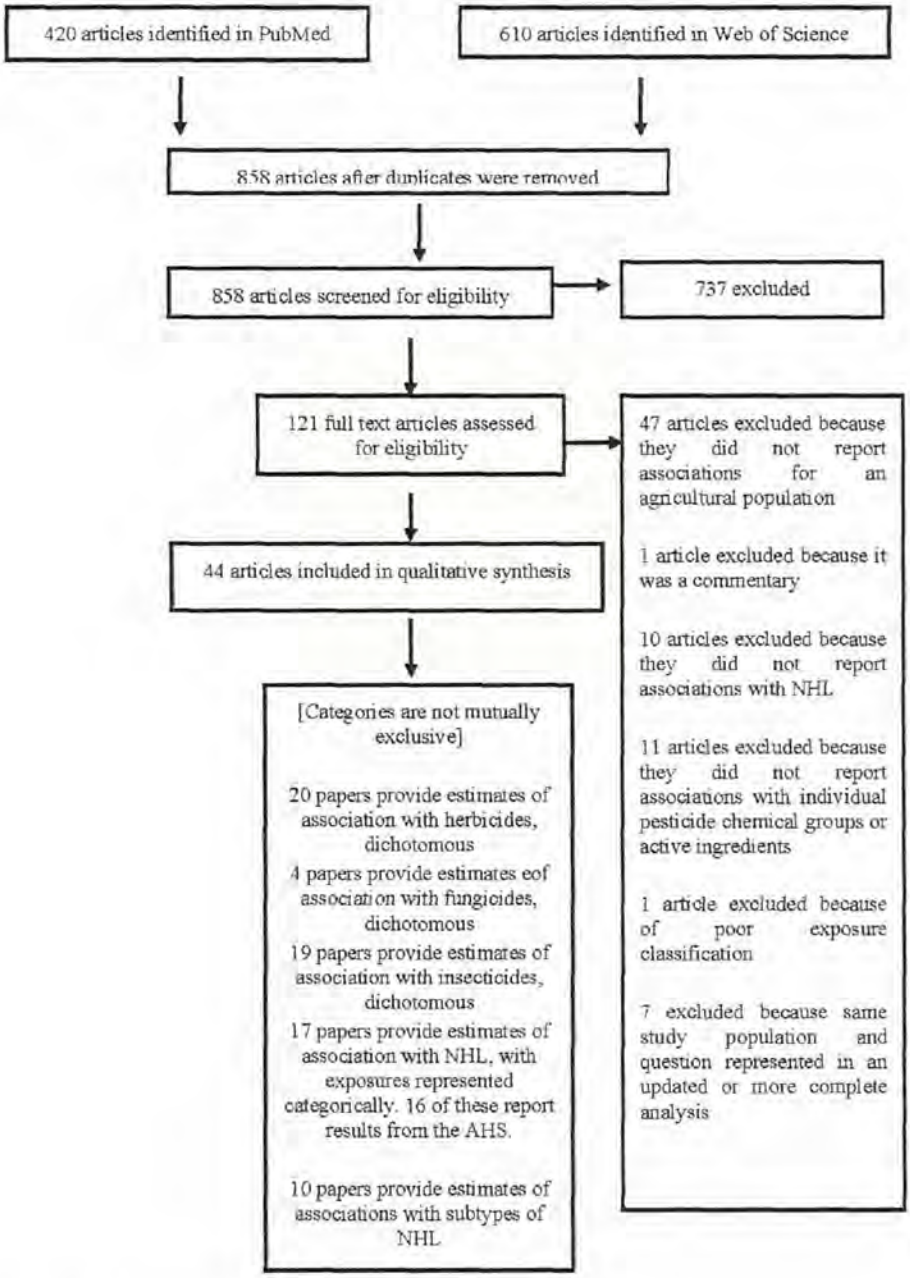
After performing meta-analyses for each active ingredient or chemical group, we repeated analyses, removing studies that differed from the others based on the above-described characteristics. In cases when results from individual studies were also represented in papers that analyzed these data pooled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

**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<br>Intensity weighted lifetime exposure days, 15 year lag<br>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<br>Used *vs.* did not use on crops and animals ,<br>Used *vs.* did not use on crops,<br>Used *vs* did not use on animals<br>Duration of use, in years (1-4, 5-9, ≥10)<br>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<br>Lifetime exposure days<br>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<br>Referent 2: Lowest quartile of exposure<br>Lifetime days of exposure<br>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 |

**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]<br>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<br>Farmers who ever used<br>Days/year of use (≤4 days, ≥5 days)<br>First lindane use (≥20 years ago, <20 years ago) | Yes | Age, proxy/direct interview, state of residence | Lindane | Yes |
| Bonner 2010 [24]<br>Iowa and North Carolina, USA | C (AHS) | NA | NA | 1993–2005 | 44,624 | Self-administered questionnaires | Referent 1: Nonexposed<br>Referent 2: Lowest tertile of exposure<br>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]<br>Iowa and North Carolina, USA | C (AHS) | NA | NA | 1993–2001 | 49,877 | Self-administered questionnaire | Referent 1: Nonexposed<br>Referent 2: Lowest tertile of exposure<br>Lifetime exposure days<br>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]<br>Iowa and North Carolina, USA | C (AHS) | NA | NA | 1993–2002 | 19,717 | Self-administered questionnaire | Referent 1: Nonexposed<br>Referent 2: Lowest tertile of exposure<br>Lifetime exposure days,<br>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]<br>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<br>Ever handled,<br>Handled prior to 1965<br>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]<br>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<br>Ever exposed, by level of industrial hygienists's degree of confidence that the participant was truly exposed to the agent:<br>Any level of confidence<br>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]<br>Iowa and North Carolina, USA | C (AHS) | NA | NA | 1993–2004 | 23,072 | Two self-administered questionnaires | Referent: Lowest tertile of exposure<br>Lifetime exposure days<br>Intensity weighted lifetime exposure days | Yes | Age, smoking, alcohol consumption, education, family history of cancer, state of residence, exposure to all pesticides | Metribuzin | 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 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 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<br>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<br>Referent 2: Lowest tertile of exposure<br>Ever used<br>Cumulative exposure days<br>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<br>Ever exposed,<br>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 |

**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]<br><br>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<br><br>Ever exposure,<br>High exposure (>median number of days for exposed participants)<br>Low exposure (<median number of days for exposed participants)<br><br>Years between first exposure and diagnosis:<br>Referent 2: 1-10years,<br>>10-20 years,<br>>20-30 years,<br>>30 years<br><br>Years between last exposure and diagnosis:<br>Referent 3: 1-10 years,<br>>10-20 years,<br>>20-30 years,<br>>30 years<br><br>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]<br><br>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<br><br>Ever use,<br><br>Duration of use (years),<br><br>Frequency of use (days/year),<br><br>First year of use | Yes | Age | Phenoxyacetic acids, Triazine herbicides, Amide herbicides, Benzoic herbicides, Carbamate herbicides, Trifluralin herbicides, Uracil herbicides | 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 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 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<br>Referent 2: Lowest tertile of exposure<br>Lifetime exposure days,<br>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<br>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<br>Lifetime exposure days,<br>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<br>Exposed,<br>Referent 2: Lowest quartile of exposure<br>*Lifetime exposure days,*<br>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 |

**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<br>Referent 2: Lowest tertile of exposure<br>Lifetime exposure days,<br>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]<br>Lifetime exposure days,<br>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<br>Referent 2: Lowest tertile of exposure<br>Lifetime exposure days,<br>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/1,506 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<br>Exposed,<br>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 | |

**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<br>Overall exposure,<br>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<br>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<br>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<br>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<br>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<br>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<br>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<br>Ever use<br>Lifetime days of exposure<br>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<br>≥100 sheep ,<br>Categories of number of sheep owned:<br>100-199 sheep,<br>200-683 sheep | Yes | Age | Hexachlorocyc-lohexane | 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 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Rusiecki 2009 [53] Iowa and North Carolina, USA | C (AHS) | NA | NA | 1993–2004 | 49,093 | Self-administered questionnaire | Referent: Nonexposed<br>Lifetime days of exposure<br>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<br>Lifetime days of exposure<br>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<br>Lifetime days of exposure<br>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<br>Ever Used<br>First used<br>Years used<br>Days/year of use<br>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 |

**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<br>Farming exposures to phenoxy herbicides<br>Any exposure to DDT<br>Any exposure to chlordane<br>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<br>Mixed or applied<br>Days/year mixing or applying<br>Years used on a farm<br>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<br>Used atrazine [1]<br>Personally handled<br>Used but did not handle<br>Duration of use (years)<br>Days/year handled<br>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]<br>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<br>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]<br>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<br>Used<br>Personally handled<br>Year since first use<br>Years of use<br>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 |

**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 |

**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 |

**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 |

**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 |

**Table 2.** *Cont.*

| 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 |

**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 |

**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 |

**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 |

**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.

**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 |

**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<br>Nonsubstantial: 1.1, 0.5–2.5<br>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<br>Non-substantial: 0.6, 0.3–1.2<br>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 |

**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] [f] | 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 |

**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 |

**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<br>Non-substantial exposure: 1.1, 0.5–2.3<br>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<br>Non-substantial exposure: 0.5, 0.1–2.0<br>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 |

**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.

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 |

**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 |

**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 |

**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 |

**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.

**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] |

**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 herbicicides 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.

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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**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.

**References**

1. Adamson, P.; Bray, F.; Costantini, A.S.; Tao, M.H.; Weiderpass, E.; Roman, E. Time trends in the registration of Hodgkin and non-Hodgkin lymphomas in Europe. *Eur. J. Cancer* 2007, *43*, 391–401.
2. Eltom, M.A.; Jemal, A.; Mbulaiteye, S.M.; Devesa, S.S.; Biggar, R.J. Trends in Kaposi's sarcoma and non-Hodgkin's lymphoma incidence in the United States from 1973 through 1998. *J. Natl. Cancer Inst.* **2002**, *94*, 1204–1210.
3. Pearce, N.; McLean, D. Agricultural exposures and non-Hodgkin's lymphoma. *Scand. J. Work Environ. Health* **2005**, *31*, 18–25.
4. Alexander, D.D.; Mink, P.J.; Adami, H.O.; Chang, E.T.; Cole, P.; Mandel, J.S.; Trichopoulos, D. The non-Hodgkin lymphomas: A review of the epidemiologic literature. *Int. J. Cancer* **2007**, *120*, 1–39.
5. Khuder, S.A.; Schaub, E.A.; Keller-Byrne, J.E. Meta-analyses of non-Hodgkin's lymphoma and farming. *Scand. J. Work Environ. Health* **1998**, *24*, 255–261.
6. Blair, A.; Freeman, L.B. Epidemiologic studies in agricultural populations: Observations and future directions. *J. Agromed.* **2009**, *14*, 125–131.
7. Beane Freeman, L.E.; Deroos, A.J.; Koutros, S.; Blair, A.; Ward, M.H.; Alavanja, M.; Hoppin, J.A. Poultry and livestock exposure and cancer risk among farmers in the agricultural health study. *Cancer Causes Control* **2012**, *23*, 663–670.
8. Merhi, M.; Raynal, H.; Cahuzac, E.; Vinson, F.; Cravedi, J.P.; Gamet-Payrastre, L. Occupational exposure to pesticides and risk of hematopoietic cancers: Meta-analysis of case-control studies. *Cancer Causes Control* **2007**, *18*, 1209–1226.
9. Sathiakumar, N.; Delzell, E.; Cole, P. Mortality among workers at two triazine herbicide manufacturing plants. *Amer. J. Ind. Med.* **1996**, *29*, 143–151.
10. Environmental Protection Agency. About Pesticides. Available online: http://www.epa.gov/pesticides/about/index.html (accessed on 20 January 2014).
11. Alavanja, M.C.; Ross, M.K.; Bonner, M.R. Increased cancer burden among pesticide applicators and others due to pesticide exposure. *Ca-A Cancer J. Clin.* **2013**, *63*, 120–142.

12. IARC (International Agency for Research on Cancer). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Available online: http://monographs.iarc.fr/ (accessed on 14 April 2014).
13. Wood, A. Compendium of Pesticide Common Names. Available online: http://www.alanwood.net/ (accessed on 22 January 2014).
14. DerSimonian, R.; Kacker, R. Random-effects model for meta-analysis of clinical trials: An update. *Contemp. Clin. Trials* **2007**, *28*, 105–114.
15. Higgins, J.P.; Thompson, S.G.; Deeks, J.J.; Altman, D.G. Measuring inconsistency in meta-analyses. *BMJ* **2003**, *327*, 557–560.
16. Egger, M.; Schneider, M.; Davey Smith, G. Spurious precision? Meta-analysis of observational studies. *BMJ* **1998**, *316*, 140–144.
17. Poole, C. Low P-values or narrow confidence intervals: Which are more durable? *Epidemiology* **2001**, *12*, 291–294.
18. Zahm, S.H.; Weisenburger, D.D.; Saal, R.C.; Vaught, J.B.; Babbitt, P.A.; Blair, A. The role of agricultural pesticide use in the development of non-Hodgkin's lymphoma in women. *Arch. Environ. Health* **1993**, *48*, 353–358.
19. Barry, K.H.; Koutros, S.; Lubin, J.H.; Coble, J.B.; Barone-Adesi, F.; Freeman, L.E.B.; Sandler, D.P.; Hoppin, J.A.; Ma, X.; Zheng, T.; Alavanja, M.C. Methyl bromide exposure and cancer risk in the Agricultural Health Study. *Cancer Cause. Control* **2012**, *23*, 807–818.
20. Baris, D.; Zahm, S.H.; Cantor, K.P.; Blair, A. Agricultural use of DDT and risk of non-Hodgkin's lymphoma: Pooled analysis of three case-control studies in the United States. *Occup. Environ. Med.* **1998**, *55*, 522–527.
21. Freeman, L.E.B.; Bonner, M.R.; Blair, A.; Hoppin, J.A.; Sandler, D.P.; Lubin, J.H.; Dosemeci, M.; Lynch, C.F.; Knott, C.; Alavanja, M.C. Cancer incidence among male pesticide applicators in the Agricultural Health Study cohort exposed to diazinon. *Amer. J. Epidemiol.* **2005**, *162*, 1070–1079.
22. Freeman, L.E.; Rusiecki, J.A.; Hoppin, J.A.; Lubin, J.H.; Koutros, S.; Andreotti, G.; Zahm, S.H.; Hines, C.J.; Coble, J.B.; Barone-Adesi, F.; *et al.* Atrazine and cancer incidence among pesticide applicators in the agricultural health study (1994–2007). *Environ. Health Perspect.* **2011**, *119*, 1253–1259.
23. Blair, A.; Cantor, K.P.; Zahm, S.H. Non-hodgkin's lymphoma and agricultural use of the insecticide lindane. *Amer. J. Ind. Med.* **1998**, *33*, 82–87.
24. Bonner, M.R.; Williams, B.A.; Rusiecki, J.A.; Blair, A.; Freeman, L.E.B.; Hoppin, J.A.; Dosemeci, M.; Lubin, J.; Sandler, D.P.; Alavanja, M.C.R. Occupational exposure to terbufos and the incidence of cancer in the Agricultural Health Study. *Cancer Cause. Control* **2010**, *21*, 871–877.
25. Bonner, M.R.; Lee, W.J.; Sandler, D.A.; Hoppin, J.A.; Dosemeci, M.; Alavanja, M.C.R. Occupational exposure to carbofuran and the incidence of cancer in the Agricultural Health Study. *Environ. Health Perspect.* **2005**, *113*, 285–289.
26. Bonner, M.R.; Coble, J.; Blair, A.; Beane Freeman, L.E.; Hoppin, J.A.; Sandler, D.P.; Alavanja, M.C. Malathion exposure and the incidence of cancer in the agricultural health study. *Amer. J. Epidemiol.* **2007**, *166*, 1023–1034.

27. Cantor, K.P.; Blair, A.; Everett, G.; Gibson, R.; Burmeister, L.F.; Brown, L.M.; Schuman, L.; Dick, F.R. Pesticides and other agricultural risk factors for non-Hodgkin's lymphoma among men in Iowa and Minnesota. *Cancer Res.* **1992**, *52*, 2447–2455.
28. Cocco, P.; Satta, G.; Dubois, S.; Pili, C.; Pilleri, M.; Zucca, M.; 't Mannetje, A.M.; Becker, N.; Benavente, Y.; de Sanjose, S.; *et al.* Lymphoma risk and occupational exposure to pesticides: Results of the Epilymph study. *Occup. Environ. Med.* **2013**, *70*, 91–98.
29. Delancey, J.O.L.; Alavanja, M.C.R.; Coble, J.; Blair, A.; Hoppin, J.A.; Austin, H.D.; Freeman, L.E.B. Occupational exposure to metribuzin and the incidence of cancer in the agricultural health study. *Ann. Epidemiol.* **2009**, *19*, 388–395.
30. De Roos, A.J.; Zahm, S.H.; Cantor, K.P.; Weisenburger, D.D.; Holmes, F.F.; Burmeister, L.F.; Blair, A. Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men. *Occup. Environ. Med.* **2003**, *60*, doi:10.1136/oem.60.9.e11.
31. De Roos, A.J.; Blair, A.; Rusiecki, J.A.; Hoppin, J.A.; Svec, M.; Dosemeci, M.; Sandler, D.P.; Alavanja, M.C. Cancer incidence among glyphosate-exposed pesticide applicators in the Agricultural Health Study. *Environ. Health Perspect.* **2005**, *113*, 49–54.
32. Eriksson, M.; Hardell, L.; Carlberg, M.; Akerman, M. Pesticide exposure as risk factor for non-Hodgkin lymphoma including histopathological subgroup analysis. *Int. J. Cancer* **2008**, *123*, 1657–1663.
33. Hardell, L.; Eriksson, M.; Nordstrom, M. Exposure to pesticides as risk factor for non-Hodgkin's lymphoma and hairy cell leukemia: Pooled analysis of two Swedish case-control studies. *Leuk. Lymphoma* **2002**, *43*, 1043–1049.
34. Hoar, S.K.; Blair, A.; Holmes, F.F.; Boysen, C.D.; Robel, R.J.; Hoover, R.; Fraumeni, J.F., Jr. Agricultural herbicide use and risk of lymphoma and soft-tissue sarcoma. *JAMA* **1986**, 256, 1141–1147.
35. Kang, D.; Park, S.K.; Beane-Freeman, L.; Lynch, C.F.; Knott, C.E.; Sandler, D.P.; Hoppin, J.A.; Dosemeci, M.; Coble, J.; Lubin, J.; *et al.* Cancer incidence among pesticide applicators exposed to trifluralin in the Agricultural Health Study. *Environ. Res.* **2008**, *107*, 271–276.
36. Koutros, S.; Lynch, C.F.; Ma, X.; Lee, W.J.; Hoppin, J.A.; Christensen, C.H.; Andreotti, G.; Freeman, L.B.; Rusiecki, J.A.; Hou, L.; *et al.* Heterocyclic aromatic amine pesticide use and human cancer risk: Results from the U.S. Agricultural Health Study. *Int. J. Cancer* **2009**, *124*, 1206–1212.
37. Koutros, S.; Mahajan, R.; Zheng, T.; Hoppin, J.A.; Ma, X.; Lynch, C.F.; Blair, A.; Alavanja, M.C. Dichlorvos exposure and human cancer risk: Results from the Agricultural Health Study. *Cancer Cause. Control* **2008**, *19*, 59–65.
38. Lee, W.J.; Blair, A.; Hoppin, J.A.; Lubin, J.H.; Rusiecki, J.A.; Sandler, D.P.; Dosemeci, M.; Alavanja, M.C. Cancer incidence among pesticide applicators exposed to chlorpyrifos in the Agricultural Health Study. *J. Natl. Cancer Inst.* **2004**, *96*, 1781–1789.
39. Lee, W.J.; Hoppin, J.A.; Blair, A.; Lubin, J.H.; Dosemeci, M.; Sandler, D.P.; Alavanja, M.C. Cancer incidence among pesticide applicators exposed to alachlor in the agricultural health study. *Amer. J. Epidemiol.* **2004**, *159*, 373–380.

40. Lynch, S.M.; Mahajan, R.; Beane Freeman, L.E.; Hoppin, J.A.; Alavanja, M.C. Cancer incidence among pesticide applicators exposed to butylate in the Agricultural Health Study (AHS). *Environ. Res.* **2009**, *109*, 860–868.
41. Lynch, S.M.; Rusiecki, J.A.; Blair, A.; Dosemeci, M.; Lubin, J.; Sandler, D.; Hoppin, J.A.; Lynch, C.F.; Alavanja, M.C. Cancer incidence among pesticide applicators exposed to cyanazine in the agricultural health study. *Environ. Health Perspect.* **2006**, *114*, 1248–1252.
42. Mahajan, R.; Blair, A.; Coble, J.; Lynch, C.F.; Hoppin, J.A.; Sandler, D.P.; Alavanja, M.C. Carbaryl exposure and incident cancer in the Agricultural Health Study. *Int. J. Cancer* **2007**, *121*, 1799–1805.
43. McDuffie, H.H.; Pahwa, P.; McLaughlin, J.R.; Spinelli, J.J.; Fincham, S.; Dosman, J.A.; Robson, D.; Skinnider, L.F.; Choi, N.W. Non-Hodgkin's lymphoma and specific pesticide exposures in men: Cross-Canada study of pesticides and health. *Cancer Epidemiol. Biomark. Prev.* **2001**, *10*, 1155–1163.
44. Miligi, L.; Costantini, A.S.; Veraldi, A.; Benvenuti, A.; Vineis, P. Cancer and pesticides: An overview and some results of the Italian Multicenter case-control study on hematolymphopoietic malignancies. In *Living in a Chemical World: Framing the Future in Light of the Past*; Blackwell Publishing: Oxford, UK, 2006; Volume 1076, pp. 366–377.
45. Mills, P.K.; Yang, R.; Riordan, D. Lymphohematopoietic cancers in the United Farm Workers of America (UFW), 1988–2001. *Cancer Cause. Control* **2005**, *16*, 823–830.
46. Orsi, L.; Delabre, L.; Monnereau, A.; Delval, P.; Berthou, C.; Fenaux, P.; Marit, G.; Soubeyran, P.; Huguet, F.; Milpied, N.; *et al.* Occupational exposure to pesticides and lymphoid neoplasms among men: Results of a French case-control study. *Occup. Environ. Med.* **2009**, *66*, 291–298.
47. Pahwa, M.; Harris, S.A.; Hohenadel, K.; McLaughlin, J.R.; Spinelli, J.J.; Pahwa, P.; Dosman, J.A.; Blair, A. Pesticide use, immunologic conditions, and risk of non-Hodgkin lymphoma in Canadian men in six provinces. *Int. J. Cancer* **2012**, *131*, 2650–2659.
48. Pearce, N.E.; Sheppard, R.A.; Smith, A.H.; Teague, C.A. Non-Hodgkin's lymphoma and farming: An expanded case-control study. *Int. J. Cancer* **1987**, *39*, 155–161.
49. Persson, B.; Dahlander, A.M.; Fredriksson, M.; Brage, H.N.; Ohlson, C.G.; Axelson, O. Malignant lymphomas and occupational exposures. *Brit. J. Ind. Med.* **1989**, *46*, 516–520.
50. Persson, B.; Fredriksson, M.; Olsen, K.; Boeryd, B.; Axelson, O. Some occupational exposures as risk factors for malignant lymphomas. *Cancer* **1993**, *72*, 1773–1778.
51. Purdue, M.P.; Hoppin, J.A.; Blair, A.; Dosemeci, M.; Alavanja, M.C. Occupational exposure to organochlorine insecticides and cancer incidence in the Agricultural Health Study. *Int. J. Cancer* **2007**, *120*, 642–649.
52. Rafnsson, V. Risk of non-Hodgkin's lymphoma and exposure to hexachlorocyclohexane, a nested case-control study. *Eur. J. Cancer* **2006**, *42*, 2781–2785.
53. Rusiecki, J.A.; Patel, R.; Koutros, S.; Beane-Freeman, L.; Landgren, O.; Bonner, M.R.; Coble, J.; Lubin, J.; Blair, A.; Hoppin, J.A.; *et al.* Cancer incidence among pesticide applicators exposed to permethrin in the Agricultural Health Study. *Environ. Health Perspect.* **2009**, *117*, 581–586.
54. Rusiecki, J.A.; Hou, L.; Lee, W.J.; Blair, A.; Dosemeci, M.; Lubin, J.H.; Bonner, M.; Samanic, C.; Hoppin, J.A.; Sandler, D.P.; *et al.* Cancer incidence among pesticide applicators exposed to metolachlor in the agricultural health study. *Int. J. Cancer* **2006**, *118*, 3118–3123.

55. Van Bemmel, D.M.; Visvanathan, K.; Freeman, L.E.B.; Coble, J.; Hoppin, J.A.; Alavanja, M.C.R. S-Ethyl-N,N-dipropylthiocarbamate exposure and cancer incidence among male pesticide applicators in the agricultural health study: A prospective cohort. *Environ. Health Perspect.* **2008**, *116*, 1541–1546.
56. Waddell, B.L.; Zahm, S.H.; Baris, D.; Weisenburger, D.D.; Holmes, F.; Burmeister, L.F.; Cantor, K.P.; Blair, A. Agricultural use of organophosphate pesticides and the risk of non-Hodgkin's lymphoma among male farmers (United States). *Cancer Cause. Control* **2001**, *12*, 509–517.
57. Woods, J.S.; Polissar, L.; Severson, R.K.; Heuser, L.S.; Kulander, B.G. Soft tissue sarcoma and non-Hodgkin's lymphoma in relation to phenoxyherbicide and chlorinated phenol exposure in western Washington. *J. Natl. Cancer Inst.* **1987**, *78*, 899–910.
58. Zahm, S.H.; Weisenburger, D.D.; Babbitt, P.A.; Saal, R.C.; Vaught, J.B.; Cantor, K.P.; Blair, A. A case-control study of non-Hodgkin's lymphoma and the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) in eastern Nebraska. *Epidemiology* **1990**, *1*, 349–356.
59. Zahm, S.H.; Weisenburger, D.D.; Cantor, K.P.; Holmes, F.F.; Blair, A. Role of the herbicide atrazine in the development of non-Hodgkin's lymphoma. *Scand. J. Work Environ. Health* **1993**, *19*, 108–114.
60. Zheng, T.; Zahm, S.H.; Cantor, K.P.; Weisenburger, D.D.; Zhang, Y.; Blair, A. Agricultural exposure to carbamate pesticides and risk of non-Hodgkin lymphoma. *J. Occup. Environ. Med.* **2001**, *43*, 641–649.
61. Alavanja, M.C.; Sandler, D.P.; McMaster, S.B.; Zahm, S.H.; McDonnell, C.J.; Lynch, C.F.; Pennybacker, M.; Rothman, N.; Dosemeci, M.; Bond, A.E.; *et al.* The Agricultural Health Study. *Environ. Health Perspect.* **1996**, *104*, 362–369.
62. Fritschi, L.; Benke, G.; Hughes, A.M.; Kricker, A.; Turner, J.; Vajdic, C.M.; Grulich, A.; Milliken, S.; Kaldor, J.; Armstrong, B.K. Occupational exposure to pesticides and risk of non-Hodgkin's lymphoma. *Amer. J. Epidemiol.* **2005**, *162*, 849–857.
63. Cocco, P.; Satta, G.; D'Andrea, I.; Nonne, T.; Udas, G.; Zucca, M.; Mannetje, A.; Becker, N.; Sanjose, S.; Foretova, L.; *et al.* Lymphoma risk in livestock farmers: Results of the Epilymph study. *Int. J. Cancer* **2013**, *132*, 2613–2618.
64. IARC (International Agency for Research on Cancer). AGRICOH: A Consortium of Agricultural Cohort Studies. Available online: http://agricoh.iarc.fr/ (accessed 15 April 2014).
65. Morton, L.M.; Turner, J.J.; Cerhan, J.R.; Linet, M.S.; Treseler, P.A.; Clarke, C.A.; Jack, A.; Cozen, W.; Maynadie, M.; Spinelli, J.J.; *et al.* Proposed classification of lymphoid neoplasms for epidemiologic research from the Pathology Working Group of the International Lymphoma Epidemiology Consortium (InterLymph). *Blood* **2007**, *110*, 695–708.
66. Sterne, J.A.; Sutton, A.J.; Ioannidis, J.P.; Terrin, N.; Jones, D.R.; Lau, J.; Carpenter, J.; Rucker, G.; Harbord, R.M.; Schmid, C.H.; *et al.* Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* **2011**, *343*, doi:10.1136/bmj.d4002.
67. Food and Agriculture Organization of the United Nations. Agricultural Production Domain. Available online: http://www.fao.org (accessed on 20 January 2014).

68. IARC (International Agency for Research on Cancer). GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012. Available online: http://globocan.iarc.fr/old/pie_site_prev.asp?selection=19260&title=Non-Hodgkin+lymphoma&sex=0&type=4&populations=2&window=1&join=1&submit=%C2%A0Execute (accessed on 10 February 2014).
69. Chiu, B.C.; Blair, A. Pesticides, chromosomal aberrations, and non-Hodgkin's lymphoma. *J. Agromed.* **2009**, *14*, 250–255.
70. Schroeder, J.C.; Olshan, A.F.; Baric, R.; Dent, G.A.; Weinberg, C.R.; Yount, B.; Cerhan, J.R.; Lynch, C.F.; Schuman, L.M.; Tolbert, P.E.; *et al*. Agricultural risk factors for t(14;18) subtypes of non-Hodgkin's lymphoma. *Epidemiology* **2001**, 12, 701–709.
71. Chiu, B.C.; Dave, B.J.; Blair, A.; Gapstur, S.M.; Zahm, S.H.; Weisenburger, D.D. Agricultural pesticide use and risk of t(14;18)-defined subtypes of non-Hodgkin lymphoma. *Blood* **2006**, *108*, 1363–1369.
72. Faustini, A.; Settimi, L.; Pacifici, R.; Fano, V.; Zuccaro, P.; Forastiere, F. Immunological changes among farmers exposed to phenoxy herbicides: Preliminary observations. *Occup. Environ. Med.* **1996**, *53*, 583–585.
73. IARC (International Agency for Research on Cancer), Arsenic, Metals, Fibres and Dusts: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. 2012. Available online: http://monographs.iarc.fr/ENG/Monographs/vol100C/ (accessed on 15 April 2014).
74. IARC (International Agency for Research on Cancer), Re-evaluation of Some Organic Chemicals, Hydrazine, and Hydrogen Peroxide: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. 1999. Available online: http://monographs.iarc.fr/ENG/Monographs/vol53/ (accessed on 15 April 2014).
75. IARC (International Agency for Research on Cancer). Occupational Exposures in Insecticide Application, and Some Pesticides: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. 1991. Available online: http://monographs.iarc.fr/ENG/Monographs/vol53/ (accessed on 14 April 2014).
76. IARC (International Agency for Research on Cancer). Some Thyrotropic Agents: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. 2001. Available online: http://monographs.iarc.fr/ENG/Monographs/vol79/volume79.pdf (accessed on 15 April 2014).
77. IARC (International Agency for Research on Cancer) Overal Evaluation of Carcinogenicity: An Update of IARC Monographs Volumes 1 to 42: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans., 1987. Available online: http://monographs.iarc.fr/ENG/Monographs/suppl7/suppl7.pdf (accessed on 15 April 2014).

# Increased Cancer Burden Among Pesticide Applicators and Others Due to Pesticide Exposure

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A growing number of well-designed epidemiological and molecular studies provide substantial evidence that the pesticides used in agricultural, commercial, and home and garden applications are associated with excess cancer risk. This risk is associated both with those applying the pesticide and, under some conditions, those who are simply bystanders to the application. In this article, the epidemiological, molecular biology, and toxicological evidence emerging from recent literature assessing the link between specific pesticides and several cancers including prostate cancer, non-Hodgkin lymphoma, leukemia, multiple myeloma, and breast cancer are integrated. Although the review is not exhaustive in its scope or depth, the literature does strongly suggest that the public health problem is real. If we are to avoid the introduction of harmful chemicals into the environment in the future, the integrated efforts of molecular biology, pesticide toxicology, and epidemiology are needed to help identify the human carcinogens and thereby improve our understanding of human carcinogenicity and reduce cancer risk. CA Cancer J Clin 2013;63:120–142. ©2013 American Cancer Society.*

Keywords: pesticides, cancer burden, carcinogen, risk, environmental cancer, public health



## Introduction

A comprehensive and successful strategy for minimizing cancer risk from pesticide use should combine research initiatives aimed at identifying pesticides that are human carcinogens with policies that attempt to reduce these exposures to workers and the general public. In this discussion, pesticides are defined as a diverse group of chemical formulations used to control pests, including insects, molds, and unwanted plants.

Pest problems in public health (ie, vectors of disease), agriculture, and commerce are not static because pests develop resistance to widely used pesticides and are periodically introduced to new geographic areas without effective natural controls. Historically, the evolution of new pests has resulted in the development of new pesticides, followed shortly thereafter by new pesticide problems, such as pest resistance and unintended toxicities. In the United States and other developed countries, regulatory toxicity testing has kept many genotoxic chemicals and animal carcinogens out of the market place.[1] An incomplete understanding of human carcinogenicity, however, seems to have resulted in allowing some human carcinogens on to the worldwide market, resulting in excess cancer risk to those who are highly exposed and those who are particularly vulnerable.[2,3] For example, an International Agency for Research on Cancer (IARC) monograph published in 1991 stated, "occupational exposures in spraying and application of non-arsenical insecticides" as a group are classified as "probable human carcinogens" (category 2A),[2] yet the identification of specific pesticides as human carcinogens has not yet been made. If current regulatory toxicity testing has been inadequate, new data from toxicology and cancer biology will need to be used in conjunction with epidemiology to help improve our regulatory procedures and more reliably identify human carcinogens.

Rather than wait for human carcinogens to be identified, several European countries, including Sweden, Denmark, the Netherlands, and others, have initiated pesticide use reduction policies that have resulted in substantially diminished

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TABLE 1. Most Commonly Used Conventional Pesticide Active Ingredients, Agricultural Market Sector, 2007 Estimates, Ranked by Range in Millions of Pounds of Active Ingredient

| ACTIVE INGREDIENT | FUNCTIONAL CLASS | CHEMICAL CLASS | RANK | RANGE |
|---|---|---|---|---|
| Glyphosate | Herbicide | Phosphinic acid | 1 | 180-185 |
| Atrazine | Herbicide | Triazine | 2 | 73-78 |
| Metam sodium | Fumigant | Dithiocarbamate | 3 | 50-55 |
| S-metolachlor | Herbicide | Acetamide | 4 | 30-35 |
| Acetochlor | Herbicide | Acetamide | 5 | 28-33 |
| 1,3-dichloropropene | Fumigant | Organochlorine | 6 | 27-32 |
| 2,4-D | Herbicide | Phenoxy acid | 7 | 25-29 |
| Methyl bromide | Fumigant | Methyl halide | 8 | 11-15 |
| Chloropicrin | Fumigant | Organochlorine | 9 | 9-11 |
| Pendimethalin | Herbicide | Dinitroaniline | 10 | 7-9 |
| Ethephon | Plant growth regulator | Ethylene generator | 11 | 7-9 |
| Chlorothalonil | Fungicide | Phthalamide | 12 | 7-9 |
| Metam potassium | Fumigant | Dithiocarbamate | 13 | 7-9 |
| Chlorpyrifos | Insecticide | Organophosphate | 14 | 7-9 |
| Copper hydroxide | Fungicide | Inorganic alkali | 15 | 6-8 |
| Simazine | Herbicide | Triazine | 16 | 5-7 |
| Trifluralin | Herbicide | Dinitroaniline | 17 | 5-7 |
| Propanil | Herbicide | Anilide | 18 | 4-6 |
| Mancozeb | Fungicide | Dithiocarbamate | 19 | 4-6 |
| Aldicarb | Insecticide | Carbamate | 20 | 3-4 |
| Acephate | Insecticide | Organophosphorus | 21 | 2-4 |
| Diuron | Herbicide | Urea | 22 | 2-4 |
| MCPA | Herbicide | Phenoxy acid | 23 | 2-4 |
| Paraquat (dipyridylium) | Herbicide | Bipyridal | 24 | 2-4 |
| Dimethenamid | Herbicide | Acetamide | 25 | 2-4 |

2,4-D indicates 2,4-dichlorophenoxyacetic acid; MCPA, 2-methyl-4-chlorophenoxyacetic acid.

*Source:* US Environmental Protection Agency Office of Pesticide Programs. Pesticide Industry Sales and Usage. 2006 and 2007 Market Estimates. Washington, DC: US Environmental Protection Agency; 2007. Available from: epa.gov/pesticides/pestsales/07pestsales/usage2007_2.htm. Accessed November 27, 2012.

pesticide use overall.[4] In the United States, a nationwide use reduction policy has met with resistance politically because of disagreements about the net benefit to health and debate concerning the disproportionate economic impact of these policies on selected groups (eg, farmers, food processors, and pesticide manufacturers) and on food prices.[1] The information available for these policy debates on cost-benefit are not yet equal since identifying the impact of pesticides on cancer risk has been difficult and progress relatively slow, while estimating the immediate economic impact of pesticide use reduction policies on agriculture and commerce is more readily quantifiable. Since pesticides are pervasive in our environment, environmental health policy in the United States has instead focused on reducing human exposure to pesticides by controlling the methods and conditions of use.[1]

The active ingredients of pesticides are a very diverse array of chemical structures. Many pesticide structures are very complex and cannot be categorized simply. A convenient classification is based on the targeted pest (eg, herbicides, insecticides, fungicides, nematicides, and rodenticides). The classes may then be subdivided into smaller subclasses based on chemical structure. Herbicides account for the largest portion of total use, followed by other pesticides, insecticides, and fungicides. The amount of pesticide used in the US in both 2006 and 2007 exceeded 1.1 billion pounds.[5]

TABLE 2. Most Commonly Used Conventional Pesticide Active Ingredient in the Home and Garden Market Sector, 2007 and 2005 Estimates, Ranked by Range in Millions of Pounds of Active Ingredient

| ACTIVE INGREDIENT | TYPE | CHEMICAL CLASS | RANK | RANGE |
|---|---|---|---|---|
| 2,4-D | Herbicide | Phenoxy acid | 1 | 8-11 |
| Glyphosate | Herbicide | Phosphinic acid | 2 | 5-8 |
| Carbaryl | Insecticide | Carbamate | 3 | 4-6 |
| MCPP | Herbicide | Phenoxy_acid | 4 | 4-6 |
| Pendimethalin | Herbicide | Dinitroaniline | 5 | 3-5 |
| Pyrethroids | Insecticide | Pyrethroid | 6 | 2-4 |
| Malathion | Insecticide | Organophophorus | 7 | 2-4 |
| Dicamba | Herbicide | Benzoic_acid | 8 | 1-3 |
| Trifluralin | Herbicide | Dinitroaniline | 9 | 1-3 |
| Pelarganoc acid | Herbicide | Fatty acid | 10 | <1 |

2,4-D indicates 2,4-Dichlorophenoxyacetic acid; MCPP, methylchlorophenoxypropionic acid.

Does not include moth controls: paradichlorobenzene (30-35 million pounds per year) and naphthalene (2-4 million pounds per year). Also does not include insect repellent N,N-diethyl-meta-toluamide (5-7 millions pound per year).

Source: US Environmental Protection Agency Office of Pesticide Programs. Pesticide Industry Sales and Usage. 2006 and 2007 Market Estimates. Washington, DC: US Environmental Protection Agency; 2007. Available from: epa.gov/pesticides/pestsales/07pestsales/usage2007_2.htm. Accessed November 27, 2012.

The amount of pesticide used in the US accounted for 22% of the total world pesticide amount used, 25% of the world herbicide amount used, 10% of the world insecticide amount used, 14% of the world fungicide amount used, and more than 25% of other pesticide amounts used in both years.[6] The most highly used pesticides in agriculture, home and garden use, and government and commercial use are identified in Tables 1, 2, and 3.[5]

## Pesticide Exposures and Control

Among members of the general public who are not applying pesticides, multiple routes of exposure are possible depending on whether the individual is an adult or a child, the location of their residence in relation to pesticide applications, whether a residence was treated with pesticides, the occupations of household members, the volatility of the compound, the persistence of the pesticides

TABLE 3. Most Commonly Used Conventional Pesticide Active Ingredients in the Industry/Commercial/Government Market Sector, 2007, 2005, 2003, and 2001 Estimates, Ranked by Range in Millions of Pounds of Active Ingredient

| ACTIVE INGREDIENT | TYPE | CHEMICAL CLASS | RANK | RANGE |
|---|---|---|---|---|
| 2,4-D | Herbicide | Phenoxy acid | 1 | 19-22 |
| Glyphosate | Herbicide | Phosphinic acid | 2 | 13-15 |
| Chlorothalonil | Fungicide | Phthalimide | 3 | 3-5 |
| MSMA | Herbicide | Organoarsenic | 4 | 2-4 |
| Diuron | Herbicide | Urea | 5 | 2-4 |
| Pendimethalin | Herbicide | Dinitroaniline | 6 | 2-4 |
| Triclopyr | Herbicide | Organochlorine | 7 | 2-4 |
| Copper sulfate | Fungicide | Inorganic sulfate | 8 | 2-4 |
| Malathion | Insecticide | Oganophosphorous | 9 | 1-3 |
| Sulfuryl fluoride | Insecticide | Inorganic fluoride | 10 | 1-3 |

2,4-D indicates 2,4-dichlorophenoxyacetic acid; MSMA, monosodium methyl arsenate.

Includes applications to homes and gardens by professional applicators. Does not include sulfur or petroleum oil. Due to lack of data, the same estimate is used for both 2005 and 2007 in this report.

Source: US Environmental Protection Agency Office of Pesticide Programs. Pesticide Industry Sales and Usage. 2006 and 2007 Market Estimates. Washington, DC: US Environmental Protection Agency; 2007. Available from: epa.gov/pesticides/pestsales/07pestsales/usage2007_2.htm. Accessed November 27, 2012.

TABLE 4. Routes of Pesticide Exposure and Exposure Control Measures

| SUBJECT | MAJOR ROUTES OF EXPOSURE | PREVENTIVE OR CORRECTIVE ACTION | REFERENCES |
|---|---|---|---|
| Pesticide applicator | Dermal | 1. Use personal protective equipment including chemically resistant gloves.<br>2. Remove all pesticide-soiled clothing as soon as possible.<br>3. Wash or shower immediately following application.<br>4. Follow all pesticide label instructions. | 14-18 |
| | Ingestion | 1. Do not eat, drink, or smoke during pesticide handling or application. | 17 |
| | Inhalation | 1. Mix or load pesticides in a well-ventilated area.<br>2. Wear appropriate respiratory protective equipment according to pesticide label instructions. | 14,17 |
| Adult bystander and children's guardians | Dermal | 1. Do not enter fields, lawns, or confined spaces where pesticides have been applied for the period specified on label instructions. Do not allow children to do so.<br>2. Interrupt take-home pathways:<br>a. Encourage family members to remove shoes and other pesticide-soiled clothing outside the home if possible or as soon as possible after entering the home.<br>b. Vacuum rug and/or clean floors if possibly soiled with pesticides.<br>c. Do not store pesticides in living areas or anywhere within the reach of children. Keep all pesticides in a locked cabinet in a well-ventilated utility area or garden shed.<br>3. Keep children and pets away from areas where pesticides were applied.<br>4. Encourage family members exposed to pesticides to wash or shower as soon as possible after exposure.<br>5. Do not have pets enter the living areas of the home when soiled with pesticides until cleaned.<br>6. Wash clothing soiled with pesticides separately from other laundry. | 6-13 |
| | Ingestion | 1. Never store pesticides in cabinets with or near food.<br>2. Always store pesticides in their original containers, complete with labels that list ingredients, directions for use, and first aid in case of accidental exposure.<br>3. Never transfer pesticides to soft drink bottles or other containers.<br>4. Rinse fruits and vegetables with water. Scrub with a brush and peel them if possible. | 3,5,6,9,10,13 |
| | Inhalation/general | 1. Do not stockpile pesticides. Purchase only what you need for immediate application.<br>2. Follow the pesticide label directions for proper disposal.<br>3. Report any symptoms possibly related to pesticide exposure to your health care provider. When possible, report the name of the product, the ingredients, and the first aid instructions contained on the product label.<br>4. If a close neighbor or someone else is applying pesticides outdoors near your home, stay indoors with your children and pets. Keep windows and doors closed. | 3,6,14,17 |
| Regulatory agencies, scientific community, and chemical manufacturers | All | 1. Identify human carcinogens and remove them from the market place or greatly curtail their use.<br>2. Identity the persistence and accumulation potential of pesticides and reduce the use of long-lived pesticides wherever possible.<br>3. Identify good pesticide work practices and educate the public in these practices.<br>4. Design more effective pesticide containers and application equipment that minimizes pesticide exposure to the applicator and to children who may come into contact with these containers. | 3,5,6 |

in the environment, and several other chemical and physical properties of the pesticides (Table 4).[3,5-18] Pesticide applications to the home by a second party can result in both dermal and respiratory exposure. Other common routes of exposure to the general public include drinking water and dietary sources.[6] To minimize nonoccupational exposures to pesticides, EPA regulations have discouraged the use of the longer-lasting pesticides such as organophosphate (OP) insecticides in the home.[5] A trend toward the use of pyrethroids and other shorter-lived pesticides is resulting in lower OP exposures among the general public.[5]

The National Academy of Sciences[3] suggested that children may experience greater risk from pesticide exposure than adults because of the behavioral, dietary, and physiological characteristics associated with development. Among children, an important source of pesticide exposure results from diet[7]; for example, the consumption of organic produce is associated with a substantially lower concentration of urinary dialkylphosphate levels (which indicate organophosphorus pesticide exposure) than in those eating conventional foods,[7,8] but we do not have substantial evidence suggesting a cancer hazard associated with this exposure.[9] Another important source of pesticide

exposure results from the transfer of pesticides from a person who is occupationally exposed.[10] For example, urinary dialkylphosphate levels have been measured in studies of children and show parental occupation or their household proximity to farmland[7,8,10-12] and self-reported residential use of pesticides by parents[12,13] are important sources of childhood exposure (Table 4).[3,5-18]

Among adults applying liquid pesticides of low volatility, dermal exposures typically account for 90% of pesticide exposures.[14-16] The dermal penetration can vary between 2% and 20% if the pesticide is left on the skin for 8 hours or longer,[15] and therefore the use of proper protective equipment including chemical-resistant gloves and protective suits when handling the pesticide can substantially reduce exposure.[17] When the skin is immediately washed after pesticide use, a substantial additional reduction takes place.[14,18] A larger fraction of the exposure would be by the respiratory route among those applying more volatile pesticides (eg, flying insect spray) and other aerosols, and thus respiratory protection appropriate to the chemical being used is usually recommended (Table 4).[3-18]

To minimize nonoccupational exposures to pesticides, EPA regulations have discouraged the use of the longer-lasting and broad-spectrum pesticides. The lipophilic bioaccumulative organochlorine (OC) insecticides that were widely used in the mid-20th century were subsequently replaced by OPs, carbamates, and pyrethroids because these compounds were more environmentally labile and did not accumulate in the food chain to the same extent as the OCs. Moreover, compounds such as pyrethroids have become extremely attractive for pest control because they exhibit greater selective lethality toward insects compared with mammals.[19] Importantly, when humans are exposed to pyrethroids, OPs, and carbamates, the compounds are generally metabolized and eliminated from the body within 24 to 48 hours as water-soluble metabolites in urine. Physiologically based pharmacokinetic models that predict the internal dose of specific pesticides as a function of time are tools used to assess chemical dosimetry following exposures, although these models are more developed in animal studies than in humans.[20]

Since a total ban on the use of chemical pesticides is unlikely to happen in any country in the foreseeable future, ensuring cancer risk reduction from pesticides will depend on identifying pesticides that are human carcinogens. This review is not exhaustive, but rather it is focused on several cancers (ie, prostate cancer, non-Hodgkin lymphoma [NHL], adult and childhood leukemia, multiple myeloma, and breast cancer) where considerable progress has been made in identifying pesticides likely to be human carcinogens by synthesizing results from epidemiology, toxicology, and cancer biology. Although more than 800 active pesticide ingredients are currently on the market in the United States and other countries, only arsenical insecticides[2] and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) (a contaminant of the phenoxy herbicide 2,4,5,-T) have been identified as human carcinogens by the IARC (category 1).[2] However, literature developed subsequent to publication of the IARC monograph suggests that chemicals in every major functional class of pesticides (ie, insecticides, herbicides, fungicides, and fumigants) are associated with human cancer. Table 5 presents a list of pesticides that have been carefully evaluated in well-designed epidemiological and/or toxicological/cancer biology studies for human carcinogenicity of the prostate, NHL, adult leukemia, and multiple myeloma.[21-68] While we discuss a potential link between pesticides and breast cancer and childhood leukemia because of widespread public anxiety about these cancers, no specific pesticide has yet been strongly linked to these cancers and therefore we do not include them in our table. The list is not exhaustive and considers only these 4 cancer sites because the literature is most developed for these sites. Other chemicals are likely to emerge as our understanding of pesticide-induced mechanisms of cancer etiology expands.

## Mechanisms of Pesticide Toxicity

Pesticides have diverse chemical structures and exhibit a variety of biological modes of action in both target and nontarget organisms.[69] Following absorption into the body, pesticides are often biotransformed to water-soluble metabolites for the purpose of detoxification and elimination. Rates of biotransformation can be rapid (hours to days), as in the case of OP insecticides, or extremely slow (years to decades), as is noted for OC insecticides, which accounts for the bioaccumulation of these lipophilic compounds in adipose tissue. Multiple mechanisms are likely involved in pesticide-mediated carcinogenesis. Most of the published literature point toward oxidative stress and/or receptor-mediated mechanisms being important determinants, whereas inflammatory and aberrant epigenetic mechanisms caused by pesticide exposure are only in a preliminary stage of development and, consequently, there is not a lot of literature to support these mechanisms at this time. However, epigenetic modifications of tumor suppressor genes and oncogenes that alter their expression in tumors have been shown to be molecular drivers of cancer pathogenesis during the promotion and progression phases. Thus, this section will briefly focus on oxidative stress and receptor-mediated toxicities that are caused by pesticides.

TABLE 5. Epidemiological and Toxicological Evidence of Carcinogenicity for Selected Cancer Sites and Pesticides

| CANCER SITE | PESTICIDE | CURRENT US EPA REGULATORY STATUS[a] | IARC CLASSIFICATION (YEAR)[b] | EXPOSURE SOURCE | EPIDEMIOLOGIC EVIDENCE | REFERENCE | TOXICOLOGICAL EVIDENCE | REFERENCE |
|---|---|---|---|---|---|---|---|---|
| Prostate | Fonofos (OP) | Not registered | Not evaluated | Occupational | 1. Monotonic increase in risk of aggressive PC. | 25 | No direct evidence for PC. | — |
| | | | | | 2. Significant interaction between exposure and genetic variants in 8q24, base excision repair, nucleotide excision repair. | 23,24,91 | Mutagenic in *S. typhimurium* and *S. cerevisae* genotoxicity assays. | 26 |
| | Terbufos (OP) | Registered | Not evaluated | Occupational | 1. Monotonic increase in risk of aggressive PC. | 25 | No direct evidence for PC. | — |
| | | | | | 2. Significant interaction between exposure and genetic variants in 8q24, base excision repair. | 23,24 | Mutagenic in *S. typhimurium* and *S. cerevisae* genotoxicity assays. | 26 |
| | Malathion (OP) | Registered | Group 3 (1987) | Occupational | 1. Monotonic increase in risk of aggressive PC. | 25 | No direct evidence for PC. | — |
| | | | | | 2. Positively associated with PC. | 102 | | |
| | Permethrin (pyrethroid) | Registered | Not evaluated | Occupational | 1. Significant interaction between exposure and genetic variants in 8q24. | 24 | No direct evidence for PC. | — |
| | Aldrin (OC) | Not registered | Group 3 (1987) | Occupational | 1. Increased in risk of PC among men with a family history of PC. | 25 | No direct evidence for PCr; | — |
| | | | | | | | Hepatocarcinogenesis in mice through a nongenotoxic mode of action. | 22 |
| | Chlordecone (OC) | Not registered | Group 2B (1987) | Environmental | 1. Increased risk of PC in highest exposure tertile. | 29 | Androgenic activity in cultured prostate cells. | 28 |
| | Lindane (HCH) | Not registered | Group 2B (1987) | Environmental | 1. Serum concentrations positively associated with prevalence of PC. | 32 | Low levels of HCH alter androgen signaling in cultured prostate cells. | 31 |
| | | | | | 2. Positively associated with PC. | 102 | Lindane induces micronuclei in cultured human prostate cells. | 30 |
| | DDT (OC) | Not registered | Group 2B (1991) | Occupational | 1. Positively associated with PC. | 102 | DDE (environmental metabolite of DDT) can bind to androgen receptor in cultured prostate cells. | 28 |
| | Dieldrin (OC) | Not registered | Group 3 (1987) | Environmental | 1. Serum concentrations positively association with prevalence of PC. | 32 | No direct evidence for PC. | — |
| | | | | | | | Induces oxidative stress and hepatocarcinogenic in mice through a nongenotoxic mode of action. | 22 |
| | | | | | | | Disrupt normal estrogen and androgen receptor function in cultured cells. | 32 |
| | Simazine (triazine) | Registered | Group 3 (1999) | Occupational | 1. Positively associated with PC. | 102 | No direct evidence for PC. | — |
| | Atrazine (triazine) | Registered | Group 3 (1999) | Occupational | 1. Not associated with PC. | 105 | No direct evidence for PC. | — |
| | Methyl bromide (methyl halide) | Registered | Group 3 (1999) | Environmental | 1. Positively associated with PC. | 35 | Mutagenic in bacterial assays. | 36 |
| | | | | | | | DNA adducts ($O^6$-methylguanine) detected in rodent forestomach and liver. | 36,37 |
| | Oxychlordane (metabolite of chlordane, an OC) | Not registered | Group 2B (2001) | Environmental | 1. No association with PC. | 38-41 | No direct evidence for PC. | — |
| | HCB (OC) | Not registered | Group 2B (2001) | Environmental | 1. No association with PC. | 40,113 | Low levels of HCB enhance androgen signaling in cultured prostate cells and mouse prostate. | 42 |
| | | | | | 2. Positively associated with PC. | 39 | | |
| | Mirex (OC) | Not registered | Group 2B (1987) | Environmental | 1. No association with PC. | 40 | No direct evidence for PC. | — |
| NHL | Lindane (HCH) | Not registered | Group 2B (1987) | Environmental | 1. Positively associated with NHL with t(14:18). | 43,52 | No direct evidence for NHL. | — |
| | | | | | 2. Positively associated with NHL. | 44 | | |
| | Dieldrin (OC) | Not registered | Group 3 (1987) | Environmental | 1. Positively associated with NHL with t(14:18). | 43,52 | No direct evidence for NHL. | — |
| | | | | | 2. Positively associated with NHL. | 54 | Increased CYP1A and 1B expression in female rat liver, kidney, and mammary tissue. | 50 |
| | | | | | 3. No association with NHL. | 58,60,126 | | |
| | Toxaphene (OC) | Not registered | Group 2B (2001) | Environmental | 1. Positively associated with NHL with t(14:18). | 43,52 | No direct evidence for NHL. | — |

TABLE 5 (Continued)

| CANCER SITE | PESTICIDE | CURRENT US EPA REGULATORY STATUS[a] | IARC CLASSIFICATION (YEAR)[b] | EXPOSURE SOURCE | EPIDEMIOLOGIC EVIDENCE | REFERENCE | TOXICOLOGICAL EVIDENCE | REFERENCE |
|---|---|---|---|---|---|---|---|---|
| | 2,4-D (phenoxy herbicide) | Registered | Group 2B (1987) | Occupational | 1. Positively associated with NHL.<br>2. No association with NHL. | 121<br>62,123,124 | No direct evidence for NHL.<br>Increased CYP1A and 1B expression in female rat liver, kidney, and mammary tissue. | —<br>50 |
| | MCPA (phenoxy herbicide) | Registered | Group 2B (1987) | Occupational | 1. Positively associated with NHL.<br>2. Positively associated with NHL among those with asthma or hay fever. | 47<br>61 | No direct evidence for NHL. | — |
| | β-Hexachlorobenzene (a metabolite of HCB; chlorinated hydrocarbon) | Not registered | Group 2B (2001) | Environmental | 1. Plasma concentrations positively associated with NHL. | 127 | No direct evidence for NHL. | — |
| | HCB (OC) | Not registered | Group 2B (2001) | Environmental | 1. No association with NHL.<br>2. Plasma concentrations positively associated with NHL. | 46,48,54,55 58,60,126<br>127 | No direct evidence for NHL. | — |
| | TCDD (OC) | Not registered | Group 1 (2012) | Occupational | 1. Positively associated with NHL mortality. | 45 | No direct evidence for NHL.<br>Increased CYP1A and 1B expression in female rat liver, kidney, and mammary tissue. | —<br>50 |
| | DDT (OC) | Not registered | Group 2B (1991) | Environmental | 1. Positively associated with NHL.<br>2. No association with NHL. | 48,55,60 126,127<br>46,54,56 59,131 | No direct evidence for NHL. | — |
| | Chlordane/oxychlordane (OC) | Not registered | Group 2B (2001) | Environmental | 1. Positively associated with NHL.<br>2. No association with NHL. | 55,60,126,127<br>48,54,58 | No direct evidence for NHL. | — |
| | Glyphosate (OP herbicide) | Registered | Not evaluated | Occupational | 1. Positively associated with NHL. | 47 | No direct evidence for NHL. | — |
| | Atrazine (triazine) | Registered | Group 3 (1999) | Occupational | 1. Superadditive effect in combination with alachlor, diazinon, and carbofuran<br>2. Positively associated with NHL with t(14:18). | 128<br>52 | No direct evidence for NHL. | — |
| | Mirex (OC) | Not registered | Group 2B (1987) | Environmental | 1.Positively associated with NHL.<br>2. No association with NHL. | 127<br>46 | No direct evidence for NHL. | — |
| Adult leukemia | Fonofos (OP) | Not registered | Not evaluated | Occupational | 1. Positively associated with leukemia. | 148 | No direct evidence for leukemia. | — |
| | Diazinon (OP) | Registered | Not evaluated | Occupational | 1. Positively associated with leukemia. | 149 | No direct evidence for leukemia. | — |
| | Metribuzin (triazinone herbicide) | Registered | Not evaluated | Occupational | 1. Positively associated with leukemia. | 150 | No direct evidence for leukemia. | — |
| | Alachlor (aniline herbicide) | Registered | Not evaluated | Occupational | 1. Positively associated in the highest-exposure category only. | 151 | No direct evidence for leukemia. | — |
| | EPTC (thiocarbamate) | Registered | Not evaluated | Occupational | 1. Positively associated in the highest-exposure category only. | 65 | No direct evidence for leukemia. | — |
| | Chlordane/heptachlor (OC) | Not registered | Group 2B (2001) | Occupational | 1. Positively associated with leukemia. | 44 | No direct evidence for leukemia. | — |
| MM | Permethrin (pyrethroid insecticide) | Registered | Group 3 (1991) | Occupational | 1. Positively associated with MM. | 156 | No direct evidence for MM. | — |
| | Captan (phthalimide fungicide) | Registered | Group 3 (1987) | Occupational | 1. Positively associated with MM. | 186 | No direct evidence for MM. | — |
| | Carbaryl (carbamate insecticide) | Registered | Group 3 (1987) | Occupational | 1. Positively associated with MM. | 186 | No direct evidence for MM. | — |

EPA indicates Environmental Protection Agency; IARC, International Agency for Research on Cancer; OP, organophosphate; PC, prostate cancer; *S. typhimurium*; *Salmonella typhimurium*; *S. cerevisae*, *Saccharomyces cerevisiae*; OC, organochlorine; HCH, hexachlorocyclohexane; DDT, dichloro-diphenyl-trichloroethane; DDE, dichlorodiphenyldichloroethylene; HCB, hexachlorobenzene; NHL, non-Hodgkin lymphoma; CYP1A/1B, cytochrome P4501A/1B; 2,4-D, 2,4-dichlorophenoxyacetic acid; MCPA, 2-methyl-4-chlorophenoxyacetic acid; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; EPTC, S-ethyl-N,N-dipropylthiocarbamate; MM, multiple myeloma.

[a]Regulation status was obtained from the Pesticide Action Network Pesticides Database (pesticideinfo.org [accessed October 20, 2012]).

[b]IARC classifications are as follows: group 1: carcinogenic to humans; group 2A, probably carcinogenic to humans; group 2B, possibly carcinogenic to humans; group 3, not classifiable regarding its carcinogenicity to humans; and group 4: probably not carcinogenic to humans.

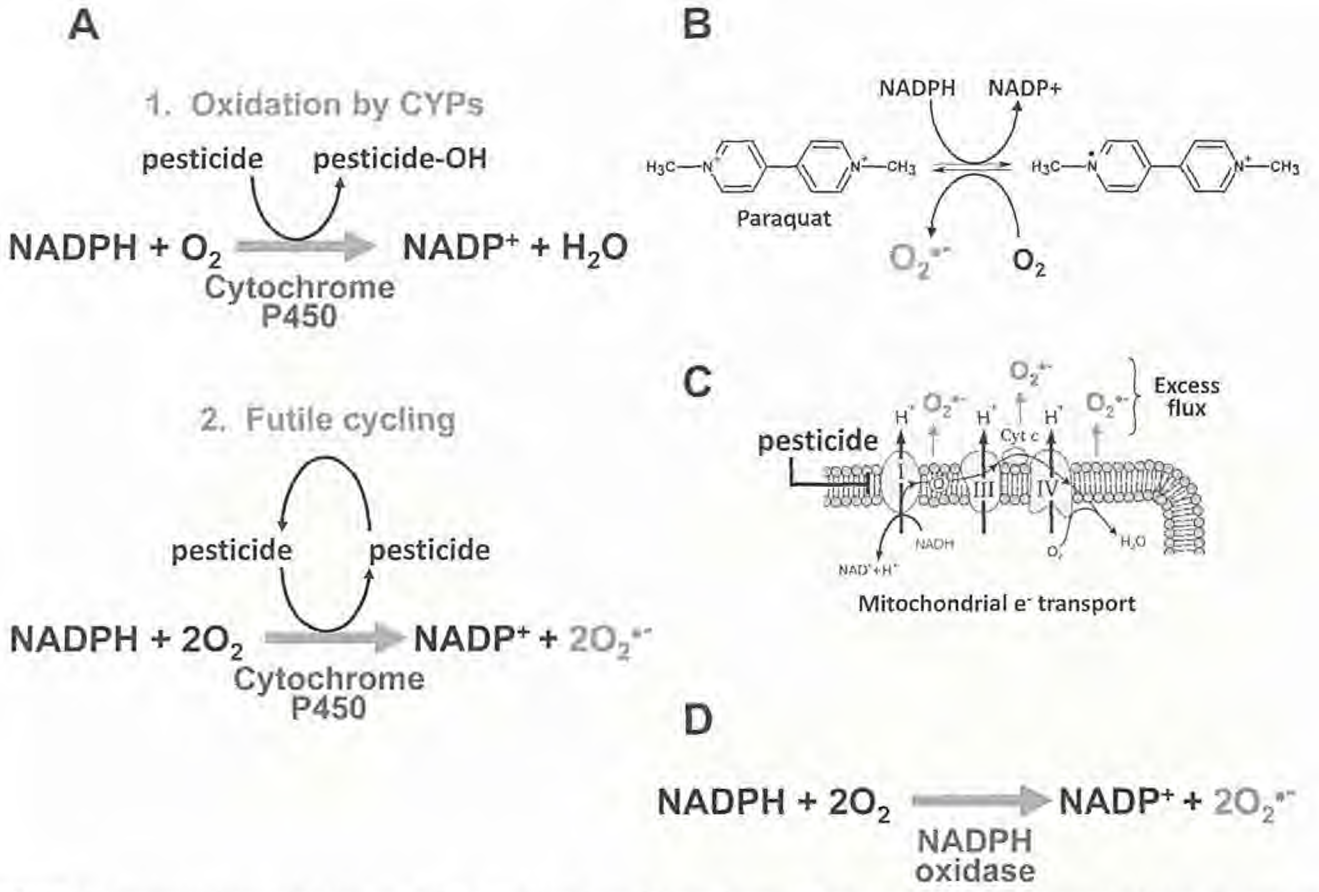


FIGURE 1. Summary of Potential Mechanisms by Which Pesticides Cause Oxidative Stress. (A) Mechanism 1 describes the normal oxidation of a pesticide catalyzed by cytochrome P450 (CYP), leading to a hydroxylated metabolite. Mechanism 2 describes futile oxidative metabolism of a pesticide by CYP450s, leading to reaction uncoupling and superoxide ($O_2$) production (eg, organochlorines, polychlorinated biphenyls cause futile cycling).[70] (B) Generation of redox-active pesticide metabolites, such as quinones or bipyridinium compounds, which undergo redox cycling leading to superoxide formation (paraquat redox cycling is shown as an example).[71] (C) Impairment of electron transport cascades in mitochondria, leading to excess superoxide flux (eg, rotenone is well known to inhibit complex I).[72] (D) Activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase by pesticides can liberate superoxide.[73] OH indicates hydroxyl radical; $H_2O$, water.

## Oxidative Stress

Exposure to pesticides may cause the net production of reactive oxygen species (ROS) in tissues when antioxidant defense mechanisms are overwhelmed. ROS are often free radicals (ie, oxygen-containing species containing an unpaired electron, such as superoxide [$O_2^{\bullet-}$] and hydroxyl radical [OH]), which renders them highly unstable in a chemical sense. There are generally 4 mechanisms by which pesticides can increase the levels of ROS, such as superoxide (Fig. 1).[70–73] However, regardless of the mechanism by which ROS are produced, a consequence of their overproduction is that they can cause extensive DNA and protein damage in cells. Although the oxidative stress hypothesis of pesticide-induced cancers is attractive, several unanswered questions remain and many details need to be filled in. For example, are tumor suppressor genes or oncogenes specifically targeted by ROS generated by pesticide exposure, thus contributing to disease? Moreover, the identification of specific biomarkers that can distinguish between pesticide exposure, oxidative stress, and disease are needed to establish the links between pesticides and disease endpoints.

## Steroid and Xenobiotic Receptors and Pesticides: Endocrine Disruption and Xenobiotic Metabolism

Although most pesticides on the market are not mutagenic in genotoxicity assays such as the Ames mutagenicity test, there is increasing epidemiological evidence of links between pesticide exposure and cancer. Therefore, it is logical to hypothesize alternative mechanisms of action by which pesticides might contribute to cancer beyond canonical DNA damage and mutagenic mechanisms. Endocrine disruptors are chemicals found in the environment (xenochemicals) that block or mimic hormone action, contributing to a wide range of pathologies. They are found in many products, including pesticides. Many xenochemicals can bind to and displace endogenous ligands for the steroid nuclear receptor family, which includes protein receptors that bind to the sex hormones estrogen

TABLE 6. Biomarkers of Exposure, Oxidative Stress, DNA Damage, and Genetic Susceptibility Relevant to Pesticide-Induced Cancers

| BIOMARKER | ANALYTE OR ENZYME ACTIVITY ASSAYED | BIOLOGICAL FLUID/SAMPLE USED | REFERENCES |
|---|---|---|---|
| Pesticide exposure | Biomonitoring of pesticides and their metabolites | Urine, serum, plasma | 76 |
| | Blood cholinesterase activity and mass spectrometric detection of OP-adducted cholinesterases | Blood | 77 |
| Oxidative stress | Malondialdehyde, F2-isoprostanes, thiobarbituric acid-reactive substances | Urine, serum, plasma | 78-81 |
| | Catalase and SOD activities | RBCs | 78 |
| | 8-oxo- or 8-OH-deoxyguanosine | Urine | 82 |
| DNA damage | Alkaline comet assay, micronuclei, chromosomal aberrations, sister chromatid exchange | Blood lymphocytes | 83-85 |
| | 8-oxo- or 8-OH-deoxyguanosine | Urine | 86,87 |
| | Apurinic/apyrimidinic endonuclease activity | Blood lymphocytes | 83 |
| | "Challenge" assay (DNA repair phenotype) | Blood lymphocytes | 88 |
| Genetic susceptibility | Paraoxonase 1 polymorphism | Lipoproteins (HDL) | 89,90 |
| | Glutathione transferase, cytochrome P450 polymorphisms | Blood lymphocytes | 23,90 |
| | Base excision repair polymorphism | Blood lymphocytes | 23 |
| | Nucleotide excision repair polymorphism | Blood lymphocytes | 91 |

OP indicates organophosphate; SOD, superoxide dismutase; RBCs, red blood cells; HDL, high-density lipoprotein.

and androgen, thus aberrantly activating receptor function and leading to changes in gene expression networks.[74,75] Inappropriate activation of androgen and estrogen receptors by pesticides is one hypothesis that might contribute to the excess cancer burden caused by pesticides, particularly the contribution of hydrophobic OCs to prostate and breast cancer risk. Therefore, although pesticides might not be genotoxic per se, their ability to bind steroid and xenobiotic receptors may cause significant alterations in gene expression programs that modulate the carcinogenic activities of common environmental pollutants.

## Biomarkers Relevant to Pesticide-Induced Cancers

Biomarkers of exposure, genetic susceptibility, and biological effects such as oxidative stress and DNA damage relevant to pesticide-induced cancers are presented in Table 6.[23,76-91] This list is not exhaustive but highlights both established markers of pesticide exposure (such as cholinesterase activity) and emerging biomarkers (such as the "challenge assay," which assesses the DNA repair capacity of cells). It should be noted that most of these biomarkers are not used in the clinic at present; however, they have usefulness in research studies that aim to determine the etiology of cancers that have been linked to agrochemical exposure.

## Cell-Based and Animal Studies to Establish Biomarkers of Pesticide Toxicity

The use of cultured animal and human cells allows high-throughput assays of pesticide toxicity to be assessed at much lower cost compared with whole-animal studies and without the ethical constraints that limit human studies. The purpose of these high-throughput cell-based assays is not to completely replace in vivo studies. Rather, it is a screening process to prioritize the environmental chemicals that will be tested in whole-animal studies. This approach has been embraced by the US EPA and National Institute of Environmental Health Sciences National Toxicology Program to establish the most important environmental chemicals to focus on and to conserve resources.[92] However, effective risk characterization of pesticides will require the integration of in vitro studies, in vivo studies, and epidemiological evidence in order to provide the best protection of public health.

In the US EPA's ToxCast research program, part of the phase 1 study examined 309 chemicals (mostly pesticides) in a high-throughput genotoxicity assay that measured the activity of the p53 transcription factor, which is activated upon DNA damage.[93] As expected, only a small fraction of the tested compounds gave positive hits (10%); a full listing of the chemicals found to be genotoxic can be found at the EPA ToxCast Web site (epa.gov/ncct/toxcast/ accessed November 27, 2012). A caveat to this study is that this high-throughput screen lacked a metabolic activation

system, which might have caused false-negative results to be reported, and positive hits were found at high concentrations of 12.5 μM or higher. With respect to the ability of pesticides to enhance ROS production in cells, high concentrations (approximately 50-100 μM) of organophosphorus pesticides were shown to induce oxidative stress and reduce the activity of antioxidant enzymes in cultured PC-12 cells, which is an in vitro model of dopaminergic neurons.[94] Evidence of DNA damage was also evident in this study. Moreover, these toxic effects could be ameliorated by vitamin E supplementation. However, except for deliberate poisoning episodes, it is highly unlikely that humans would ever be exposed to such high supraphysiological concentrations of pesticide. An earlier study, also using PC-12 cells treated with pesticides (endrin, chlordane, alachlor, fenthion, and chlorpyrifos) but at a much lower concentration (100 nM), demonstrated increased levels of DNA single-strand breaks compared with untreated cells when assessed by the alkaline elution method.[95] Cultured neuroblastoma cells (SH-SY5Y) exposed to fipronil, a phenylpyrazole insecticide, exhibited elevated amounts of ROS and were more likely to undergo apoptosis (cell suicide) compared with untreated cells.[96] Apoptosis was found to correlate with the extent of oxidative stress caused by the fipronil. Thus, these representative descriptive reports do suggest that pesticides can enhance levels of ROS in cultured cells. However, mechanistic information in this area is sparse and much more work is required.

In whole-animal studies, enhanced ROS production and lipid peroxidation in Sprague-Dawley rat liver and brain was found following treatments with the pesticides endrin, chlordane, alachlor, fenthion, or chlorpyrifos.[95,96] In addition, DNA single-strand breaks were also elevated in the livers and brains of pesticide-treated rats. Thus, oxidative stress can be elicited in cultured cells and intact animals by pesticides that have very different chemical structures. There is no chemical similarity between OPs (eg, chlorpyrifos) and OCs (eg, chlordane) and thus it is unlikely that these different classes of pesticides elicit toxicities through a common mode of action. This again highlights the complexity of studying the biological effects of pesticides and trying to find common mechanisms of action. Future studies will need to become more systematic in their approach to selecting pesticides for further mechanistic study. Moreover, animal studies occasionally give conflicting results, even for chemicals thought to exhibit well-defined mechanisms of toxicity. For example, paraquat is well known to induce oxidative stress in human lung, and an in vivo study using rats demonstrated that paraquat could significantly enhance the production of 8-OH-deoxyguanosine, particularly in the brain, lung, and heart.[97] However, in another study, no significant effects on the level of oxidized deoxyguanosine in rat liver, lung, or urine were found following a single intraperitoneal injection of 20 mg/kg of paraquat compared with untreated controls.[98] Therefore, these examples highlight the discordance that often exists between animal and human studies, and the challenge that epidemiologists and toxicologists face when trying to reconcile such conflicting reports.

## Exposure to Pesticides and Select Cancer Sites

A growing body of epidemiological, molecular biology, and toxicological evidence assessing the link (or lack of a link) between specific pesticides and specific cancers is becoming available in the scientific literature. While space limitations prevent a comprehensive review of all cancers here, the emerging multidiscipline literature is well illustrated in the case of prostate cancer, NHL, leukemia, multiple myeloma, and breast cancer. In should be noted that tumor sites in rodents following treatment with pesticides almost never concord with human epidemiological findings, which is probably due to species differences and different exposure scenarios. An additional challenge is trying to estimate the degree of caution that should be exercised when using a compound if the specific pesticide can induce tumors in nontarget tissues in cancer bioassays. For example, risk assessors would be concerned with their risk estimates if a tested pesticide could cause liver tumors in a rodent, even though it is highly unlikely that the pesticide would cause liver tumors in human epidemiologic data.

### Prostate Cancer

Prostate cancer is the most common cancer diagnosed among men in the United States, accounting for an estimated 28.5% of all cancers diagnosed in men in 2012.[99] Approximately 241,740 cases will be diagnosed in 2012, with an estimated 28,170 deaths occurring.[99] Prostate cancer ranks second after lung cancer as the underlying cause of death in men, accounting for an estimated 9.3% of all cancer deaths in men.[99] Prostate cancer risk associated with pesticides has been evaluated in over 100 occupational studies worldwide (mostly among farmers and other pesticide users). Results from meta-analyses based on these studies are consistent with a weak, positive association between farming and prostate cancer.[100] More recent epidemiologic evidence from a number of different studies now, more convincingly, shows that prostate cancer is related to pesticide use specifically.

In one of the largest prospective studies of pesticide exposures published to date, the Agricultural Health Study (AHS), which was conducted in Iowa and North Carolina, a small but significant excess prostate cancer risk was

observed among both farmers (19% excess) and commercial pesticide applicators (28% excess).[21] Among the 1962 incident prostate cancer cases that developed in the AHS cohort from 54,412 pesticide applicators that were cancer free at the start of the observation period,[21] 3 OP insecticides and an OC insecticide were significantly associated with a monotonic increase in the risk of aggressive prostate cancer as the metric of exposure increased. In this study, aggressive prostate cancer was defined as having one or more of the following tumor characteristics: distant stage, poorly differentiated grade, Gleason score of 7 or higher, or fatal prostate cancer (underlying-cause prostate cancer). The OP chemicals identified include fonofos, which is no longer registered for use in the United States, and 2 other OP insecticides currently used widely in the United States and worldwide: malathion and terbufos. However, the biological mechanisms by which these compounds might cause prostate cancer is uncertain. In vitro studies demonstrated that fonofos and terbufos were both genotoxic in *Salmonella typhimurium* and *Saccharomyces cerevisiae*,[26] although no studies have determined whether these 2 OPs can cause DNA damage in mammalian cells. In addition, the recent study by Koutros et al[25] demonstrated that a significantly increased risk of prostate cancer was observed among men with documented exposure to fonofos or aldrin and a family history of prostate cancer, whereas there was no increased risk among men without a family history. These results suggest an important genetic component contributes to the prostate cancer risk associated with selected pesticides.

Aldrin is an OC insecticide that was extensively used worldwide until 1970, when it was banned in the United States and most other countries. Animal studies suggest that OCs such as aldrin and dieldrin can induce hepatocarcinogenesis in mice through a nongenotoxic mode of action in which the slow oxidative metabolism of these compounds, or futile cycling leading to cytochrome P450 decoupling (Fig. 1A), is accompanied by increased levels of ROS, the depletion of hepatic antioxidant defenses (particularly α-tocopherol), and elevated lipid peroxidation.[22] It was also shown that dieldrin, which is structurally related to aldrin, can induce oxidative stress, resulting in the modulation of gene expression that favors the expansion of latent initiated preneoplastic cells in mouse liver.[23] However, the "tumor promoter-like" effects of OCs such as aldrin and dieldrin do not seem to occur in rat, dog, and monkey liver. Thus, because of the inconsistency in the induction of hepatocarcinomas caused by OC exposure in various species, it is unclear whether results from studies in mice can be translated to humans. Moreover, the organ specificity of cancer in the mouse model caused by OCs, such as dieldrin, does not concord with the human epidemiological findings. Furthermore, prostate tumors are not detected in mice following treatment with dieldrin.

In the AHS, significant interactions between terbufos and fonofos exposures and genetic variants on chromosome 8q24,[24] in the base excision repair pathway,[23] and in the nucleotide excision repair pathway[91] and prostate cancer risk were observed. Although more studies are needed to verify these reports, one interpretation of these findings is that DNA damage elicited by terbufos and fonofos is inefficiently repaired by individuals with DNA repair gene variants, which may contribute to disease development. An alternative explanation is that terbufos and fonofos (or their metabolites) do not directly damage DNA; however, these compounds may promote the growth of initiated cells found in genetic backgrounds of inefficient DNA repair.

In other analyses from the AHS project, occupational exposure to petroleum oil herbicides and the presence of single nucleotide polymorphisms (SNPs) in genes that encode xenobiotic metabolizing enzymes caused the risk of prostate cancer to be 3.7 times higher than in individuals who possess the same SNP but did not use petroleum oil herbicides.[101] One xenobiotic metabolizing enzymes identified with a variant allele linked to petroleum oil herbicide exposure and a higher prostate cancer risk was found in the gene that encodes microsomal epoxide hydrolase, which is an important detoxication enzyme of reactive epoxides.[27] Epoxides are chemicals that are formed via cytochrome P450-mediated monooxygenation of carcinogens, such as benzo(a)pyrene found in cigarette smoke and aflatoxin B1, which is produced by the mold *Aspergillus flavus*. Epoxides produced in vivo are often chemically unstable and can covalently modify DNA, thus forming DNA adducts with a propensity to cause mutation. Thus, components of petroleum oil herbicides may be bioactivated to reactive epoxides that can damage DNA, and this risk may be modified by SNPs in microsomal epoxide hydrolase.

In a case-control study of prostate cancer conducted on 709 consecutive cases of histologically confirmed prostate cancer identified between June 2004 and December 2007 in Guadeloupe, a French archipelago in the Caribbean, prostate cancer risk increased with increasing plasma chlordecone concentration (ie, Kepone [Allied Signal Company and LifeSciences Product Company, Hopewell, VA]).[29] Chlordecone is a chlorinated polycyclic ketone insecticide that was used extensively in the French West Indies for more than 30 years, but was banned in the United States in 1975 and worldwide in 2009. Chlordecone is an endocrine disruptor with estrogenic activity.[29] A 1.77-fold excess risk of prostate cancer was observed in individuals in the highest tertile of exposure compared with those not exposed ($P$ for trend = .002).

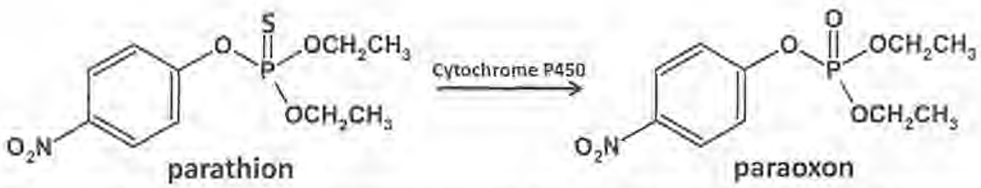


FIGURE 2. Oxidative Desulfuration of the Organophosphate Insecticide Parathion. Parathion is oxidized by cytochrome P450s to the reactive oxon metabolite paraoxon.

Stronger associations were observed among those with a positive family history of prostate cancer. Among subjects with plasma chlordecone concentrations above the limit of detection and 2 at-risk genetic polymorphisms, the risk of prostate cancer was 5.23-fold higher than for those without the exposure or the genetic polymorphism. OC pesticide exposure is often associated with an increased risk of hormone-related cancers, including prostate cancer. After adjustment for other covariates, analysis of National Health and Nutrition Examination Survey (NHANES) data showed that serum concentrations of lindane ($P$ for trend = .02), transnonachlor ($P$ for trend = .002), and dieldrin ($P$ for trend = .04) were significantly associated with the risk of prostate cancer.[32] A popular hypothesis for the toxic mechanism of hydrophobic OCs and other chlorinated pesticides is that they disrupt normal estrogen and androgen receptor functions, thus causing altered gene expression programs to be induced in cells, paving the way for malignant cell development.[42] For example, in vivo and in vitro data from mice and cultured cells suggest that low levels of hexachlorobenzene (HCB) can weakly agonize androgen action and thus enhance androgen signaling, whereas high levels of HCB interfere with androgen signaling.[31] In addition, genotoxic mechanisms may also be in play for OCs. For instance, the OC lindane was found to induce micronuclei in cultured human prostate cells following treatment at very low concentrations ($10^{-12}$-$10^{-10}$ M) for 24 hours.[30] Thus, both receptor- and genotoxic-mediated toxicities may be at work for OCs and prostate cancer.

Collectively, these studies seem to show that subpopulations with specific genetic characteristics may be particularly vulnerable to the carcinogenic effects of certain OC and OP insecticides. A recent study from Canada also found a significantly increased risk of prostate cancer caused by malathion,[102] and a recent study from the AHS found an excess risk of prostate cancer among occupational users of terbufos.[103] OPs, such as malathion, parathion, and terbufos, can be bioactivated by cytochrome P450-mediated monooxygenation reactions to yield the oxon metabolites (see Figure 2 for example of bioactivation of parathion). Oxons are exquisitely potent compounds that inhibit serine hydrolases via covalent modification of the catalytic serine residue in the enzyme active site.[104] Serine hydrolases participate in a wide variety of physiological and pathophysiological processes, including signal transduction in neural tissue, digestion, immune response, xenobiotic detoxification, and the clotting cascade. Thus, inhibition of these enzymes may lead to a variety of pathological effects. In contrast to most OP compounds, malathion is generally thought to be safe to humans because it contains 2 labile carboxylic acid ester bonds that are easily hydrolyzed by carboxylesterases, thus producing nontoxic products. Nevertheless, human are highly exposed to malathion and this compound can be converted to malaoxon in mammals, which can inhibit serine hydrolases and lead to unwanted toxicities.

A significant association between prostate cancer risk and exposure to dichlorodiphenyltrichlorethane (DDT), a chlorinated insecticide (1.68-fold excess risk for those highly exposed compared with those not exposed); simazine, a triazine herbicide (1.89-fold excess risk for those highly exposed compared with those not exposed); and lindane, a chlorinated insecticide (2.02-fold excess risk for those highly exposed compared with those not exposed) was observed among 1516 prostate cancer cases and 4994 age-matched controls in a population-based case-control study in British Columbia, Canada.[102] Atrazine, a triazine herbicide, was previously suspected of being associated with prostate cancer in a small study of pesticide manufacturing workers,[33] but was not associated with prostate cancer in a much larger evaluation done in the AHS study.[105] Atrazine is one of the most heavily used pesticides in the United States and concerns have been raised about the high levels detected in groundwater. Atrazine is rapidly metabolized to polar metabolites that are readily excreted in the urine of both rodents and humans.[106,107] However, its major quantitative metabolite, dialkylchlorotriazine, was recently shown to covalently modify proteins both in vitro and in vivo,[108] suggesting that dialkylchlorotriazine has the potential to alter protein and cellular function. In addition, there are concerns about the neuroendocrine-disrupting effects of this herbicide.[34]

In contrast to occupational settings, relatively little epidemiology has been conducted to characterize the role that environmental or residential exposures may have in the etiology of prostate cancer. The added complexity in assessing often unknown or poorly quantified environmental exposure to pesticides is a likely explanation.

While the greatest cancer risks from carcinogenic chemicals might be expected to occur among those with long-term occupational exposures, recently, male residents of California's intensely agricultural Central Valley who had ambient exposure to methyl bromide were observed to have a 1.62-fold excess risk of prostate cancer compared with those with no ambient exposure. Similar risks were not observed for simazine, maneb (a dicarbamate fungicide), or paraquat dichloride (a bipyridinium dichloride herbicide).[35] Similar to many methyl halides, methyl bromide was found to be positive in a battery of mutagenicity test systems.[36] Mutation formation is not dependent on the presence of an exogenous enzyme activation system, and thus methyl halides can directly modify DNA because of the relative ease of breaking the carbon-halide bond.[36] Indeed, methyl bromide can directly methylate calf thymus DNA in aqueous solution.[37] Moreover, methyl bromide causes aberrant DNA methylation in rats and mice in vivo,[109,110] and can generate the highly mutagenic $O^6$-methyl guanine lesion.[37,109] Glutathione conjugation of methyl bromide is the primary mechanism of its detoxification and this reaction is catalyzed by the glutathione S-transferase theta-1 (GSTT1) isoform.[111] The frequency of the GSTT1 null polymorphism in the human population is 20% for whites and 80% for Asians; these individuals do not express a functional GSTT1 enzyme.[112] Future studies that examine the null GSTT1 genotype, methyl bromide exposure, and prostate cancer risk might be worth pursuing because individuals who cannot express GSTT1 would be predicted to have a higher prostate cancer risk. However, it should be noted that methyl bromide is being phased out of use because of its ability to deplete atmospheric ozone.

It is also important to point out that prostate tissue has the ability to both activate and detoxify genotoxins and to repair any consequential DNA damage. The expression of mRNA transcripts for phase 1-activating enzymes such as cytochrome P450 1A2 (*CYP1A2*), *CYP1A1*, and *CYP1B1* has been demonstrated in human prostate.[38] This indicates that carcinogens can be metabolized in situ within the prostate tissue into reactive intermediates that damage macromolecules. Nevertheless, much more mechanistic toxicology studies need to be performed to determine whether occupational exposure to pesticides such as methyl bromide can cause prostate cancer. In light of the increasing epidemiological database linking specific pesticides with prostate cancer, it is reasonable to assume that much more will be learned in the future.

Nonoccupational exposure to OC insecticides was investigated in 4 case-control studies by measuring the concentrations of selected OC insecticides in serum,[41] adipose tissue,[39] or plasma.[40,113] Aronson et al[40] reviewed medical records for male participants aged 50 years to 80 years who visited one of 5 urology clinics in Kingston, Ontario, Canada between 1997 and 1999. Of the 7 OC insecticides assayed (*p,p'*-dichlorodiphenyldichloroethylene [DDE], *p,p'*-DDT, *trans*-nonachlor, oxychlordane, HBC, $\beta$-hexachlorocyclohexane, and mirex), none was associated with prostate cancer.[40]

Ritchie and Vial[41] also examined concentrations of OC insecticides in serum from a case-control study of men with prostate cancer in Iowa. Of the 8 analytes reported, only 3 (*p,p'*-DDE [100% cases, 99% controls], *trans*-nonachlor [98% cases, 88% controls], and oxychlordane [91% cases, 82% controls]) had detectable concentrations above 50% for both the cases and controls, but none of these 3 pesticides was clearly associated with prostate cancer. In a case-control study nested in the Japan Public Health Center-based Prospective Study,[113] 201 incident prostate cancer cases were identified through December 31, 2005. Nine analytes were assayed, including *o,p'*-DDT, *p,p'*-DDT, *p,p'*-DDE, trans-nonachlor, cis-nonachlor, oxychlordane, HCB, mirex, and $\beta$-HCH. However, none of these analytes was associated with prostate cancer.

In a small case-control study comprised of 58 cases and 23 controls, Hardell et al[39] found positive associations between prostate cancer and HCB (odds ratio [OR], 3.15; 95% confidence interval [95% CI], 1.04-9.54), *p,p'*-DDE (OR, 2.39; 95% CI, 0.81-7.09), trans-chlordane (OR, 3.49; 95% CI, 1.08-11.2), and MC6 (OR, 2.71; 95% CI, 0.87-8.42). With the exception of HCB, none of the ORs achieved statistical significance and all point estimates were imprecise due to the small number of study participants.

In summary, a number of specific pesticides have been linked to prostate cancer risk in occupational settings in an increasing number of studies. In many cases, this risk seems to be enhanced by a family history of prostate cancer. Although the enhanced prostate cancer risk may be a result of common occupational exposures among family members, there is increasing evidence that specific genetic polymorphisms in key genetic pathways may play an important etiologic role. Since the "at-risk genetic polymorphisms" are relatively common in the population, controlling the pesticide exposure rather than genetic testing may be the more desirable public health cancer control measure. Occupational exposures to some, but not all, OP and chlorinated pesticides have been associated with prostate cancer, but other pesticide categories have also been implicated in prostate cancer etiology. Studies of other pesticides with interesting preliminary gene environment analyses are now being completed.

## Non-Hodgkin Lymphoma

NHLs are a heterogeneous group of over 20 different B- and T-cell neoplasms affecting the immune system/lymphatic system and arising primarily in the lymph nodes.[114,115] Interest in the etiology of NHL has increased

because incidence rates have nearly doubled in Western countries during the interval from the 1960s through the mid-1990s. The established risk factors for NHL include genetic susceptibility and a previous history of malignant disease[116] and different immunosuppressive states including human immunodeficiency virus; autoimmune diseases such as Sjogren syndrome, systemic lupus erythematosus, rheumatoid arthritis, and psoriasis; and celiac disease.[117] Organ transplant recipients receiving immunosuppressive therapy are at a more than 100-fold excess risk of NHL.[118] However, these conditions cannot account for the increases observed.[118] Exposure to pesticides, particularly phenoxy acid herbicides, has been suggested as a cause of NHL,[119] but the evidence has been inconsistent. In Sweden, Hardell et al observed a 6-fold increased risk of NHL among those who used phenoxy acid herbicides.[120] In Kansas, Hoar et al observed a significant 2-fold increased risk among those who used phenoxy acid herbicides and the risk was highest for those who used 2,4-dichlorophenoxyacetic acid (2,4-D) for 21 days or more during the course of 1 year.[121] In Nebraska, a nonsignificant 50% excess risk of NHL was observed among users of 2,4-D, but the risk did increase to over 3-fold for those who used the herbicide 20 or more days per year.[122] Little evidence of an association between phenoxy acid herbicides and NHL was observed in New Zealand,[123] Washington state,[62] or Minnesota and Iowa.[124] A meta-analysis of 13 case-control studies published between 1993 and 2005 observed an overall significant meta-OR between occupational exposure to pesticides and NHL (OR, 1.35; 95% CI, 1.2-1.5). When observations were limited to those individuals with more than 10 years of exposure, the risk increased (OR, 1.65; 95% CI, 1.08-1.95).[125] While the meta-analysis supports the hypothesis that pesticides are associated with NHL, they lack sufficient detail about pesticide exposure and other information on risk factors for hematopoietic cancers to identify specific causes.[125]

Since the publication of the meta-analysis by Merhi et al,[125] several new population-based studies have been published suggesting that specific pesticides play an important role in NHL etiology. In a case-cohort study using a population-based prospective Danish cohort of 57,053 persons, 256 cohort members were diagnosed with NHL.[126] Eight pesticides and 10 polychlorinated biphenyls congeners were measured in adipose tissue collected at enrollment, prior to cancer onset among the 256 NHL cases and in 256 cancer-free individuals randomly selected from the cohort. A higher risk of NHL was observed among those with higher prediagnostic adipose tissue levels of DDT, cis-nonachlor, and oxychlordane than among those with lower adipose tissue levels.[126] No clear association was found between NHL and polychlorinated biphenyls. A Swedish study by Eriksson et al of 910 cases and 1016 controls observed a significant excess risk of NHL associated with the phenoxy herbicide 2-methyl-4-chlorophenoxyacetic acid. (MCPA) (OR, 2.81; 95% CI, 1.27-6.22) and glyphosate (OR, 2.02; 95% CI, 1.16-3.71). Insecticides overall demonstrated an OR of 1.28 (95% CI, 0.96-1.72) and impregnating agents (ie material used as a water-repellent and antifungal treatment of wood, brick, plaster, and roof tiles) showed an OR of 1.57 (95% CI, 1.07-2.30). 2,4-D and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) have been banned from Sweden and therefore could not be evaluated.[47] Several important observations have been made in a population-based case-control study conducted in 6 Canadian provinces including Quebec, Ontario, Manitoba, Saskatchewan, Alberta, and British Columbia with cases diagnosed between September 1, 1991 and December 31, 1994. An increased risk of 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).[52] In this same case-control study, 6 pesticides/pesticide analytes also showed a significant association with NHL (beta-hexachlorocyclohexane, *p, p'*-dichloro-DDE, HCB, mirex, oxychlordane, and transnonachlor).[127] 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). However, 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 plasma levels of HCB, beta-HCB, or DDE.[46] In yet another case-control study from the 6 Canadian provinces, the risk of NHL increased with the number of different pesticides used.[53] ORs increased even further when the analyses were restricted to "potentially carcinogenic" pesticides; one pesticide had an OR of 1.30 (95% CI, 0.90-1.88), 2 to 4 pesticides had an OR of 1.54 (95% CI, 1.11-2.12), and more than 4 pesticides had an OR of 1.94 (95% CI, 1.17-3.23). These results are somewhat similar to those reported by De Roos et al, who pooled data from 3 NHL case-control studies conducted in the 1980s in 4 American Midwestern states. A superadditive effect was observed in which atrazine amplified the risk of NHL when used in combination with several other pesticides including alachlor, diazinon, and carbofuran.[128] In yet another article from the 6 Canadian provinces study, the joint effect of pesticide exposure and immune suppression was preliminarily evaluated.[61] Study participants with asthma or hay fever had nonsignificantly elevated risks of NHL associated with the use of MCPA (OR, 2.67; 95% CI, 0.90-7.93) compared with participants without any of these conditions (OR, 0.81; 95% CI, 0.39-1.70).

Two epidemiological studies reported that the association of NHL with pesticides was largely limited to NHL cases with the t(14;18) chromosomal translocation.[43,52] In the study by Schroeder et al conducted in Iowa and Minnesota, patients with NHL with the t(14:18) translocation were found to have significantly elevated levels of dieldrin (OR, 3.7; 95% CI, 1.9-7.0), lindane (OR, 2.3; 95% CI, 1.3-3.9), toxaphene (OR, 3.0; 95% CI, 1.5-6.1), and atrazine (OR, 1.7; 95% CI, 1.0-2.8).[52] In the study by Chiu et al conducted in Nebraska, farmers diagnosed with NHL with a t(14:18) translocation were found to have significantly elevated levels of dieldrin (OR, 2.4; 95% CI, 0.8-7.0), toxaphene (OR, 3.2; 95% CI, 0.8-12.5), and lindane (OR, 3.5; 95% CI, 1.4-8.4) compared with nonfarmers. In the prospective AHS, lindane use was associated with a significantly elevated risk of NHL.[44] In a Dutch cohort of workers involved in the manufacturing of chlorophenoxy herbicides, predicted TCDD levels were associated with a significant increase in mortality from NHL (OR, 1.36; 95% CI, 1.06-1.74).[45]

Cytogenetic and molecular studies of individuals exposed to a number of pesticides, such as lindane and 2,4-D, are beginning to reveal a role of pesticides in the induction of chromosomal rearrangements, particularly the t(14;18) translocation that occurs with high frequency in patients with NHL.[57] This translocation appears to be one step in the progression of a normal cell to a cancer cell; however, it is unclear whether pesticides (or other toxicants) cause the t(14;18) translocation or whether they are generated during the course of malignant transformation as a result of the developing genomic instability that arises during disease progression. Polymerase chain reaction-based quantitation of the t(14;18) translocation frequency in peripheral blood lymphocytes, as described by Fuscoe,[129] might be a promising biomarker to use in studies of pesticide-exposed populations. A direct connection between agricultural pesticide use, frequency of the t(14;18) translocation in the blood, and malignant progression to follicular lymphoma has been observed in a prospective cohort study of farmers.[130] This study indicated that the t(14;18) translocation appeared to be an early event in NHL and suggested a molecular connection between agricultural pesticides, the t(14;18) translocation frequency in the blood, and clonal progression, but links to specific pesticides were not possible. However, the mechanistic molecular connection between pesticides and the t(14;18) translocation is still unclear and establishing this link will require much more work. Nevertheless, the higher prevalence of the t(14;18) translocation in pesticide-exposed workers compared with controls is a provocative finding and the replication of this finding in another pesticide-exposed population will be an important follow-up study. Moreover, for the t(14;18) translocation to be used as a biomarker, these findings would ideally be validated in an animal model treated with pesticides. This would provide an even stronger case for studying this biomarker in human populations.

We identified 15 studies that reported on nonoccupational exposure to pesticides and NHL. The vast majority of these studies focused on OC insecticides (11 of 15 studies) and used serum,[48,58,131] plasma,[46,54-56,59] or adipose tissue[53,60,126] concentrations of the OC compounds as the estimate of exposure. Of these 11 studies, 7 measured chlordane/heptachlor or their metabolite (eg, oxychlordane, heptachlor epoxide) concentrations. Four studies[55,60,126,127] observed positive associations between chlordanes and NHL, whereas the 3 other studies did not observe an association.[48,54,58]

In addition to oxychlordane and related compounds (eg, heptachlor), 10 of these studies examined the association between concentrations of DDT or its metabolite, DDE, and NHL. Five studies[48,55,60,126,127] demonstrated either positive or suggestive associations, whereas the other 5 studies[46,54,56,59,131] did not observe an association between DDT or DDE and NHL.

While a number of other OC insecticides were measured in these studies, coverage of specific insecticides was less frequent. For instance, only one study[127] assayed for mirex, finding a positive association (OR, 1.44; 95% CI, 1.08-1.92). Conversely, HCB was assessed in 8 of these studies,[46,48,54,55,58,60,126,127] of which only one observed an association. $\beta$-Hexachlorocyclohexane concentrations were positively associated with NHL in only 2[52,123] of the 6 studies that measured it in either plasma, serum, or adipose tissue. Dieldrin levels were assayed in 4 studies,[54,58,60,126] with only one[54] finding evidence of a positive association with NHL.

In summary, NHL is not one disease but many related diseases with seemingly different etiologies. Few studies of pesticides have been large enough to evaluate the potential link between NHL subtypes and specific pesticide exposures. Nonetheless, new evidence linking NHL with specific chlorinated pesticide use and 2 studies linking the number of different pesticides used with NHL give further support to earlier findings suggesting that specific pesticides are etiologically linked to NHL. Preliminary evidence suggests asthma, allergies, or asthma and allergies and hay fever combined with the use of specific pesticides (eg, MCPA) may enhance the risk of NHL. Although it is possible that t(14;18) translocations are an initiating event in a causative cascade leading to an NHL subtype, follicular lymphoma, much more work needs to be done to establish this. Nevertheless, it has been shown that NHL subtypes with t(14;18) translocations are associated with the chlorinated insecticides dieldrin, lindane, and toxaphene and the triazine herbicide atrazine. Lindane also has been

observed to be directly associated with NHL in a large prospective study performed in the United States. In yet another large case-control study in Sweden, the authors linked the use of glyphosate and MCPA to NHL. Although the epidemiological evidence for certain pesticides and NHL is growing, little is known about the biological/toxicological mechanisms by which these compounds may be contributing to this disease (Table 5).

## Leukemia

### *Childhood Leukemia*

Acute lymphocytic leukemia comprises about 80% of all childhood leukemia cases, while acute myeloid leukemia comprises most of the remaining 20%.[49] Male children have a higher incidence of leukemia overall compared with female children. It is estimated that less than 10% of childhood leukemia cases have an identified etiology. Established associations include ionizing radiation, Down syndrome, and other genetic syndromes.[132] In the United States and Europe, there is concern that overall rates of childhood cancer have been increasing since 1970.[133] Early life exposures to pesticides are suspected to be responsible for some of these childhood leukemias. A number of recent systematic reviews of the etiological literature[134-137] reached a somewhat similar conclusion (ie, the current literature is limited). Chief among these limitations are that exposure measures relying on substitutes for information about parental pesticide use itself such as in farm-related activities or crops produced has proven to be inadequate; case-control studies tended to suffer from at least some case-recall bias; cohort studies have been too small to generate a sufficient number of exposed cases, thereby mitigating firm etiological conclusions; many available studies (both case-control and cohort) were too small to reliably evaluate leukemia subtypes and all were too small to identify specific pesticides that might be linked to childhood leukemia; and controlling for potentially confounding factors is difficult when so little is known about the etiology of childhood leukemia generally. Nonetheless, a number of important observations have been made in meta-analyses associated with these reviews (ie, an excess risk of overall leukemia is observed with maternal pesticide exposure from home and garden use[135] or maternal occupational exposure but not with paternal occupational pesticide exposure).[136,137] Meta-analyses of childhood leukemia were elevated for prenatal maternal occupational exposure to both insecticides and herbicides.[136] While elevated risks of childhood leukemia were also observed in meta-analyses of children living in homes where professional pesticide applications were done before pregnancy, during pregnancy, and during the first 3 years of the child's life,[134] Vinson et al observed the maternal-associated leukemia risks to be particularly high for exposures that took place prior to birth.[135] While data are limited, it seems both acute lymphocytic leukemia and acute myeloid leukemia in children may be linked to pesticide exposure.[136] Excess childhood leukemia risks did not appear to be related to the proximity of a home to a farm,[137] nor to carpet-tested levels of chlordane, DDT, DDE, methoxychlor, or pentachlorophenol.[138]

Experimental studies in animal models support the biological plausibility of a link between maternal pesticide exposure and leukemia because the exposure of pregnant females to carcinogens can produce cancer in offspring.[139] Transplacental exposure to select fungicides produced lymphomas in mice.[140] Furthermore, the role of epigenetics in germ cell genomic reprogramming has gained increased attention since it was shown that exposure of gestating female rats during the period of gonadal development to either vinclozolin (a fungicide) or methoxychlor (an insecticide) induced elevated incidences of male infertility and altered sperm quality in offspring up to 4 generations.[141,142] Moreover, prostate lesions, altered gene expression patterns, and cancer were detected in some adult progeny.[142] These provocative findings have caused renewed interest in developmental and reproductive toxicities, such as childhood leukemias, caused by environmental chemicals. At this point, work in this area is in a nascent stage of development and much more needs to be done.

Linking specific pesticides to childhood leukemia would most likely lead to the cancelation of registration of that pesticide in the United States and many other nations. Since such a specific link has not yet been made, prudent public health policy would dictate limiting maternal exposure to pesticides prenatally and during early child- hood and limiting direct childhood exposure whenever possible.

### *Adult Leukemia*

Adult-onset leukemias are a heterogeneous category of hematopoietic malignancies, including chronic and acute subtypes that have different etiologies. Causal associations with leukemia have been demonstrated for 3 agents: benzene,[63] formaldehyde,[64] and ionizing radiation.[143] Other suspected occupational causes include pesticides, infectious agents, electromagnetic fields, and solvents and aromatic hydrocarbons.[144]

A meta-analysis of 14 cohort studies of workers in plants manufacturing pesticides showed a meta-rate ratio of 1.43 (95% CI, 1.05-1.94) for leukemia.[145] A recent meta-analysis of 13 cases and controls examining the association between occupational exposures and hematopoietic cancers observed an OR of 1.35 (95% CI, 0.9-2.0).[125] Epidemiological evidence was insufficient to permit the identification of a specific pesticide in either of these meta-analyses.

OPs have been associated with leukemia and other immunologically related cancers in the epidemiological literature.[65,146-151] The leukemogenic effects of OPs may be related to immune function perturbation. In the AHS, leukemia risk was elevated for the high category of intensity-weight exposure-days for the OP insecticide fonofos (relative risk [RR], 2.67; 95% CI, 1.06-6.70 [*P* value for trend = .04])[148] and diazinon was associated with leukemia (RR, 3.36; 95% CI, 1.08-10.49 [*P* value for trend = 0.026]).[149] A positive association with leukemia was also observed for several herbicides including metribuzin, a selective triazinone herbicide (RR, 2.42; 95% CI, 0.82-7.19 [*P* value for trend = .08]),[150] and the use of the herbicides alachlor[151] and S-ethyl-N,N-dipropylthiocarbamate (EPTC),[65] although the risk associated with both of these herbicides was limited to the highest exposure group and thus further follow-up will be necessary.

The IARC has judged that the weight of evidence suggests that the OC insecticides chlordane, heptachlor, DDT, and toxaphene are possible human carcinogens, whereas other OCs are not classifiable as to their carcinogenicity.[66] In the AHS, chemical-specific associations with leukemia were observed for chlordane/heptachlor (RR, 2.1 [95% CI, 1.1-3.9]), which are structurally related compounds that occur together in technical-grade products of each chemical.[44]

In a prospective study of peripheral blood obtained up to 77 months before a diagnosis of chronic lymphocytic leukemia (CLL) was made, prediagnostic B-cell clones were present in 44 of 45 patients with CLL.[67] Use of B-cell clones as prediagnostic markers of CLL may be a valuable tool in evaluating the link between specific pesticides and CLL.

While the evidence linking pesticide exposure to leukemia is abundant, the evidence linking a specific pesticide to a specific leukemia subtype, which could be used to more stringently regulate use of the pesticide or cancel its registration, is largely nonexistent. Recent epidemiological evidence linking specific pesticides to leukemia has established hypotheses that need to be evaluated in other studies (eg, the associations between leukemia overall and diazinon [an OP insecticide currently in widespread use] and several OC insecticides no longer in use in the United States or other developed countries are of particular interest).[65,66,146-151] Linking leukemia to specific pesticides that are used at high levels occupationally should help to identify the chemical agents responsible for childhood cancers as well. The use of preclinical biomarkers (eg, monoclonal B-cell lymphocytosis) to study the etiology of CLL may be a powerful approach for this leukemia subtype.[67] In addition, it has been shown that arylhydrocarbon receptor activation and cyclooxygenase-2 overexpression in lymphoma cell lines lead to resistance to apoptosis,[152] which might be relevant for the development of lymphomas in vivo caused by pesticide exposures.

## Multiple Myeloma

Multiple myeloma is a malignancy of the blood, characterized by a clonal expansion of plasma cells and the production of a monoclonal immunoprotein that can be found in the blood or urine. Clonal expansion of plasma cells is accompanied by osteolytic bone destruction, renal failure, anemia, and hypercalcemia.[153] Following a diagnosis of multiple myeloma, the median length of survival is approximately 3 years. Approximately 21,700 new cases are diagnosed annually.[99] Incidence among blacks is twice that among whites but the survival among blacks is significantly better compared with whites.[154] The underlying cause of multiple myeloma is unknown.[153]

A systematic review of case-control studies of the role of occupational exposure to pesticides in the development of multiple myeloma showed a pooled OR for working farmers of 1.39 (95% CI, 1.18-1.65) and an OR for pesticide exposure of 1.47 (95% CI, 1.11-1.94). For working on a farm for more than 10 years, the OR was 1.87 (95% CI, 1.15-3.16).[125] None of these studies, however, was able to identify a specific exposure that was associated with multiple myeloma. In the AHS, an excess risk of multiple myeloma was observed in the cohort.[155] In a follow-up study, a 1.42-fold (95% CI, 1.00-fold to 1.81-fold) risk of multiple myeloma was observed among cohort members in North Carolina compared with the rest of the state, but a similar excess risk was not observed in Iowa.[21] The cause of this excess could not yet be explained, but a separate analysis of the AHS cohort observed a statistically significant risk of multiple myeloma among pesticide applicators in the highest exposure group for the insecticide permethrin (RR, 5.72; 95% CI, 2.76-11.87 [*P* value for trend = .01]) compared with never-users.[156] A cautious interpretation of these results is warranted because the analysis was driven by only 10 exposed cases in the highest exposure group. Positive associations between the fungicide captan (OR, 2.35; 95% CI, 1.11-3.27) and the insecticide carbaryl (OR, 1.89; 95% CI, 0.98-3.67) and multiple myeloma were observed in a recent Canadian population-based case-control study conducted among men in 6 Canadian provinces (ie, Quebec, Ontario, Manitoba, Saskatchewan, Alberta, and British Columbia).[186] The study consisted of 342 multiple myeloma cases and 1506 controls.

Recent data have shown that multiple myeloma is consistently preceded by monoclonal gammopathy of undetermined significance (MGUS).[157] MGUS is a premalignant plasma cell proliferative disorder without

symptoms or evidence of end-organ damage, but cases do have a lifelong 1% annual risk of progression to multiple myeloma.

In the AHS cohort, the age-adjusted prevalence of MGUS was 1.9-fold (95% CI, 1.3-fold to 2.7-fold) higher among male pesticide applicators compared with men from Olmsted County, Minnesota.[158] In the AHS cohort, a 5.6-fold (95% CI, 1.9-fold to 16.6-fold), 3.9-fold (95% CI, 1.5-fold to 10.0- fold), and 2.4-fold (95% CI, 1.1-fold to 5.3-fold) increased risk of MGUS was observed among users of the chlorinated insecticide dieldrin, the fumigant mixture carbon tetrachloride/carbon disulfide, and the fungicide chlorothalonil, respectively. A previous AHS examination determined that a relationship between exposure and disease is not likely confounded by farming or nonfarming activities.[68]

In summary, although the evidence linking pesticide exposure to multiple myeloma has increased in recent years, few studies have been able to assess the link between specific pesticides and multiple myeloma or its precursor MGUS. It is therefore not surprising that we do not yet observe consistent associations. Clearly, additional epidemiological evidence is needed to test the hypothesis that specific pesticides are positively associated with multiple myeloma before firm conclusions can be reached. The use of preclinical biomarkers of multiple myeloma (ie, MGUS) may be a powerful approach to evaluate these etiological hypotheses.

## Nonoccupational OC Insecticide Exposure and Breast Cancer

Breast cancer is the most common cancer among women in the United States, accounting for an estimated 226,870 cases in 2012 and 39,510 deaths.[99] Male breast cancer is relatively rare, with an estimated 2190 cases in 2012 and 410 deaths.[99] Epidemiologic studies of occupational pesticide exposure and breast cancer risk are quite limited. Conversely, the open literature is replete with epidemiologic studies that have investigated nonoccupational exposure to OC compounds, including OC insecticides. Given this paucity in occupational studies, we will focus only on the nonoccupational studies of OC insecticides and breast cancer.

In 1993, Wolff et al[159] published a report observing that the risk of breast cancer was higher among women with high serum concentrations of DDE, the major metabolite of DDT, compared with women with low levels. Since then, a substantial number of epidemiologic studies have been conducted and published investigating this hypothesis.

In 2002, Calle et al[160] published a review article evaluating the then-current literature and concluded that: "At present, there is substantial epidemiologic evidence regarding the possible association between organochlorines (as measured in blood and adipose tissue) and the risk of breast cancer. The evidence does not support an association."[160]

Lopez-Cervantes et al[161] arrived at a similar conclusion using meta-analysis to review the epidemiologic evidence for tissue DDE concentrations and breast cancer. In our current review, we update the literature since 2002. We identified 11 published studies[32,162-171] that reported on associations between measured serum, plasma, or adipose tissue concentrations of OC insecticides and breast cancer, which were not included in either the review by Calle et al or Lopez-Cervantes et al.[160,161] Two studies[162,167] were excluded from our review because risk estimates (eg, ORs) were not reported. A third study[32] was excluded because the case definition included prevalent breast cancer. Of the remaining 8 studies, the results were mixed. While 4 studies[163,165,169,170] did not observe an association between OC concentrations, the other 4 studies[164,166,168,171] did observe positive associations.

However, an important caveat to this conclusion remains largely unexplored: the importance that age at exposure may have in breast cancer development. Lopez-Cervantes et al point out that there is a paucity of evidence regarding exposure at critical time periods.[161] Exposures that occur during early life and adolescence are hypothesized to have etiologic importance for breast cancer.[172,173] During mammary gland development, breast epithelium may be particularly susceptible to environmental carcinogens.[174,175] For instance, exposure to ionizing radiation at an early age confers an increased risk of developing breast cancer as compared with exposure that occurs at later ages.[176,177] Regarding early-life exposure to OC insecticides and breast cancer risk, Cohn et al[168] conducted a nested case-control study among a cohort of female members of the Kaiser Permanente Health Plan in Oakland, California and used stored blood samples that were collected between 1959 and 1967 to assay for serum *p,p'*-DDT. They found that that increasing serum *p,p'*-DDT concentrations were positively associated with breast cancer risk, but only among those women exposed prior to 14 years of age.[168] Caution is warranted in interpreting the results for this one study. While the unique circumstances surrounding the study permitted the investigation of early-life exposure to DDT and future breast cancer risk during a time when DDT was actively being used in the United States, replication will be difficult, as the authors note. Overall, these additional studies do not provide compelling evidence to revise the overall conclusion of the previous reviews that the evidence does not support an association between OC insecticides and breast cancer risk.

While the number of epidemiologic studies that have investigated OC compounds is substantial, few epidemiologic studies have been conducted to investigate

non-OC pesticides and breast cancer risk. We identified just 8 published studies that reported on nonoccupational and non-OC insecticide exposure and breast cancer.[178-185] Of these 8 reports, 4 were case-control studies[181-184] that lacked pesticide-specific exposure information and the fourth was an ecologic study in design.[185] The 3 remaining studies[178-180] assessed exposure to a number of specific pesticides, but overall, these studies are too few to provide a meaningfully review.

## Conclusions

Assessing the magnitude of the cancer risk from pesticide exposures in the workplace can be difficult because exposures are usually intermittent, pesticide metabolites have a short half-life, and biomarkers of exposure are often nonspecific to the exposure. Assessing cancer risk from pesticide exposures in the general environment is even more challenging. Nonetheless, the available scientific evidence does strongly suggest that pesticides do cause cancer in both those who use the pesticides directly and those who are exposed because of applications others make. The problem may well be more extreme in developing counties where regulatory controls are weaker or nonexistent.

The mechanisms by which pesticides cause cancer are probably numerous, but are incompletely understood. Cancer risk does not seem to be limited to one functional class of pesticides (eg, herbicide, insecticide, or fungicide) or to one chemical class (eg, OCs, OPs, or triazines). Direct genotoxicity is an important mechanism but many nongenotoxic mechanisms seem to be operating as well. Genetic susceptibility to the carcinogenic effects of some pesticides also appears to be an important aspect of the disease mechanism. The genetic susceptibilities that have been identified to date are common to large segments of the population and therefore do not lend themselves to controlling risk through the identification of susceptible individuals. Controlling exposures is the key to limiting cancer risk. Well-designed epidemiological studies with molecular components will help to identify human carcinogens currently on the market, while an increased understanding of the underlying mechanisms of carcinogenesis will help prevent the introduction of new carcinogens to the marketplace.

Until a more complete understanding of pesticide carcinogenesis is achieved, balancing the potential, albeit uncertain, carcinogenic risk with the health benefits derived from the use of pesticides that can mitigate disease-carrying pests or increase fruit and vegetable production will remain a public health and clinical quandary. In the meantime, health care providers should emphasize the importance of minimizing personal exposures to all pesticides to control cancer risk. ■

## References

1. Fenner-Crisp PE. Risk assessment and risk management: the regulatory process. In: Kriger R, ed. Handbook of Pesticide Toxicology. 2nd ed. San Diego, CA: Academic Press; 2001:681-690.
2. International Agency for Research on Cancer. Occupational Exposures in Insecticide Applications, and Some Pesticides. IARC Monograph on the Evaluation of Carcinogenic Risk to Humans. Vol 53. Lyon, France: IARC; 1991.
3. National Academy of Sciences. Pesticide in the Diets of Infants and Children. Washington DC: National Academic Press; 1993.
4. World Wildlife Fund. Pesticide Reduction Programmes in Denmark, the Netherlands and Sweden. Gland, Switzerland: World Wildlife Fund International; 1992.
5. US Environmental Protection Agency Office of Pesticide Programs. Pesticide Industry Sales and Usage. 2006 and 2007 Market Estimates. Washington, DC: US Environmental Protection Agency; 2007. epa.gov/pesticides/pestsales/07pestsales/usage 2007_2.htm. Accessed November 27, 2012.
6. Centers for Disease Control and Prevention. Fourth National Report Human Exposure to Environmental Chemicals. Atlanta, GA: Centers for Disease Control and Prevention; 2009. cdc.gov/exposure report/pdf/fourthreport.pdf. Accessed November 27, 2012.
7. Curl CL, Fenske RA, Kissel JC, et al. Evaluation of take-home organophosphorous pesticide exposure among agricultural workers and their children. *Environ Health Perspect*. 2002;110:A787-A792.
8. Lu C, Fenske RA, Simcox NJ, Kalman D. Pesticide exposure of children in an agricultural community: evidence of household proximity to farmland and take home exposure pathways. *Environ Res*. 2000;84: 290-302.
9. Kushi LH, Doyle C, McCollough M, et al; American Cancer Society 2010 Nutrition and Physical Activity Guidelines Advisory Committee. American Cancer Society Guidelines on nutrition and physical activity for cancer prevention: reducing the risk of cancer with healthy food choices and physical activity. *CA Cancer J Clin*. 2012;62:30-67.
10. Curwin BD, Hein MJ, Sanderson WT, et al. Urinary pesticide concentrations among children, mothers and fathers living in farm and non-farm households in Iowa. *Ann Occup Hyg*. 2007;51:53-65.
11. Lambert WE, Lasarev M, Muniz J, et al. Variation in organophosphate pesticide metabolites in urine of children living in agricultural communities. *Environ Health Perspect*. 2005;113:504-508.
12. Aprea C, Strambi M, Novelli MT, Lunghini L, Bozzi N. Biologic monitoring of exposure to organphosphorou- pesticides in 195 Italian children. *Environ Health Perspect*. 2000;108:521-525.
13. Krieger RI, Bernard CE, Dinoff TM, Ross JH, Williams RL. Biomonitoring of persons exposed to insecticides used in residences. *Ann Occup Hyg*. 2001;45(suppl 1): S143-S153.
14. PHED Surrogate Exposure Guide. Estimations of Worker Exposure. The Pesticide Handler Exposure Database. Version 1.1. Washington, DC: US Environmental Protection Agency; 1997.
15. Thongsinthusak T, Ross JH, Saiz SG, Krieger RI. Estimation of dermal absorption using the exponential saturation model. *Reg Toxicol Pharmacol*. 1999;29:37-43.
16. Ross JH, Driver JH, Cochran RC, Thongsinthusak T, Krieger RI. Could pesticide toxicology studies be more relevant to occupational risk assessment? *Ann Occup Hyg*. 2001;45(suppl 1):S5-S17.
17. Thomas KW, Dosemeci M, Coble JB, et al. Assessment of a pesticide exposure intensity algorithm in the agricultural health study. *J Expo Sci Environ Epidemiol*. 2010; 20:559-569.
18. EUROPOEM. The Development, Maintenance and Dissemination of a European Predictive Operator Exposure Model (EUROPOEM) Database. Final Report. AIR3 CT93-1370. Carshalton, UK: BIBRA International; 1997.
19. Casida JE, Quistad GB. Golden age of insecticide research: past, present, or future? *Annu Rev Entomol*. 1998;43:1-16.

20. Clewell HJ, Tan YM, Campbell JL, Andersen ME. Quantitative interpretation of human biomonitoring data. *Toxicol Appl Pharmacol*. 2008;231:123-133.

21. Koutros S, Alavanja MCR, Lubin JH, et al. An update of cancer incidence in the Agricultural Health Study. *J Occup Environ Med*. 2010;52:1098-1105.

22. Stevenson DE, Walborg EF Jr, North DW, et al. Monograph: reassessment of human cancer risk of aldrin/dieldrin. *Toxicol Lett*. 1999;109:123-186.

23. Barry KH, Koutros S, Berndt SI, et al. Genetic variation in base excision repair pathway genes, pesticide exposure, and prostate cancer risk. *Environ Health Perspect*. 2011;119:1726-1732.

24. Koutros S, Beane Freeman LE, Berndt SI, et al. Pesticide use modifies the association between genetic variants on chromosome 8q24 and prostate cancer. *Cancer Res*. 2010;70:9224-9233.

25. Koutros S, Beane Freeman LE, Lubin JH, et al. Risk of total and aggressive prostate cancer and pesticide use in the Agricultural Health Study. *Am J Epidemiology*. 21 Nov 2012 [Epub ahead of print].

26. Gentile JM, Gentile GJ, Bultman J, Sechrest R, Wagner ED, Plewa MJ. An evaluation of the genotoxic properties of insecticides following plant and animal activation. *Mutat Res*. 1982;101:19-29.

27. Decker M, Arand M, Cronin A. Mammalian epoxide hydrolases in xenobiotic metabolism and signalling. *Arch Toxicol*. 2009;83:297-318.

28. Schrader TJ, Cooke GM. Examination of selected food additives and organochlorine food contaminants for androgenic activity in vitro. *Toxicol Sci*. 2000;53:278-288.

29. Multigner L, Ndong JR, Giusti A, et al. Chlordecone exposure and risk of prostate cancer. *J Clin Oncol*. 2010;28:3457-3462.

30. Kalantzi OI, Hewitt R, Ford KJ, et al. Low dose induction of micronuclei by lindane. *Carcinogenesis*. 2004;25:613-622.

31. Ralph JL, Orgebin-Crist MC, Lareyre JJ, Nelson CC. Disruption of androgen regulation in the prostate by the environmental contaminant hexachlorobenzene. *Environ Health Perspect*. 2003;111:461-466.

32. Xu X, Dailey AB, Talbott EO, Ilacqua VA, Kearney G, Asal NR. Associations of serum concentrations of organochlorine pesticides with breast cancer and prostate cancer in U.S. adults. *Environ Health Perspect*. 2010;118:60-66.

33. MacLennan PA, Delzell E, Salhiakumar N, et al. Cancer incidence among triazine herbicide manufacturing workers. *J Occup Environ Med*. 2002;44:1048-1058.

34. Fraites MJ, Cooper RL, Buckalew A, Jayaraman S, Mills L, Laws SC. Characterization of the hypothalamic-pituitary-adrenal axis response to atrazine and metabolites in the female rat. *Toxicol Sci*. 2009;112:88-99.

35. Cockburn M, Mill P, Zhang X, Zadnick J, Goldberg D, Ritz B. Prostate cancer and ambient pesticide exposure in agriculturally intensive areas in California. *Am J Epidemiol*. 2011;173:1280-1288.

36. Bolt HM, Gansewendt B. Mechanisms of carcinogenicity of methyl halides. *Crit Rev Toxicol*. 1993;23:237-253.

37. Starratt AN, Bond EJ. In vitro methylation of DNA by the fumigant methyl bromide. *J Environ Sci Health B*. 1988;23:513-524.

38. Williams JA, Martin FL, Muir GH, Hewer A, Grover PL, Phillips DH. Metabolic activation of carcinogens and expression of various cytochromes P450 in human prostate tissue. *Carcinogenesis*. 2000;21:1683-1689.

39. Hardell L, Andersson SO, Carlberg M, et al. Adipose tissue concentrations of persistent organic pollutants and the risk of prostate cancer. *J Occup Environ Med*. 2006;48:700-707.

40. Aronson KJ, Wilson JW, Hamel M, et al. Plasma organochlorine levels and prostate cancer risk. *J Expo Sci Environ Epidemiol*. 2010;20:434-445.

41. Ritchie JM, Vial SL, Fuortes LJ, Guo H, Reedy VE, Smith EM. Organochlorines and risk of prostate cancer. *J Occup Environ Med*. 2003;45:692-702.

42. Shanle EK, Xu W. Endocrine disrupting chemicals targeting estrogen receptor signaling: identification and mechanisms of action. *Chem Res Toxicol*. 2011;24:6-19.

43. Chiu BC, Dave BJ, Blair A, Gapstur SM, Zahm SH, Weisenberger DD. Agricultural pesticide use and risk of t(14;18)-defined subtypes of non-Hodgkin lymphoma. *Blood*. 2006;108:1363-1369.

44. Purdue MP, Hoppin JA, Blair A, Dosemeci M, Alavanja MC. Occupational exposure to organochlorine insecticides and cancer incidence in the Agricultural Health Study. *Int J Cancer*. 2007;120:642-649.

45. Boers D, Portengen L, Turner WE, Bueno-de-Mesquita HB, Heederick D, Vermeulen R. Plasma dioxin levels and cause-specific mortality in an occupational cohort of workers exposed to chlorphenoxy herbicides, chlorphenols and contaminants. *Occup Environ Med*. 2012;69:113-118.

46. Cocco P, Brennan P, Ibba A, et al. Plasma polychlorobiphenyl and organochlorine pesticide level and risk of major lymphoma subtypes. *Occup Environ Med*. 2008;65:132-140.

47. Eriksson M, Hardell L, Carlberg M, Akerman M. Pesticide exposure as risk factor for non-Hodgkin lymphoma including histopathological subgroup analysis. *Int J Cancer*. 2008;123:1657-1663.

48. Viel JF, Floret N, Deconinck E, Focant JF, DePauw E, Cahn JY. Increased risk of non-Hodgkin lymphoma and serum organochlorine concentrations among neighbors of a municipal solid waste incinerator. *Environ Int*. 2011;37:449-453.

49. Howlader N, Noone AM, Krapcho M, et al., (eds). *SEER Cancer Statistics Review, 1975-2009 (Vintage 2009 Populations)*. Bethesda, MD: National Cancer Institute. seer.cancer.gov/csr/1975_2009_pops09/, based on November 2011 SEER data submission, posted to the SEER web site, 2012. Accessed November 27, 2012.

50. Badawi AF, Cavalieri EL, Rogan EG. Effect of chlorinated hydrocarbons on expression of cytochrome P450 1A1, 1A2 and 1B1 and 2- and 4-hydroxylation of 17beta-estradiol in female Sprague-Dawley rats. *Carcinogenesis*. 2000;21:1593-1599.

51. McDuffie HH, Pahwa P, Karunanayake CP, Spinelli JJ, Dosman JA. Clustering of cancer among families of cases with Hodgkin Lymphoma (HL), Multiple Myeloma (MM), Soft Tissue Sarcoma (STS) and control subjects. *BMC Cancer*. 2009;9:70.

52. Schroeder JC, Olshan AF, Baric A, et al. Agricultural risk factors for t(14;18) subtypes of non-Hodgkin's lymphoma. *Epidemiology*. 2001;12:701-709.

53. Hohenadel K, Harris SA, McLaughlin JR, et al. Exposure to multiple pesticides and risk of non-Hodgkin lymphoma in men from six Canadian provinces. *Int J Environ Res Public Health*. 2011;8:2320-2330.

54. De Roos AJ, Hartge P, Lubin JH, et al. Persistent organochlorine chemicals in plasma and risk of non-Hodgkin's lymphoma. *Cancer Res*. 2005;65:11214-11226.

55. Hardell K, Carlberg M, Hardell L, et al. Concentrations of organohalogen compounds and titres of antibodies to Epstein-Barr virus antigens and the risk for non-Hodgkin lymphoma. *Oncol Rep*. 2009;21:1567-1576.

56. Bertrand KA, Spiegelman D, Aster JC, et al. Plasma organochlorine levels and risk of non-Hodgkin lymphoma in a cohort of men. *Epidemiology*. 2010;21:172-180.

57. Chiu BC, Blair A. Pesticides, chromosomal aberrations, and non-Hodgkin's lymphoma. *J Agromedicine*. 2009;14:250-255.

58. Cantor KP, Stricklanl PT, Brock JW, et al. Risk of non-Hodgkin's lymphoma and prediagnostic serum organochlorines: beta-hexachlorocyclohexane, chlordane/heptachlor-related compounds, dieldrin, and hexachlorobenzene. *Environ Health Perspect*. 2003;111:179-183.

59. Laden F, Bertrand KA, Altshul L, Aster JC, Korrick SA, Sagiv SK. Plasma organochlorine levels and risk of non-Hodgkin lymphoma in the Nurses' Health Study. *Cancer Epidemiol Biomarkers Prev*. 2010;19:1381-1384.

60. Quintana PJ, Delfino RJ, Korrick S, et al. Adipose tissue levels of organochlorine pesticides and polychlorinated biphenyls and risk of non-Hodgkin's lymphoma. *Environ Health Perspect*. 2004;112:854-861.

61. Pahwa M, Harris SA, Hohenadel K, et al. Pesticide use, immunologic conditions, and risk of non-Hodgkin lymphoma in Canadian men in six provinces. *Int J Cancer*. 2012;131:2650-2659.

62. Woods JS, Polissar L, Severson RK, Heuser LS, Kulander BG. Soft tissue sarcoma and non-Hodgkin's lymphoma in relation to phenoxyherbicide and chlorinated phenol exposure in western Washington. *J Natl Cancer Inst*. 1987;78:899-910.

63. Descatha A, Jenabian A, Conso F, Ameille J. Occupational exposures and haematological malignancies: an overview on human recent data. *Cancer Causes Control*. 2005;16:939-953.

64. International Agency For Research on Cancer. Formaldehyde, 2-Butoxyethanol and 1-tert-Butoxypropan-2-ol. Vol 88. IARC Monograph on the Evaluation of Carcinogenic Risk to Humans. Lyon, France: IARC; 2006.

65. van Bemmel DM, Visvanathan K, Beane Freeman LE, Coble J, Hoppin JA, Alavanja MC. S-ethyl-N,N-dipropylthiocarbamate exposure and cancer incidence among male pesticide applicators in the Agricultural Health Study: a prospective cohort. *Environ Health Perspect*. 2008;116:1541-1546.

66. International Agency For Research on Cancer. Some Thyrotropic Agents. IARC Monograph on the Evaluation of Carcinogenic Risk to Humans. Vol 79. Lyon, France; IARC; 2001.

67. Landgren O, Alibatar M, Ma W, et al. B-cell clones as early markers for chronic lymphocytic leukemia. *N Engl J Med*. 2009;360:659-667.

68. Coble J, Hoppin JA, Engel L, et al. Prevalence of exposure to solvents, metals, grain dust, and other hazards among farmers in the Agricultural Health Study. *J Expo Anal Environ Epidemiol*. 2002;12:418-426.

69. Casida JE. The greening of pesticide-environment interactions: some personal observations. *Environ Health Perspect*. 2012;120:487-493.

70. Green RM, Hodges NJ, Chipman JK, O'Donovan MR, Graham M. Reactive oxygen species from the uncoupling of human cytochrome P450 1B1 may contribute to the carcinogenicity of dioxin-like polychlorinated biphenyls. *Mutagenesis*. 2008;23:457-463.

71. Banerjee BD, Seth V, Ahmed RS. Pesticide-induced oxidative stress: perspectives and trends. *Rev Environ Health*. 2001;16:1-40.

72. Sherer TB, Richardson JR, Testa CM, et al. Mechanism of toxicity of pesticides acting at complex I: relevance to environmental etiologies of Parkinson's disease. *J Neurochem*. 2007;100:1469-1479.

73. Choi YJ, Seelbach MJ, Pu H. Polychlorinated biphenyls disrupt intestinal integrity via NADPH oxidase-induced alterations of tight junction protein expression. *Environ Health Perspect*. 2010;118:976-981.

74. Schug TT, Janesick A, Blumberg B, Heindel JJ. Endocrine disrupting chemicals and disease susceptibility. *J Steroid Biochem Mol Biol*. 2011;127:204-215.

75. Kretschmer XC, Baldwin WS. CAR and PXR: xenosensors of endocrine disrupters? *Chem Biol Interact*. 2005;155:111-128.

76. Barr DB, Thomas K, Curwin B, et al. Biomonitoring of exposure in farmworker studies. *Environ Health Perspect*. 2006;114:936-942.

77. Kim JH, Stevens RC, MacCoss MJ, et al. Identification and characterization of biomarkers of organophosphorus exposures in humans. *Adv Exp Med Biol*. 2010;660:61-71.

78. Kadiiska MB, Gladen BC, Baird DD, et al. Biomarkers of oxidative stress study II: are oxidation products of lipids, proteins, and DNA markers of CCl4 poisoning? *Free Radic Biol Med*. 2005;38:698-710.

79. Morrow JD, Awad JA, Boss HJ, Blair IA, Roberts LJ 2nd. Non-cyclooxygenase-derived prostanoids (F2-isoprostanes) are formed in situ on phospholipids. *Proc Natl Acad Sci U S A*. 1992;89:10721-10725.

80. Milne GL, Yin H, Hardy KD, Davies SS, Roberts LJ 2nd. Isoprostane generation and function. *Chem Rev*. 2011;111:5973-5996.

81. Wu X, Cai H, Xiang YB, et al. Intra-person variation of urinary biomarkers of oxidative stress and inflammation. *Cancer Epidemiol Biomarkers Prev*. 2010;19:947-952.

82. Watters JL, Satia JA, da Costa KA, et al. Comparison of three oxidative stress biomarkers in a sample of healthy adults. *Biomarkers*. 2009;14:587-595.

83. Simoniello MF, Kleinsorge EC, Scagnetti JA, et al. Biomarkers of cellular reaction to pesticide exposure in a rural population. *Biomarkers*. 2010;15:52-60.

84. Kaslotis KM, Kyriakopoulou K, Emmanouil C, et al. Monitoring of systemic exposure to plant protection products and DNA damage in orchard workers. *Toxicol Lett*. 2012;210:182-188.

85. Singh S, Kumar V, Thakur S, et al. DNA damage and cholinesterase activity in occupational workers exposed to pesticides. *Environ Toxicol Pharmacol*. 2011;31:278-285.

86. Atherton KM, Williams FM, Egea Gonzalez FJ, et al. DNA damage in horticultural farmers: a pilot study showing an association with organophosphate pesticide exposure. *Biomarkers*. 2009;14:443-451.

87. Muniz JF, McCauley L, Scherer J, et al. Biomarkers of oxidative stress and DNA damage in agricultural workers: a pilot study. *Toxicol Appl Pharmacol*. 2008;227:97-107.

88. Au WW, Giri AK, Ruchirawat M. Challenge assay: a functional biomarker for exposure-induced DNA repair deficiency and for risk of cancer. *Int J Hyg Environ Health*. 2010;213:32-39.

89. Costa LG, Giordano G, Furlong CE. Pharmacological and dietary modulators of paraoxonase 1 (PON1) activity and expression: the hunt goes on. *Biochem Pharmacol*. 2011;81:337-344.

90. Singh S, Kumar V, Thakur S, et al. Paraoxonase-1 genetic polymorphisms and susceptibility to DNA damage in workers occupationally exposed to organophosphate pesticides. *Toxicol Appl Pharmacol*. 2011;252:130-137.

91. Barry KH, Koutros S, Andreotti G, et al. Genetic variation in nucleotide excision repair pathway genes, pesticide exposure and prostate cancer risk. *Carcinogenesis*. 2012;33:331-337.

92. Kavlock R, Chandler K, Houck K, et al. Update on EPA's ToxCast program: providing high throughput decision support tools for chemical risk management. *Chem Res Toxicol*. 2012;25:1287-1302.

93. Knight AW, Little S, Houck K, et al. Evaluation of high-throughput genotoxicity assays used in profiling the US EPA ToxCast chemicals. *Regul Toxicol Pharmacol*. 2009;55:188-199.

94. Lu XT, Ma Y, Wang C, Zhang XF, Jin da Q, Huang LL. Cytotoxicity and DNA damage of five organophosphorus pesticides mediated by oxidative stress in PC12 cells and protection by vitamin E. *J Environ Sci Health B*. 2012;47:445-454.

95. Bagchi D, Bagchi M, Hassoun EA, Stohs SJ. In vitro and in vivo generation of reactive oxygen species, DNA damage and lactate dehydrogenase leakage by selected pesticides. *Toxicology*. 1995;104:129-140.

96. Ki YW, Lee JE, Park JH, Shin IC, Koh HC. Reactive oxygen species and mitogen-activated protein kinase induce apoptotic death of SH-SY5Y cells in response to fipronil. *Toxicol Lett*. 2012;211:18-28.

97. Tokunaga I, Kubo S, Mikasa H, Suzuki Y, Morita K. Determination of 8-hydroxydeoxyguanosine formation in rat organs: assessment of paraquat-evoked oxidative DNA damage. *Biochem Mol Biol Int*. 1997;43:73-77.

98. Sorensen M, Loft S. No significant paraquat-induced oxidative DNA damage in rats. *Free Radic Res*. 2000;32:423-428.

99. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin*. 2012;62:10-29.

100. Van Maele-Fabry G, Willems JL. Prostate cancer among pesticide applicators: a meta-analysis. *Int Arch Occup Environ Health*. 2004;77:559-570.

101. Koutros S, Andreotti G, Berndt SI, et al. Xenobiotic metabolizing gene variants, pesticide use and the risk of prostate cancer. *Pharmacogenet Genomics*. 2011;21:615-623.

102. Band PR, Abanto Z, Bert J, et al. Prostate cancer risk and exposure to pesticides in British Columbia farmers. *Prostate*. 2011;71:168-183.

103. Bonner MR, Williams BA, Rusiecki JA, et al. Occupational exposure to terbufos and the incidence of cancer in the Agricultural Health Study. *Cancer Causes Control*. 2010;21:871-877.

104. Crow JA, Bittles V, Herring KL, Borazjani A, Potter PM, Ross MK. Inhibition of recombinant human carboxylesterase 1 and 2 and monoacylglycerol lipase by chlorpyrifos oxon, paraoxon and methyl paraoxon. *Toxicol Appl Pharmacol*. 2012;258:145-150.

105. Beane Freeman LE, Rusiecki JA, Hoppin JA, et al. Atrazine and cancer incidence in the Agricultural Health Study (1994-2007). *Environ Health Perspect*. 2011;119:1253-1259.

106. Ross MK, Jones TL, Filipov NM. Disposition of the herbicide 2-chloro-4-(ethylamino)-6-(isopropylamino)-s-triazine (Atrazine) and its major metabolites in mice: a liquid chromatography/mass spectrometry analysis of urine, plasma, and tissue levels. *Drug Metab Dispos*. 2009;37:776-786.

107. Panuwet P, Restrepo PA, Magsumbol M, et al. An improved high-performance liquid chromatography-tandem mass spectrometric method to measure atrazine and its metabolites in human urine. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2010;878:957-962.

108. Dooley GP, Reardon KF, Prenni JE, et al. Proteomic analysis of diaminochlorotriazine adducts in wistar rat pituitary glands and LbetaT2 rat pituitary cells. *Chem Res Toxicol*. 2008;21:844-851.

109. Pleisa V, Steenwinkel MJ, van Delft JH, Baan RA, Kyrtopoulos SA. Methyl bromide causes DNA methylation in rats and mice but fails to induce somatic mutations in lambda lacZ transgenic mice. *Cancer Lett*. 1999;135:21-27.

110. Gansewendt B, Foest U, Xu D, Hallier E, Bolt HM, Peter H. Formation of DNA adducts in F-344 rats after oral administration or inhalation of [14C]methyl bromide. *Food Chem Toxicol*. 1991;29:557-563.

111. Pemble S, Schroeder KR, Spencer SR, et al. Human glutathione S-transferase theta (GSTT1): cDNA cloning and the characterization of a genetic polymorphism. *Biochem J*. 1994;300(pt 1):271-276.

112. Landi S. Mammalian class theta GST and differential susceptibility to carcinogens: a review. *Mutat Res*. 2000;463:247-283.

113. Sawada N, Iwasaki M, Inoue M, et al. Plasma organochlorines and subsequent risk of prostate cancer in Japanese men: a nested case-control study. *Environ Health Perspect*. 2010;118:659-665.

114. Dreiher J, Kordysh E. Non-Hodgkin lymphoma and pesticide exposure: 25 years of research. *Acta Haematol*. 2006;116:153-164.

115. Campo E, Swerdlow SH, Harris NL, Pileri S, Stein H, Jaffe ES. The 2008 WHO classification of lymphoid neoplasms and

beyond: evolving concepts and practical applications. *Blood*. 2011;117:5019-5032.

116. Wang SS, Slager SL, Brennan P, et al. Family history of hematopoietic malignancies and risk of non-Hodgkin lymphoma (NHL): a pooled analysis of 10 211 cases and 11 905 controls from the International Lymphoma Epidemiology Consortium (InterLymph). *Blood*. 2007;109:3479-3488.

117. Grulich AE, Vajdic CM. The epidemiology of non-Hodgkin lymphoma. *Pathology*. 2005;37:409-419.

118. Fisher SG, Fisher RI. The epidemiology of non-Hodgkin's lymphoma. *Oncogene*. 2004;23:6524-6534.

119. Dich J, Zahm SH, Hanberg A, Adami HO. Pesticides and cancer. *Cancer Causes Control*. 1997;8:420-443.

120. Hardell L, Eriksson M, Lenner P, Lundgren E. Malignant lymphoma and exposure to chemicals, especially organic solvents, chlorophenols and phenoxy acids: a case-control study. *Br J Cancer*. 1981;43:169-176.

121. Hoar SK, Blair A, Holmes FF, et al. Agricultural herbicide use and risk of lymphoma and soft-tissue sarcoma. *JAMA*. 1986;256:1141-1147.

122. Zahm SH, Weisenburger DD, Babbitt PA, et al. A case-control study of non-Hodgkin's lymphoma and the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) in eastern Nebraska. *Epidemiology*. 1990;1:349-356.

123. Pearce NE, Sheppard RA, Smith AH, Teague CA. Non-Hodgkin's lymphoma and farming: an expanded case-control study. *Int J Cancer*. 1987;39:155-161.

124. Cantor KP, Blair A, Everett G, et al. Pesticides and other agricultural risk factors for non-Hodgkin's lymphoma among men in Iowa and Minnesota. *Cancer Res*. 1992;52:2447-2452.

125. Merhi M, Raynal H, Cahuzac E, Vinson F, Cravedi JP, Gamet-Payrastre L. Occupational exposure to pesticides and risk of hematopoietic cancers: meta-analysis of case-control studies. *Cancer Causes Control*. 2007;18:1209-1226.

126. Brauner EV, Sorensen M, Gaudreau E, et al. A prospective study of organochlorines in adipose tissue and risk of non-Hodgkin lymphoma. *Environ Health Perspect*. 2012;120:105-111.

127. Spinelli JJ, Ng CH, Weber JP, et al. Organochlorines and risk of non-Hodgkin lymphoma. *Int J Cancer*. 2007;121:2767-2775.

128. De Roos AJ, Zahm SH, Cantor KP, et al. Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men. *Occup Environ Med*. 2003;60:E11.

129. Fuscoe JC. Simultaneous quantification of t(14;18) and HPRT exon 2/3 deletions in human lymphocytes. *Methods Mol Biol*. 2005;291:171-178.

130. Agopian J, Navarro JM, Gac AC, et al. Agricultural pesticide exposure and the molecular connection to lymphomagenesis. *J Exp Med*. 2009;206:1473-1483.

131. Rothman N, Cantor KP, Blair A, et al. A nested case-control study of non-Hodgkin lymphoma and serum organochlorine residues. *Lancet*. 1997;350:240-244.

132. Buffler PA, Kwan ML, Reynolds P, Urayama KY. Environmental and genetic risk factors for childhood leukemia: appraising the evidence. *Cancer Invest*. 2005;23:6-75.

133. Buka I, Koranteng S, Osornio Vargas AR. Trends in childhood cancer incidence: review of environmental linkages. *Pediatr Clin North Am*. 2007;54:177-203, x.

134. Bailey HD, Armstrong BK, de Klerk NH, et al; Aus-ALL Consortium. Exposure to professional pest control treatments and the risk of childhood acute lymphoblastic leukemia. *Int J Cancer*. 2011;129:1678-1688.

135. Vinson F, Merhi M, Baldi I, Raynal H, Gamet-Payrastre L. Exposure to pesticides and the risk of childhood cancer: a meta-analysis of recent epidemiologic studies. *Occup Environ Med*. 2011;68:694-702.

136. Van Maele-Fabry G, Lantin A, Hoet P, Lison D. Childhood leukaemia and parental occupational exposure to pesticides: a systematic review and meta-analysis. *Cancer Causes Control*. 2010;21:787-809.

137. Wigle DT, Turner MC, Krewski D. A systematic review and meta-analysis of childhood leukemia and parental occupational pesticide exposure. *Environ Health Perspect*. 2009;117:1505-1513.

138. Ward MH, Colt JS, Metayer C, et al. Residential exposure to polychlorinated biphenyls and organochlorine pesticides and risk of childhood leukemia. *Environ Health Perspect*. 2009;117:1007-1013.

139. Autrup H. Transplacental transfer of genotoxins and transplacental carcinogenesis. *Environ Health Perspect*. 1993;101(suppl 2):33-38.

140. Borzsonyi M, Pinter A, Surjan A, Farkas I. Transplacental induction of lymphomas in Swiss mice by carbendazim and sodium nitrite. *Int J Cancer*. 1976;17:742-747.

141. Anway MD, Cupp AS, Uzumcu M, Skinner MK. Epigenetic transgenerational actions of endocrine disruptors and male fertility. *Science*. 2005;308:1466-1469.

142. Anway MD, Skinner MK. Transgenerational effects of the endocrine disruptor vinclozolin on the prostate transcriptome and adult onset disease. *Prostate*. 2008;68:517-529.

143. International Agency For Research on Cancer. Ionizing Radiation. IARC Monograph on the Evaluation of Carcinogenic Risk to Humans. Vol 75. Lyon, France; IARC; 2000.

144. International Agency For Research on Cancer. A Review of Human Carcinogens. Chemical Agents and Related Occupations. IARC Monograph on the Evaluation of Carcinogenic Risk to Humans. Vol 100F. Lyon, France; IARC; 2012.

145. Van Maele-Fabry G, Duhayon S, Martens C, Lison D. Risk of leukaemia among pesticide manufacturing workers: a review and meta-analysis of cohort studies. *Environ Res*. 2008;106:121-137.

146. Clavel J, Hemon D, Mandereau L, Delmontte B, Severin F, Flandrin C. Farming, pesticide use and hairy-cell leukemia. *Scand J Work Environ Health*. 1996;22:285-293.

147. Brown LM, Blair A, Gibson R, et al. Pesticide exposures and other agricultural risk factors for leukemia among men in Iowa and Minnesota. *Cancer Res*. 1990;50:6585-6591.

148. Mahajan R, Blair A, Lynch CF, et al. Fonofos exposure and cancer incidence in the agricultural health study. *Environ Health Perspect*. 2006;114:1838-1842.

149. Beane Freeman LE, Bonner MR, Blair A, et al. Cancer incidence among male pesticide applicators in the Agricultural Health Study cohort exposed to diazinon. *Am J Epidemiol*. 2005;162:1070-1079.

150. Delancey JO, Alavanja MC, Coble J, et al. Occupational exposure to metribuzin and the incidence of cancer in the Agricultural Health Study. *Ann Epidemiol*. 2009;19:388-395.

151. Lee WJ, Hoppin JA, Blair A, et al. Cancer incidence among pesticide applicators exposed to alachlor in the Agricultural Health Study. *Am J Epidemiol*. 2004;159:373-380.

152. Vogel CF, Li W, Sciullo E, et al. Pathogenesis of aryl hydrocarbon receptor-mediated development of lymphoma is associated with increased cyclooxygenase-2 expression. *Am J Pathol*. 2007;171:1538-1548.

153. Kyle RA, Rajkumar SV. Plasma cell disorders. In: Goldman L, Ausiello DA, eds. Cecil Textbook of Medicine. 22nd ed. Philadelphia: WB Saunders; 2004:1184-1195.

154. Waxman AJ, Mink PJ, Devesa SS, et al. Racial disparities in incidence and outcome in multiple myeloma: a population-based study. *Blood*. 2010;116:5501-5506.

155. Alavanja MCR, Sandler DP, Lynch CF, et al. Cancer incidence in the Agricultural Health Study. *Scand J Work Environ Health*. 2005;31(suppl 1):39-45.

156. Rusiecki JA, Patel R, Koutros S, et al. Cancer incidence among pesticide applicators exposed to permethrin in the Agricultural Health Study. *Environ Health Perspect*. 2009;117:581-586.

157. Landgren O, Kyle RA, Pfeiffer RM, et al. Monoclonal gammopathy of undetermined significance (MGUS) consistently precedes multiple myeloma: a prospective study. *Blood*. 2009;113:5412-5417.

158. Landgren O, Kyle RA, Hoppin JA, et al. Pesticide exposure and risk of monoclonal gammopathy of undetermined significance in the Agricultural Health Study. *Blood*. 2009;113:6386-6391.

159. Wolff MS, Toniolo PG, Lee EW, Rivera M, Dubin N. Blood levels of organochlorine residues and risk of breast cancer. *J Natl Cancer Inst*. 1993;85:648-652.

160. Calle EE, Frumkin H, Henley SJ, Savitz DA, Thun MJ. Organochlorines and breast cancer risk. *CA Cancer J Clin*. 2002;52:301-309.

161. Lopez-Cervantes M, Torres-Sanchez L, Tobias A, Lopez-Carrillo L. Dichlorodiphenyldichloroethane burden and breast cancer risk: a meta-analysis of the epidemiologic evidence. *Environ Health Perspect*. 2004;112:207-214.

162. Malhur V, Bhatnagar P, Sharma RG, Acharya V, Sexana R. Breast cancer incidence and exposure to pesticides among women originating from Jaipur. *Environ Int*. 2002;28:331-336.

163. Soliman AS, Wang X, DiGiovanni J, et al. Serum organochlorine levels and history of lactation in Egypt. *Environ Res*. 2003;92:110-117.

164. Ibarluzea Jm J, Fernandez MF, Santa-Marina L, et al. Breast cancer risk and the combined effect of environmental estrogens. *Cancer Causes Control*. 2004;15:591-600.

165. McCready D, Aronson KJ, Chu W, Fan W, Vesprini D, Narod SA. Breast tissue organochlorine levels and metabolic genotypes

in relation to breast cancer risk Canada. *Cancer Causes Control*. 2004;15:399-418.

166. Cassidy RA, Natarajan S, Vaughan GM. The link between the insecticide heptachlor epoxide, estradiol, and breast cancer. *Breast Cancer Res Treat*. 2005;90: 55-64.
167. Siddiqui MK, Anand M, Mehrotra PK, Sarangi R, Mathur N. Biomonitoring of organochlorines in women with benign and malignant breast disease. *Environ Res*. 2005;98:250-257.
168. Cohn BA, Wolff MS, Cirillo P, Sholtz RI. DDT and breast cancer in young women: new data on the significance of age at exposure. *Environ Health Perspect*. 2007; 115:1406-1414.
169. Iwasaki M, Inoue M, Sasazuki S, Kurahashi N, Itoh H, Usuda M, Tsugane S; Japan Public Health Center-based Prospective Study Group. Plasma organochlorine levels and subsequent risk of breast cancer among Japanese women: a nested case-control study. *Sci Total Environ*. 2008;402: 176-183.
170. Itoh H, Iwasaki M, Hanaoka T, et al. Serum organochlorines and breast cancer risk in Japanese women: a case-control study. *Cancer Causes Control*. 2009;20: 567-580.
171. Charlier C, Albert A, Herman P, et al. Breast cancer and serum organochlorine residues. *Occup Environ Med*. 2003;60: 348-351.
172. Fenton SE. Endocrine-disrupting compounds and mammary gland development: early exposure and later life consequences. *Endocrinology*. 2006;147(suppl 6):S18-S24.
173. Rudel RA, Fenton SE, Ackerman JM, Euling SY, Makris SL. Environmental exposures and mammary gland development: state of the science, public health implications, and research recommendations. *Environ Health Perspect*. 2011;119: 1053-1061.
174. Russo J, Calaf G, Sohi N, et al. Critical steps in breast carcinogenesis. *Ann N Y Acad Sci*. 1993;698:1-20.
175. Russo J, Hu YF, Yang X, Russo IH. Developmental, cellular, and molecular basis of human breast cancer. *J Natl Cancer Inst Monogr*. 2000;27:17-37.
176. Tokunaga M, Land CE, Tokuoka S, Nishimori I, Soda M, Akiba S. Incidence of female breast cancer among atomic bomb survivors, 1950-1985. *Radiat Res*. 1994; 138:209-223.
177. Land CE. Studies of cancer and radiation dose among atomic bomb survivors. The example of breast cancer. *JAMA*. 1995; 274:402-407.
178. McElroy JA, Gangnon RE, Newcomb PA, et al. Risk of breast cancer for women living in rural areas from adult exposure to atrazine from well water in Wisconsin. *J Expo Sci Environ Epidemiol*. 2007;17: 207-214.
179. Engel LS, Hill DA, Hoppin JA, et al. Pesticide use and breast cancer risk among farmers' wives in the agricultural health study. *Am J Epidemiol*. 2005;161: 121-135.
180. Reynolds P, Hurley SE, Gunier RB, Yerabati S, Quach T, Hertz A. Residential proximity to agricultural pesticide use and incidence of breast cancer in California, 1988-1997. *Environ Health Perspect*. 2005; 113:993-1000.
181. Brody JG, Aschengrau A, McKelvey W, Rudel RA, Swartz CH, Kennedy T. Breast cancer risk and historical exposure to pesticides from wide-area applications assessed with GIS. *Environ Health Perspect*. 2004;112:889-897.
182. O'Leary ES, Vena JE, Freudenheim JL, Brasure J. Pesticide exposure and risk of breast cancer: a nested case-control study of residentially stable women living on Long Island. *Environ Res*. 2004;94: 134-144.
183. Teitelbaum SL, Gammon MD, Britton JA, Neugut AI, Levin B, Stellman SD. Reported residential pesticide use and breast cancer risk on Long Island, New York. *Am J Epidemiol*. 2007;165:643-651.
184. Farooq U, Joshi M, Nookala V, et al. Self-reported exposure to pesticides in residential settings and risk of breast cancer: a case-control study. *Environ Health*. 2010;9:30.
185. Muir K, Rattanamongkolgul S, Smallman-Raynor M, Thomas M, Downer S, Jenkinson C. Breast cancer incidence and its possible spatial association with pesticide application in two counties of England. *Public Health*. 2004;118:513-520.
186. Pawha P, Karunanayake CP, Dosman JA, Spinelli JJ, McDuffie HH, McLaughlin JR. Multiple myeloma and exposure to pesticides: a Canadian case-control study. *J Agromedcine*. 2012;17:40-50.