Non-Hodgkin lymphoma risk and organophosphate and carbamate insecticide use in the north American pooled project

Stella Koutros a,*, Shelley A. Harris b,c,d, John J. Spinelli e,f, Aaron Blair a, John R. McLaughlin c,g, Sheila Hoar Zahm h, Sungduk Kim a, Paul S. Albert a, Linda Kachuri i, Manisha Pahwa b, Kenneth P. Cantor a, Dennis D. Weisenburger j, Punam Pahwa k,l, Larissa A. Pardo a, James A. Dosman k, Paul A. Demers b,c,f, Laura E. Beane Freeman a

aDivision of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, MD, USA
bOccupational Cancer Research Centre, Cancer Care Ontario, Toronto, Canada
cDalla Lana School of Public Health, University of Toronto, Toronto, Canada
dPrevention and Cancer Control, Cancer Care Ontario, Toronto, Canada
ePopulation Oncology, BC Cancer, Vancouver, Canada
fSchool of Population and Public Health, University of British Columbia, Vancouver, Canada
gPublic Health Ontario, Toronto, Canada
hSheila Zahm Consulting, Hermon, ME, USA
iDepartment of Epidemiology & Biostatistics, University of California San Francisco, San Francisco, CA, USA
jCity of Hope, Duarte, CA, USA
kCanadian Centre for Health and Safety in Agriculture, University of Saskatchewan, Saskatoon, Canada
lCommunity Health and Epidemiology, College of Medicine, University of Saskatchewan, Saskatoon, Canada

Abstract

Organophosphates and carbamates have been among the most commonly used insecticides, with both agricultural and residential uses. Previous studies have suggested associations of non-Hodgkin lymphoma (NHL) with some of these chemicals; however, many studies have been limited in their ability to evaluate associations with lymphoma subtypes. We evaluated the use
of eleven organophosphate and two carbamate insecticides in association with NHL in the North American Pooled Project, which includes data from case-control studies in the United States and Canada (1690 cases/5131 controls). We used unconditional logistic regression adjusting for potential confounders, including use of other pesticides, to estimate odds ratios (OR) and 95% confidence intervals (CI) for associations between these chemicals and NHL overall, and NHL subtypes, i.e., follicular (FL), diffuse large B-cell (DLBCL), small lymphocytic lymphoma (SLL) and others. Ever use of malathion was associated with increased risk of NHL overall (OR = 1.43; 95% CI: 1.14–1.81) compared with never users. Categories using tertiles of duration (< 4 yrs., 4–12 yrs., and > 12yrs) also showed a significant exposure-response for increasing years of use of malathion and risk of NHL (OR < 4vsUnex = 1.33 (0.88, 2.03), OR 4–12vsUnex = 1.42 (1.02, 1.96), OR > 12vsUnex = 1.55 (1.05, 2.28, p-trend < 0.01)). In addition, malathion use was statistically significantly associated with FL (OR = 1.58; 95% CI: 1.11–2.27) and DLBCL (OR = 1.61; 95% CI: 1.16–2.22) while there were no apparent associations with SLL or other subtypes, the p-value for heterogeneity across subtypes, however, was not significant. These results support previous studies suggesting an association between insecticide use and NHL overall, and provide new information on associations with NHL subtypes.

1. Introduction

Organophosphates (OPs) and carbamates are classes of insecticides frequently used in agriculture and for public health and residential purposes. Over the last decade in the United States and Canada, chlorpyrifos, acephate and malathion were among the most commonly used OPs and carbaryl was one of the most widely used carbamate insecticides for conventional use in homes and gardens.(EPA, 2017; Health Canada, 2015) Pesticides, including some OPs and carbamates, have been linked to several adverse human health outcomes, including cancer.(Blair et al., 2015; Koutrros et al., 2013) The International Agency for Research on Cancer (IARC) lists the OPs malathion and diazinon as probable human carcinogens (Group 2A) and dichlorvos as possibly carcinogenic to humans (Group 2B).(IARC, 2015) In earlier assessments, IARC classified carbaryl(IARC, 1987a) and the OP trichlorfon(IARC, 1987b) as not classifiable as to their carcinogenicity in humans (Group 3). Few other OP or carbamate insecticides have been assessed for carcinogenicity.

Population-based case-control studies from the U.S.(Cantor et al., 1992; Waddell et al., 2001; Zheng et al., 2001) and Canada(McDuffie et al., 2001) have demonstrated varied positive associations between non-Hodgkin lymphoma (NHL) and reported use of the OPs malathion, diazinon, coumaphos, chlorpyrifos, and fonofos, as well as the carbamate insecticides carbofuran and carbaryl. In addition, data from a large prospective cohort study of pesticide applicators found positive associations between NHL and the OPs terbufos and diazinon.(Alavanja et al., 2014; Bonner et al., 2010) Not all studies, however, have supported these positive associations.(Bonner et al., 2007; Mills et al., 2005) Associations between individual insecticides and NHL have varied in magnitude and statistical significance and many studies have been limited in their ability to evaluate associations with subtypes for this heterogeneous disease. Thus, more data are needed to explore these associations.
Here, we pooled data from four large population-based case-control studies from the U.S. and Canada to allow a more detailed evaluation of possible relationships between the use of several OP and carbamate insecticides and risk of NHL among 1690 cases and 5131 controls.

2. Methods

2.1. Study population

The current pooled analysis is comprised of three population-based case-control studies conducted by the U.S. National Cancer Institute in Kansas, Iowa/Minnesota, and Nebraska in the 1980s (Cantor et al., 1992; Hoar et al., 1986; Zahm et al., 1990) and the Cross Canada Study of Pesticides and Health (CCSPH) which was conducted in Quebec, Ontario, Manitoba, Saskatchewan, Alberta, and British Columbia between 1991 and 1994 (McDuffie et al., 2001). Cases included incident NHL diagnoses who were at least 19 years of age. NHL histology codes from each study were reexamined for the pooled effort and categorized to the International Classification of Diseases for Oncology First Edition (ICD-Oe1) to classify NHL overall and the following subtypes: follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), small lymphocytic lymphoma (SLL), and “other”. The “other” sub-type included all cases whose histologies were unknown or not FL, DLBCL, or SLL. Pathology reviews in the original studies were conducted to standardize and validate NHL diagnoses. The current analysis includes 1690 NHL cases and 5131 controls. Controls for the studies were selected from the general population using different methods (depending on the study), including random digit dialing, voter lists, health insurance records, Medicare listings for those 65 years or older, and from state mortality files for deceased cases. Cases and controls were frequency matched on location (state/province) and age (± 2 or 5 years); in some states, the matching was done on additional variables, including sex and race, as well as vital status and year of death for deceased cases (Iowa, Minnesota, Nebraska, Kansas). Demographic data, agricultural exposures (including pesticide use), and other covariates related to NHL risk factors, such as lifestyle, medical and occupational history, were obtained via postal or interviewer-administered questionnaires (either in person or by telephone) from study participants or proxy respondents (if subjects were deceased (U.S. studies) or required assistance due to illness or disability (CCSPH)).

Investigators of individual studies received human subjects approval prior to collection of data. The pooling project was approved by the Health Sciences Research Ethics Board, University of Toronto (#25166) and an exemption was obtained from the Office of Human Subjects Research, U.S. National Institutes of Health (#11351).

2.2. Pesticide exposure

Information on pesticide use was harmonized across the four studies, including data on self-reported use of 11 OPs and two carbamate insecticides. For the current analysis, we included OP and carbamate insecticides with at least ten exposed cases of NHL overall. This resulted in the inclusion of the following specific insecticides for analysis (in order from highest to lowest prevalence of use): malathion (OP), diazinon (OP), carbofuran (carbamate), carbaryl (carbamate), fonofos (OP), phorate (OP), dimethoate (OP), terbufos (OP), coumaphos (OP), and...
and dichlorvos (OP). Additional information on numbers of days per year of use and number of total years of use for specific pesticide active ingredients was also collected. Information was not collected on days per year (Iowa, Minnesota, and Kansas) or duration (Kansas) for individual pesticides (only for herbicides and insecticides as groups). For studies with duration of use information for specific pesticides, we imputed values for those with missing duration information using a stratified sampling scheme. Using individuals with duration information, we first cross-classified data by categories of duration, age, sex, respondent type, and study site. For subjects missing duration information, we created five imputed values by sampling with replacement a value for duration of exposure conditional on the levels for the other factors. We carried out five separate analyses and combined OR results using the SAS MIANALYZE procedure (SAS, version 9.4 (Cary, North Carolina)).

2.3. Statistical analysis

Unconditional logistic regression was used to calculate ORs and 95% CIs for associations between ever use of individual OP and carbamate insecticides and the risk of NHL overall and for histological subtypes (FL, DLBCL, SLL, and other). Categories for days per year and years of use of each insecticide were created based on the distribution among controls and were grouped as either above or below the median or according to tertiles. Based on the observed relationship between these factors and risk of NHL, all models were adjusted for age, sex, state/province, and family history of lymphatic or hematopoietic cancer in a first-degree relative. Proxy respondent status was also evaluated as a potential covariate and effect modifier of the observed pesticide relationships (using a likelihood ratio test). The relationship between individual pesticides reported by participants (ever/never) was evaluated using the Phi coefficient. Additional modeling was done to further adjust for ever/never pesticide co-exposures based on this relationship (those phi coefficient ≥0.35). We also explored adjustment of all models with other pesticides that have been previously linked to NHL (2,4-D, dicamba, glyphosate, atrazine, lindane, chlor-dane, and DDT) in the individual studies comprising the pooled analysis or other studies. Finally, we mutually adjusted models for pesticides with significant associations observed in the current pooled analysis. A sensitivity analysis was conducted to compare risk estimates for duration of use with and without imputed duration. As an alternate approach, we conducted a weighted quantile sum logistic regression analysis using duration of OP and carbamate insecticide use to analyze the pesticides as a mixture. (Carrico et al., 2015) This was done using the same covariates as adjustment variables and with the imputed datasets. Since the prevalence of ever use for a number of pesticides was very low (e.g., for Trichlorfon even the 99th percentile for duration was zero), we used normalized continuous durations (Z-scores) as measures of exposure. As a sensitivity analysis, we also fit a model using pesticide exposure percentiles. These mixture analyses were done using the gWQS package (R package that is available in the R-CRANS Library to perform logistic regression with weighted quantile sums).

We computed tests for linear trend using the Wald test, treating the median value for each category among control subjects as continuous. P-values for heterogeneity across NHL subtypes were conducted using polytomous logistic regression using a Wald test. All
3. Results

The mean age of NHL cases (62.7 years) was comparable to that of controls (61.7 years) (Table 1). Most participants were male (cases: 89.1%, controls: 86.2%) and about a third of case and control interviews were provided by proxy respondents (cases: 31.5%, controls: 33%). A larger proportion of NHL cases had a first-degree relative with lymphatic or hematopoietic cancer (8.2%) than controls (3.9%). Cases were also slightly more likely to have ever been diagnosed with a medical condition (32.3%) than controls (27.1%). Around two-thirds of cases and controls had reported to have ever lived on a farm or ranch (65.2%, v. 63.9%) and < 10% had reported to have ever used personal protective equipment (6.2% v. 6.0%). Proxy respondent status did not materially impact observed point estimates (by > 10%) and was not retained in the final models, nor did we observe significant effect modification by proxy status.

There was a significantly increased risk of NHL among ever users of malathion (OR = 1.63, 95% CI = 1.33, 2.00), diazinon (OR = 1.69, 95% CI = 1.27, 2.24), fonofos (OR = 1.75, 95% CI = 1.21, 2.55), and carbaryl (OR = 1.62, 95% CI = 1.20, 2.18) in comparison with never users of that pesticide (Table 2). After mutual adjustment for these four chemicals, the risk of NHL was attenuated for each insecticide, with only the risk of NHL among ever users of malathion remaining statistically significant (OR = 1.43, 95% CI = 1.14, 1.81). This increased risk was not impacted by additional adjustment for other pesticides correlated with malathion or with any pesticide previously linked to NHL in these studies (data not shown). Elevated OR for ever use of dimethoate, coumaphos, trichlorfon, chlorpyrifos, and carbofuran were also further attenuated after adjustment for other insecticides (data not shown). Exposure-response analyses evaluating years of use of malathion showed that the OR was highest among those who reported using malathion ≥6 years compared to never users (n = 103 cases) (OR = 1.57; 95% CI = 1.18, 2.10, p-value for trend < 0.01, Table 3). Expanded categories using tertiles of duration of malathion use (< 4 yrs., 4–12 yrs., and > 12 yrs) also showed a significant exposure-response for increasing years of use of malathion and risk of NHL (OR < 4vsUnex = 1.33 (0.88, 2.03), OR4–12vsUnex = 1.42 (1.02, 1.96), OR > 12vsUnex = 1.55 (1.05, 2.28, p-trend < 0.01)). These results were similar when considering data without imputation (data not shown) and across studies (no heterogeneity by study, p = 0.93). There were no additionally significant trends between risk and duration of use (years) for any other insecticide after mutual adjustment (Table 3); results for increasing years of dimethoate and coumaphos approached unity after adjusting for other insecticides (not shown). Results evaluating days per year of use were limited (data available for only for 2 of the 4 studies). These analyses also show a significant association between malathion use and NHL (Supplemental Table 2).

When we evaluated the association between a mixture of all OP and carbamate insecticides and NHL risk, we found a statistically significant association between pesticide duration and NHL risk. For a unit change in the weighted normalized (Z-score) across pesticides, there was a 38% (95% CI: 18% to 61%, p-value < 0.0001) increased risk of NHL. In the weighted
normalized sum, malathion, carbaryl, fonofos, diazinon, and coumaphos duration play the biggest role with all of their associated weights being above 0.10 (0.31, 0.19, 0.17, 0.13, and 0.10, respectively). The results were very similar when using the percentiles rather than standardized exposure durations (42% increased risk per weighted percentile unit, p-value < 0.0001, with the same five pesticides playing the largest role in the weighted sum).

Table 4 shows the association between ever use of OP and carbamate insecticides and lymphoma subtypes. There were positive associations between ever use of malathion and both FL (OR = 1.80, 95% CI = 1.31, 2.46) and DLBCL (OR = 1.77, 95% CI = 1.33, 2.35) subtypes compared to never users; these associations held after mutual adjustment for other pesticides (FL: OR = 1.58, 95% CI = 1.11, 2.27; DLBCL: OR = 1.61, 95% CI = 1.16, 2.22); increases in risk were also evident with increasing duration of exposure for these subtypes (Supplemental Table 3). Ever use of diazinon was associated with FL (OR = 1.75, 95% CI = 1.14, 2.71), DLBCL (OR = 1.74, 95% CI = 1.17, 2.60), and SLL (OR = 2.24, 95% CI = 1.17, 4.30) subtypes, however these associations were attenuated and became non-significant after adjustment for malathion, fonofos, and carbaryl. A similar attenuation in risk was observed between ever use of fonofos and FL and DLBCL subtypes. A significant increased risk was observed between ever use of coumaphos and SLL (OR = 3.97, 95% CI = 1.60, 9.84), however this was based on only six exposed cases. Ever use of the carbamate insecticide carbaryl was significantly associated with FL (OR = 1.66, 95% CI = 1.05, 2.64) and SLL (OR = 2.59, 95% CI = 1.39, 4.85) NHL subtypes, with only the association between ever use of carbaryl and SLL remaining significant after mutual adjustment for other pesticides (OR = 2.12, 95% CI = 1.01, 4.42). A significant increased risk was also observed for ever use of carbofuran and DLBCL. This, however, was no longer significant after adjusting for the top five correlated pesticides, (OR = 1.43, 95% CI = 0.86, 2.40). None of the tests for heterogeneity across NHL subtypes for each pesticide were statistically significant (all p-value for heterogeneity > 0.05).

4. Discussion

Pooling of data from three case-control studies from the United States and one from Canada provided one of the largest efforts to evaluate possible associations between commonly used insecticides and NHL. Our results show that increasing duration of exposure to OP and carbamate insecticides significantly increased the risk of NHL. Analysis of these pesticides as a mixture or by individual use suggests that the OP insecticide malathion is particularly associated with risk of NHL overall and that use may be associated with FL and DLBCL subtypes. Few other positive individual associations were observed for other OP and carbamate insecticides and risk of NHL or its subtypes, after controlling for other pesticides.

Malathion is currently classified by IARC as probably carcinogenic to humans (Group 2A) in 2015 (IARC, 2015) and the by U.S. Environmental Protection Agency as having “suggestive evidence of carcinogenicity” in a draft review in 2016.(EPA, 2016) In both instances, it was noted that human data were limited, with the most consistent evidence being for NHL and for prostate cancer. Data from the individual case-control studies in the U.S.(Cantor et al., 1992; Waddell et al., 2001) and Canada,(McDuffie et al., 2001) included
in the current pooled analysis, contributed to these earlier evaluations of a malathion use and NHL risk. Our pooled analyses of the data from these studies confirm prior associations with ever use of malathion and NHL risk in 1690 cases after adjustment for use of other pesticides. In addition, we show a significant exposure-response relationship with years of malathion use. Data from the prospective Agricultural Health Study (AHS) cohort (n = 495 cases with malathion use information, n = 179 exposed cases with quantitative data) indicate no association between ever use of malathion and NHL (RR_{ever} = 0.9, 95% CI = 0.8, 1.1) or for lifetime-days of use in the highest exposure category (RR_{high} = 0.9, 95% CI = 0.6, 1.3). (Alavanja et al., 2014) Data from two other large cohort studies, which used crop exposure matrices to assess malathion use, also showed no association between use and NHL risk. (Leon et al., 2019) Differences in results between the current study and these cohorts could be due to different times between exposure and disease development (latent period), different uses of products containing malathion over time (including use on animals), different referent populations (general population versus occupationally exposed), or study design (cohort versus case-control).

A major advantage of this pooled analysis is larger numbers to evaluate possible links between insecticide exposure and NHL subtypes. This is important given the etiologic heterogeneity observed in lymphoma. (Morton et al., 2014) Farming occupations have been linked to FL (Fritschi et al., 2005), DLBCL (Cerhan et al., 2014; Ferri et al., 2017) and multiple myeloma (Ferri et al., 2017; Perrotta et al., 2008) in some studies. Here, we observed an association between malathion and FL and DLBCL subtypes as well as an association between SLL and the carbamate insecticide carbaryl. Few studies have evaluated specific pesticide use by NHL subtypes. No increased risks were reported for carbaryl use and SLL/chronic B-cell lymphocytic lymphoma (CLL)/mantle-cell lymphoma (MCL) subtype in the AHS cohort. (Alavanja et al., 2014) Given the inconsistent risk associations between carbaryl and NHL, as well as the small number of exposed SLL cases (n = 12) in this pooled analysis, it is possible that either of these contrasting observations could be due to chance. The observed associations between malathion and risk were robust in the current analysis, however, these too are not consistent with results from other studies. (Alavanja et al., 2014; Leon et al., 2019) The AHS reports relative risks (RR) for malathion and FL of RR_{ever vs. never} = 1.3, 95% CI = 0.7, 2.4 (60 cases) and RR_{high use} = 1.6, 95% CI = 0.6, 4.4 (20 cases). (Alavanja et al., 2014) These are similar in magnitude to those reported here in 468 cases, OR_{ever vs. never} = 1.58, 95% CI = 1.11, 2.27, suggesting that if an association truly exists, the magnitude of effect is modest. No statistically significant heterogeneity was indicated by subtype in our study. Thus, more powerful studies will be needed to further explore this link.

There is mechanistic data supporting the carcinogenic potential of malathion. Purported mechanisms of action include direct genotoxicity (of either malathion or its metabolite malaoxon, (S-(1,2-dicarboethoxyethyl)O,O-dimethyl phosphorothiolate)) (Blasiak et al., 1999; Pluth et al., 1996), disruption of critical cellular pathways involved in cellular proliferation (IARC, 2015), and the induction of oxidative stress (Abdollahi et al., 2004) and inflammation. (Banerjee et al., 1998; Galloway and Handy, 2003) Aside from the known links between autoimmune and chronic inflammatory disorders and lymphoma (Ekstrom Smedby et al., 2008), none of the above noted pathways have been concretely linked to
the development of lymphoma. Some studies have suggested that pesticide exposure is associated with common chromosomal alterations t(14;18)(q32;q21) occurring in FL and DLBCL. (Chiu et al., 2006; Schroeder et al., 2001) Future studies examining potential biological mechanisms directly linking malathion exposure and lymphoma will be valuable.

OP and carbamate insecticides have short half-lives and leave the body within 24–48 h after exposure, thus, exposure assessment is typically questionnaire-based. (Bouchard et al., 2003) Pooling of data from four case-control studies created one of the largest resources with detailed historical use of specific OP and carbamate insecticides. This allows for a powerful assessment of risk for NHL overall, for exposure-response analyses, and by NHL subtypes. Despite these advantages, we cannot rule out the possibility of recall bias. In addition to differential case recall, some interviews were obtained from proxy respondents which could also be a source of differential exposure misclassification. A previous methodologic effort to evaluate case-response bias in the Nebraska study (included in this pooled effort) showed no evidence of case-response bias for any pesticide or for the number of pesticides reported. (Blair and Zahm, 1993) Further, when we compared risks from proxy versus self-respondents, however, we found no significant differences in the reported risk estimates for the positive associations observed in this study. In addition, our results for malathion show consistent associations with NHL overall and for FL and DLBCL in exposure-response analyses which are less susceptible to modest errors in exposure misclassification. (Marshall et al., 1981) Since there were more missing data on days/year of use (only available in two of four studies) we chose not to impute for days/year. Results for malathion use, however, are still significantly elevated despite the decrease in power in these analyses (Supplemental Table 2). And finally, although the study is quite large, the numbers of exposed cases is small in some analyses by subtype of NHL. This could explain the lack of observed statistical heterogeneity by subtype. Further, classification for subtypes of NHL have evolved over time and thus, the current analysis which includes ‘other’ types which were unclassifiable, as well as those defining SLL, would not be comparable with current classifications.

In conclusion, data from this large, pooled analysis of four case-control studies suggest a positive association between increasing years of malathion use and risk of NHL. These data add to a growing body of evidence, much of which comes from the individual case-control studies included here, suggesting that malathion may be carcinogenic in humans. Although there are few other studies that can explore the observed findings, more data are needed for evaluation of subtype-specific findings. In addition, mechanistic data are still needed to provide a biologically plausible link between malathion use and NHL.

Supplementary Material
Refer to Web version on PubMed Central for supplementary material.

Acknowledgements
The contributions of the late Dr. Helen McDuffie to the Canadian study and of the late Dr. Leon Burmeister to the U.S. studies are recognized. The authors also thank Mr. Joe Barker at IMS Inc., for harmonizing the data for studies included in the NAPP.
Funding

This analysis was conducted with the support of a Prevention Research Grant from the Canadian Cancer Society Research Institute (CCSRI) (#703055) and the Intramural Research Program of the National Institutes of Health, National Cancer Institute, Division of Cancer Epidemiology (Z01 CP010119). The funders did not play a role in study design, analysis, interpretation of results, or preparation of the manuscript for publication.

References

Abdollahi M, Mostafalou S, Pourmournihamadi S, Shadnia S, 2004. Oxidative stress and cholinesterase inhibition in saliva and plasma of rats following subchronic exposure to malathion. Comp. Biochem. Physiol., Part C: Toxicol. Pharmacol 137, 29–34.

Alavanja MC, Hofmann JN, Lynch CF, Hines CJ, Barry KH, Barker J, Buckman DW, Thomas K, Sandler DP, Hoppin JA, Koutros S, Andreotti G, Lubin JH, Blair A, Beane Freeman LE, 2014. Non-hodgkin lymphoma risk and insecticide, fungicide and fumigant use in the Agricultural Health Study. PLoS One 9, e109332. [PubMed: 25337994]

Banerjee BD, Pasha ST, Hussain QZ, Koner BC, Ray A, 1998. A comparative evaluation of immunotoxicity of malathion after subchronic exposure in experimental animals. Indian J. Exp. Biol 36, 273–282. [PubMed: 9754060]

Blair A, Zahm SH, 1993. Patterns of pesticide use among farmers: implications for epidemiologic research. Epidemiology 4, 55–62. [PubMed: 8420582]

Blair A, Ritz B, Wesseling C, Freeman LB, 2015. Pesticides and human health. Occup. Environ. Med 72, 81–82. [PubMed: 25540410]

Blasiak J, Jalszynski P, Trzecki A, Szyfter K, 1999. In vitro studies on the genotoxicity of the organophosphorus insecticide malathion and its two analogues. Mutat. Res 445, 275–283. [PubMed: 10575436]

Bonner MR, Coble J, Blair A, Beane Freeman LE, Hoppin JA, Sandler DP, Alavanja MC, 2007. Malathion exposure and the incidence of cancer in the Agricultural Health Study. Am. J. Epidemiol 166, 1023–1034. [PubMed: 17720683]

Bonner MR, Williams BA, Rusiecki JA, Blair A, Beane Freeman LE, Hoppin JA, Dosemeci M, Lubin J, Sandler DP, Alavanja MC, 2010. Occupational exposure to terbufos and the incidence of cancer in the Agricultural Health Study. Cancer Causes Control 21, 871–877. [PubMed: 20155313]

Bouchard M, Gosselin NH, Brunet RC, Samuel O, Dumoulin MJ, Carrier G, 2003. A toxicokinetic model of malathion and its metabolites as a tool to assess human exposure and risk through measurements of urinary biomarkers. Toxicol. Sci 73, 182–194. [PubMed: 12657741]

Cantor KP, Blair A, Everett G, Gibson R, Burmeister LF, Brown LM, Schuman L, Dick FR, 1992. Pesticides and other agricultural risk factors for non-Hodgkin’s lymphoma among men in Iowa and Minnesota. Cancer Res. 52, 2447–2455. [PubMed: 1568215]

Carrico C, Gennings C, Wheeler DC, Factor-Litvak P, 2015. Characterization of weighted quantile sum regression for highly correlated data in a risk analysis setting. J. Agric. Biol. Environ. Stat 20, 100–120. [PubMed: 30505142]

Cerhan JR, Kricker A, Paltiel O, Flowers CR, Wang SS, Monnereau A, Blair A, Dal Maso L, Kane EV, Nieters A, Foran JM, Miligi L, et al., 2014. Medical history, lifestyle, family history, and occupational risk factors for diffuse large B-cell lymphoma: the InterLymph non-Hodgkin lymphoma subtypes project. J. Natl. Cancer Inst. Monogr 2014, 15–25. [PubMed: 25174023]

Chiu BC, Dave BJ, Blair A, Gapstur SM, Zahm SH, Weisenburger DD, 2006. Agricultural pesticide use and risk of t(14;18)-defined subtypes of non-Hodgkin lymphoma. Blood 108, 1363–1369. [PubMed: 16621961]

Ekstrom Smedby K, Vajdic CM, Falster M, Engels EA, Martinez-Maza O, Turner J, Hjalgrim H, Vineis P, Seniori Costantini A, Bracci PM, Holly EA, Willett E, et al., 2008. Autoimmune disorders and risk of non-Hodgkin lymphoma subtypes: a pooled analysis within the InterLymph Consortium. Blood 111, 4029–4038. [PubMed: 18263783]

Environmental Protection Agency (EPA), 2016. Malathion: Human Health Draft Risk Assessment for Registration Review. U.S. Environmental Protection Agency, Washington, DC. https://
Environmental Protection Agency (EPA), 2017. Pesticides Industry Sales and Usage, 2008–2012, Market Estimates. U.S. Environmental Protection Agency, Washington, DC. https://www.epa.gov/sites/production/files/2017-01/documents/pesticides-industry-sales-usage-2016_0.pdf, Accessed date: 27 September 2019.

Ferri GM, Specchia G, Mazza P, Ingravallo G, Intranuovo G, Guastadisegno CM, Congedo ML, Lagioia G, Loparco MC, Giordano A, Perrone T, Guadio F, et al., 2017. Risk of lymphoma subtypes by occupational exposure in Southern Italy. J. Occup. Med. Toxicol 12, 31. [PubMed: 29201133]

Fritschi L, Benke G, Hughes AM, Kricker A, Turner J, Vajdic CM, Grulich A, Milliken S, Kaldor J, Armstrong BK, 2005. Occupational exposure to pesticides and risk of non-Hodgkin’s lymphoma. Am. J. Epidemiol 162, 849–857. [PubMed: 16177143]

Galloway T, Handy R, 2003. Immunotoxicity of organophosphorous pesticides. Ecotoxicology 12, 345–363. [PubMed: 12739880]

Hoar SK, Blair A, Holmes PF, Boyes CD, Robel RJ, Hoover R, Fraumeni JF Jr., 1986. Agricultural herbicide use and risk of lymphoma and soft-tissue sarcoma. JAMA 256, 1141–1147. [PubMed: 3801091]

International Agency for Research on Cancer (IARC), 1987a. Some Carbamates, Thiocarbamates and Carbazides. IARC Monogr. Eval. Carcinog. Risks Hum 12.

International Agency for Research on Cancer (IARC), 1987b. Miscellaneous Pesticides. IARC Monogr. Eval. Carcinog. Risks Hum 30.

IARC, 2015, 2015. International Agency for Research on Cancer (IARC), Malathion. 112 IARC, Lyon, France.

Health Canada, 2015. Pest Control Products Sales Report 2015. https://www.canada.ca/en/health-canada/services/consumer-product-safety/reports-publications/pesticides-pest-management/corporate-plans-reports/pest-control-products-sales-report.html, Accessed date: 29 September 2019.

Koutros S, Beane Freeman LE, Lubin JH, Heltshe SL, Andreotti G, Barry KH, DellaValle CT, Hoppin JA, Sandler DP, Lynch CF, Blair A, Alavanja MC, 2013. Risk of total and aggressive prostate cancer and pesticide use in the Agricultural Health Study. Am. J. Epidemiol 177, 59–74. [PubMed: 23171882]

Leon ME, Schinasi LH, Lebailly P, Beane Freeman LE, Nordby KC, Ferro G, Monnercaau A, Brouwer M, Tual S, Baldi I, Kjaerheim K, Hofmann JN, Kristensen P, Koutros S, Straif K, Kromhout H, Shucz J, 2019. Pesticide use and risk of non-Hodgkin lymphoid malignancies in agricultural cohorts from France, Norway, and the USA: A meta-analysis from the AGRICOH Consortium. Int. J. Epidemiol 10.1093/ije/dyz017. (submitted).

Marshall JR, Priore R, Graham S, Brasure J, 1981. On the distortion of risk estimates in multiple exposure level case-control studies. Am. J. Epidemiol 113, 464–473. [PubMed: 7211828]

McDuffie HH, Pahtwa P, McLaughlin JR, Spinelli JJ, Fincham S, Dosman JA, Robson D, Skinnider LF, Choi NW, 2001. Non-Hodgkin’s lymphoma and specific pesticide exposures in men: cross-Canada study of pesticides and health. Cancer Epidemiol. Biomark. Prev 10, 1155–1163.

Mills PK, Yang R, Riordan D, 2005. Lymphohematopoietic cancers in the United Farm Workers of America (UFW), 1988–2001. Cancer Causes Control 16, 823–830. [PubMed: 16132792]

Morton LM, Slager SL, Cerhan JR, Wang SS, Vajdic CM, Skibola CF, Bracci PM, de Sanjose S, Smedby KE, Chiu BC, Zhang Y, Mbulaitzye SM, et al., 2014. Etiologic heterogeneity among non-Hodgkin lymphoma subtypes: the InterLymph Non-Hodgkin Lymphoma Subtypes Project. J. Natl. Cancer Inst. Monogr 2014, 130–144. [PubMed: 25174034]

Perrotta C, Staines A, Cocco P, 2008. Multiple myeloma and farming. A systematic review of 30 years of research. Where next? J. Occup. Med. Toxicol 3, 27. [PubMed: 19014617]

Pluth JM, Nicklas JA, O’Neill JP, Albertini RJ, 1996. Increased frequency of specific genomic deletions resulting from in vitro malathion exposure. Cancer Res. 56, 2393–2399. [PubMed: 8625317]
Schroeder JC, Olshan AF, Baric R, Dent GA, Weinberg CR, Yount B, Cerhan JR, Lynch CF, Schuman LM, Tolbert PE, Rothman N, Cantor KP, Blair A, 2001. Agricultural risk factors for t(14;18) subtypes of non-Hodgkin’s lymphoma. Epidemiology 12, 701–709. [PubMed: 11679800]

Waddell BL, Zahm SH, Baris D, Weisenburger DD, Holmes F, Burmeister LF, Cantor KP, Blair A, 2001. Agricultural use of organophosphate pesticides and the risk of non-Hodgkin’s lymphoma among male farmers (United States). Cancer Causes Control 12, 509–517. [PubMed: 11519759]

Zahm SH, Weisenburger DD, Babbitt PA, Saal RC, Vaught JB, Cantor KP, Blair A, 1990. A case-control study of non-Hodgkin’s lymphoma and the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) in eastern Nebraska. Epidemiology 1, 349–356. [PubMed: 2078610]

Zheng T, Zahm SH, Cantor KP, Weisenburger DD, Zhang Y, Blair A, 2001. Agricultural exposure to carbamate pesticides and risk of non-Hodgkin lymphoma. J. Occup. Environ. Med 43, 641–649. [PubMed: 11464396]
Table 1
Demographic characteristics of lymphoma cases and controls in the NAPP.

| Variable                                      | Cases N (%) | Controls N (%) |
|-----------------------------------------------|-------------|----------------|
|                                               | 1690 (100%) | 5131 (100%)    |
| Histological sub-type                         |             |                |
| Follicular Lymphoma (EL)                      | 468 (27.69) |                |
| Diffuse Large B Cell Lymphoma (DLBCL)         | 647 (38.28) |                |
| Small Lymphocytic Lymphoma (SLL)              | 171 (10.12) |                |
| Follicular Lymphoma (FL)                      | 404 (23.91) |                |
| State/Province                                |             |                |
| U.S.                                          |             |                |
| Iowa                                          | 292 (17.28) | 604 (11.77)    |
| Minnesota                                     | 329 (19.47) | 642 (12.51)    |
| Nebraska                                      | 368 (21.78) | 1449 (28.24)   |
| Kansas                                        | 188 (11.12) | 930 (18.13)    |
| Canada                                        |             |                |
| Quebec                                        | 117 (6.92)  | 291 (5.67)     |
| Ontario                                       | 142 (8.40)  | 585 (11.40)    |
| Manitoba                                      | 34 (2.01)   | 113 (2.20)     |
| Saskatchewan                                  | 29 (1.72)   | 91 (1.77)      |
| Alberta                                       | 65 (3.85)   | 196 (3.82)     |
| British Columbia                              | 126 (7.46)  | 230 (4.48)     |
| Age (years)                                   |             |                |
| ≥19 to ≤29                                    | 26 (1.54)   | 277 (5.40)     |
| ≥20 to ≤29                                    | 97 (5.74)   | 445 (8.67)     |
| ≥30 to ≤39                                    | 159 (9.41)  | 514 (10.02)    |
| ≥40 to ≤49                                    | 288 (17.04) | 726 (14.15)    |
| ≥50 to ≤59                                    | 564 (33.37) | 1264 (24.63)   |
| ≥60 to ≤69                                    | 402 (23.79) | 1189 (23.17)   |
| ≥70 to ≤79                                    | 137 (8.11)  | 610 (11.89)    |
| ≥80                                           | 17 (1.01)   | 106 (2.07)     |
| Sex                                           |             |                |
| Male                                          | 1506 (89.11)| 4424 (86.22)   |
| Female                                        | 184 (10.89) | 707 (13.78)    |
| Respondent type                               |             |                |
| Self                                          | 1140 (67.46)| 3372 (65.72)   |
| Proxy                                         | 533 (31.54) | 1692 (32.98)   |
| Unknown/missing                               | 17 (1.01)   | 67 (1.31)      |
| Lymphohematopoietic cancer in a first-degree relative |         |                |
| No                                            | 1493 (88.34)| 4790 (93.35)   |
| Yes                                           | 139 (8.22)  | 202 (3.94)     |
| Unknown/missing                               | 58 (3.43)   | 139 (2.71)     |
Table 2

Associations between ever use of organophosphate and carbamate insecticides and lymphoma in the NAPP\textsuperscript{a}.

| Pesticide—Ever use | Cases | Controls | OR (95% CI) | OR (95% CI)\textsuperscript{b} |
|--------------------|-------|----------|-------------|-----------------------------|
| **Organophosphate (OP)** |       |          |             |                             |
| Malathion           |       |          |             |                             |
| Never used          | 1518  | 4839     | 1           | 1                           |
| Ever used           | 172   | 292      | 1.63 (1.33, 2.00) | 1.43 (1.14, 1.81) |
| Diazinon            |       |          |             |                             |
| Never used          | 1605  | 4994     | 1           | 1                           |
| Ever used           | 85    | 137      | 1.69 (1.27, 2.24) | 1.25 (0.90, 1.74) |
| Fonofos             |       |          |             |                             |
| Never used          | 1640  | 5053     | 1           | 1                           |
| Ever used           | 50    | 78       | 1.75 (1.21, 2.55) | 1.23 (0.81, 1.87) |
| Phorate             |       |          |             |                             |
| Never used          | 1644  | 5022     | 1           | 1                           |
| Ever used           | 46    | 109      | 1.07 (0.75, 1.54) |  |  |
| Dimethoate          |       |          |             |                             |
| Never used          | 1665  | 5056     | 1           | 1                           |
| Ever used           | 35    | 75       | 1.34 (0.89, 2.03) |  |  |
| Tefbufos            |       |          |             |                             |
| Never used          | 1657  | 5046     | 1           | 1                           |
| Ever used           | 33    | 85       | 0.94 (0.62, 1.44) |  |  |
| Dichlorvos          |       |          |             |                             |
| Never used          | 1665  | 5078     | 1           | 1                           |
| Ever used           | 25    | 53       | 1.04 (0.64, 1.71) |  |  |
| Coumaphos           |       |          |             |                             |
| Never used          | 1665  | 5091     | 1           | 1                           |
| Ever used           | 25    | 40       | 1.56 (0.93, 2.62) |  |  |
| Famphur             |       |          |             |                             |
| Never used          | 1670  | 5078     | 1           | 1                           |
| Ever used           | 20    | 53       | 1.02 (0.60, 1.73) |  |  |
| Trichlorfon         |       |          |             |                             |
| Never used          | 1680  | 5115     | 1           | 1                           |
| Ever used           | 10    | 16       | 1.80 (0.80, 4.05) |  |  |
| Chlorpyrifos        |       |          |             |                             |
| Never used          | 1680  | 5110     | 1           | 1                           |
| Ever used           | 10    | 21       | 1.77 (0.82, 3.81) |  |  |
| **Carbamate**       |       |          |             |                             |
| Carbofuran          |       |          |             |                             |
| Never used          | 1612  | 4969     | 1           | 1                           |
| Ever used           | 78    | 162      | 1.29 (0.97, 1.71) |  |  |
| Carbaryl            |       |          |             |                             |

\textsuperscript{a}NAPP = National Agricultural Pesticide Exposure Study.

\textsuperscript{b}Adjusted for age, sex, race, and other exposures.
| Pesticide—Ever use | Cases  | Controls | OR (95% CI) | OR (95% CI)<sup>b</sup> |
|--------------------|--------|----------|-------------|--------------------------|
| Never used         | 1615   | 5004     | 1           | 1                        |
| Ever used          | 75     | 127      | 1.62 (1.20, 2.18) | 1.17 (0.84, 1.64)        |

<sup>a</sup> Adjusted for age, study, gender, family history of lymphohematopoietic cancer.

<sup>b</sup> Mutually adjusted for: malathion, diazinon, fonofos, carbaryl; results not shown for non-significant pesticides (all further attenuated towards unity).
Table 3

Associations between duration of organophosphate and carbamate insecticide use and lymphoma in the NAPP.

| Pesticide | Cases | Controls | OR<sup>a</sup> (95% CI) | OR<sup>b</sup> (95% CI) |
|-----------|-------|----------|--------------------------|--------------------------|
| Organophosphate (OP) | | | | |
| Malathion | | | | |
| Unexposed | 1352  | 3903 | 1 | 1 |
| < 6 years | 65 | 128 | 1.40 (1.01, 1.92) | 1.25 (0.90, 1.75) |
| ≥ 6 years | 103 | 152 | 1.79 (1.38, 2.32) | 1.57 (1.18, 2.10) |
| P<sub>trend</sub> | < 0.0001 | < 0.01 |
| Diazinon | | | | |
| Unexposed | 1437 | 4048 | 1 | 1 |
| < 8 years | 49 | 66 | 2.03 (1.36, 3.02) | 1.51 (0.97, 2.34) |
| ≥ 8 years | 34 | 69 | 1.30 (0.84, 2.01) | 0.97 (0.61, 1.55) |
| P<sub>trend</sub> | 0.08 | 0.96 |
| Fonofos | | | | |
| Unexposed | 1471 | 4107 | 1 | 1 |
| < 6 years | 26 | 37 | 1.80 (1.02, 3.16) | 1.25 (0.69, 2.28) |
| ≥ 6 years | 23 | 39 | 1.64 (0.90, 3.00) | 1.20 (0.63, 2.27) |
| P<sub>trend</sub> | 0.03 | 0.47 |
| Phorate | | | | |
| Unexposed | 1474 | 4078 | 1 | 1 |
| < 6 years | 22 | 52 | 0.98 (0.58, 1.67) | |
| ≥ 6 years | 24 | 53 | 1.21 (0.72, 2.02) | |
| P<sub>trend</sub> | 0.45 | |
| Dimethoate | | | | |
| Unexposed | 1485 | 4113 | 1 | 1 |
| < 8 years | 17 | 35 | 1.36 (0.75, 2.47) | |
| ≥ 8 years | 18 | 35 | 1.46 (0.81, 2.65) | |
| P<sub>trend</sub> | 0.07 | |
| Terbufos | | | | |
| Unexposed | 1487 | 4098 | 1 | 1 |
| < 4 years | 12 | 37 | 0.77 (0.40, 1.51) | |
| ≥ 4 years | 21 | 48 | 1.06 (0.62, 1.81) | |
| P<sub>trend</sub> | 0.94 | |
| Dichlorvos | | | | |
| Unexposed | 1496 | 4131 | 1 | 1 |
| < 10 years | 10 | 18 | 1.18 (0.53, 2.60) | |
| ≥ 10 years | 14 | 34 | 0.88 (0.46, 1.69) | |
| P<sub>trend</sub> | 0.80 | |
| Coumaphos | | | | |
| Unexposed | 1496 | 4148 | 1 | 1 |

*Environ Int. Author manuscript; available in PMC 2020 June 01.*
| Pesticide | Cases | Controls | OR<sup>a</sup> (95% CI) | OR<sup>b</sup> (95% CI) |
|-----------|-------|----------|-------------------------|-------------------------|
|          | < 4 years | 7 | 13 | 1.11 (0.40, 3.11) | |
|          | ≥ 4 years | 17 | 22 | 1.89 (0.99, 3.62) | |
|          | P<sub>trend</sub> | | | 0.05 | |
| Carbamate | Carbofuran | | | | |
|          | Unexposed | 1449 | 4040 | 1 | |
|          | < 8 years | 44 | 71 | 1.50 (1.01, 2.22) | |
|          | ≥ 8 years | 27 | 72 | 0.91 (0.57, 1.45) | |
|          | P<sub>trend</sub> | | | 0.83 | |
|          | Carbaryl | | | | |
|          | Unexposed | 1447 | 4064 | 1 | 1 |
|          | < 6 years | 38 | 63 | 1.50 (0.97, 2.30) | 1.11 (0.70, 1.74) |
|          | ≥ 6 years | 35 | 56 | 1.75 (1.13, 2.70) | 1.24 (0.78, 1.99) |
|          | P<sub>trend</sub> | | | < 0.01 | 0.35 |

<sup>a</sup> Adjusted for age, study, gender, family history of lymphohematopoietic cancer.

<sup>b</sup> Mutually adjusted for: malathion, diazinon, fonofos, carbaryl; results not shown for non-significant pesticides (all further attenuated towards unity).
Table 4

Associations between ever use of organophosphate and carbamate insecticides and lymphoma subtypes in the NAPPa.

| Pesticide   | FL (n = 468) | DLBCL (n = 647) | SLL (n = 171) | Other (n = 400) |
|-------------|-------------|-----------------|---------------|-----------------|
|             | Cases       | OR (95% CI)     | Cases         | OR (95% CI)     | Cases          | OR (95% CI)     | Cases          | OR (95% CI)     |
| Organophosphate (OP) |             |                 |               |                 |               |                 |               |                 |
| Malathion   |             |                 |               |                 |               |                 |               |                 |
| Never used  | 413         | 1               | 579           | 1               | 154           | 1               | 368           | 1               |
| Ever used   | 55          | **1.80 (1.31, 2.46)** | **1.58 (1.11, 2.27)** | **1.61 (1.16, 2.22)** | **1.50 (0.89, 2.54)** | **1.04 (0.57, 1.91)** | **1.27 (0.86, 1.87)** | **1.18 (0.77, 1.83)** |
| Diazinon    |             |                 |               |                 |               |                 |               |                 |
| Never used  | 441         | 1               | 615           | 1               | 160           | 1               | 385           | 1               |
| Ever used   | 27          | **1.75 (1.14, 2.71)** | **1.20 (0.72, 2.02)** | **1.26 (0.79, 2.03)** | **2.24 (1.17, 4.30)** | **1.67 (0.77, 3.61)** | **1.30 (0.75, 2.25)** | **1.10 (0.59, 2.07)** |
| Fonofos     |             |                 |               |                 |               |                 |               |                 |
| Never used  | 450         | 1               | 629           | 1               | 166           | 1               | 391           | 1               |
| Ever used   | 18          | **1.95 (1.14, 3.34)** | **1.35 (0.73, 2.48)** | **1.22 (0.67, 2.22)** | **1.87 (0.73, 4.81)** | **1.02 (0.35, 2.95)** | **1.39 (0.68, 2.84)** | **1.18 (0.54, 2.61)** |
| Phorate     |             |                 |               |                 |               |                 |               |                 |
| Never used  | 456         | 1               | 631           | 1               | 163           | 1               | 390           | 1               |
| Ever used   | 12          | 0.83 (0.45, 1.54) | 16            | 1.09 (0.63, 1.88) | 8             | 1.91 (0.89, 4.10) | 10            | 1.05 (0.54, 2.05) |
| Dimethoate  |             |                 |               |                 |               |                 |               |                 |
| Never used  | 457         | 1               | 634           | 1               | 169           | 1               | 391           | 1               |
| Ever used   | 11          | 1.62 (0.85, 3.12) | 13            | 1.26 (0.69, 2.31) | 2             | ¶               | 9             | 1.42 (0.70, 2.89) |
| Terbufos    |             |                 |               |                 |               |                 |               |                 |
| Never used  | 458         | 1               | 637           | 1               | 166           | 1               | 392           | 1               |
| Ever used   | 10          | 0.83 (0.43, 1.64) | 10            | 0.85 (0.43, 1.67) | 5             | 1.46 (0.57, 3.75) | 8             | 1.02 (0.48, 2.15) |
| Dichlorvos  |             |                 |               |                 |               |                 |               |                 |
| Never used  | 457         | 1               | 644           | 1               | 169           | 1               | 391           | 1               |
| Ever used   | 11          | 1.31 (0.67, 2.57) | 3             | ¶               | 2             | ¶               | 9             | 1.75 (0.84, 3.64) |
| Coumaphos   |             |                 |               |                 |               |                 |               |                 |
| Never used  | 462         | 1               | 638           | 1               | 165           | 1               | 396           | 1               |
| Ever used   | 6           | 1.09 (0.45, 2.63) | 9             | 1.63 (0.78, 3.42) | 6             | **3.97 (1.60, 9.84)** | 4             | ¶               |
| Pesticide | FL (n = 468) | DLBCL (n = 647) | SLL (n = 171) | Other (n = 400) |
|-----------|--------------|-----------------|---------------|----------------|
|           | Cases | OR (95% CI) | Cases | OR (95% CI) | Cases | OR (95% CI) | Cases | OR (95% CI) |
| Carbamate |       |             |       |             |       |             |       |             |
| Carbofuran |       |             |       |             |       |             |       |             |
| Never used | 444 | 1 | 615 | 1 | 164 | 1 | 385 | 1 |
| Ever used  | 24  | 1.25 (0.80, 1.97) | 32  | 1.50 (1.00, 2.23) | 7  | 1.10 (0.50, 2.42) | 15 | 1.08 (0.63, 1.88) |
| Carbaryl   |       |             |       |             |       |             |       |             |
| Never used | 445 | 1 | 621 | 1 | 159 | 1 | 386 | 1 |
| Ever used  | 23  | 1.66 (1.05, 2.64) | 26  | 1.52 (0.99, 2.35) | 12 | 2.59 (1.39, 4.85) | 14 | 1.29 (0.73, 2.27) |

- Results suppressed where case count was low (n < 5).
- Adjusted for the top five correlated pesticides.
- Adjusted for age, study, gender, family history of lymphohematopoietic cancer; All tests for heterogeneity across NHL subtypes resulted in p > 0.05.
- Mutually adjusted for: malathion, diazinon, fonofos, carbaryl; results not shown for non-significant pesticides (all further attenuated towards unity).