A Meta-analysis of Sub-lethal Pesticide Exposure and Effects on Sensitive Receptors: Children

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Abbreviations: OR - odds ratio; CI - confidence interval; CBT - childhood brain tumor .

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SUMMARY: A systematic review of the existing observational epidemiologic studies revealed positive associations between residential indoor insecticide exposures during childhood and childhood hemotopoietic cancers, including leukemia and lymphoma. A weaker positive association between childhood herbicide exposure and leukemia was also observed.

ABSTRACT

Background and objective: There is an increasing concern of chronic low level pesticide exposure during childhood and their influence on childhood cancers. In this meta-analysis, we aimed to examine associations between residential childhood pesticide exposures and childhood cancers.

Method: We included all observational studies published in PubMed before February 2014. Effect sizes and 95% confidence intervals (CIs) were calculated using a random effect model with inverse variance weights. The literature search yielded 267 studies that were matched to the keywords, and sixteen studies were included in the meta-analysis.

Results: We found that childhood exposure to indoor residential insecticides was associated with a significant increase in risk of childhood leukemia (OR=1.47; 95% CI, 1.26-1.72; I^2=30%) and childhood lymphomas (OR=1.43; 95% CI, 1.15-1.78; I^2=0%). This risk was further elevated for acute leukemia (OR= 1.59; 95% CI, 1.39-1.81; I^2=0%). A significant increase of risk for leukemia was also associated with herbicide exposure (OR=1.25; 95% CI, 1.09-1.44; I^2=0%). A positive but not statistically significant association between home pesticides or herbicide exposure during childhood and childhood brain tumor was observed. There was no statistically significant association between outdoor insecticide exposures and any types of childhood cancers.

Concussions: Results from the meta-analysis indicated that children exposed to indoor insecticides would have higher risk of childhood hemotopoietic cancers. Because of the limited studies, further researches are needed to confirm the association between indoor pesticide exposures and childhood cancers. Meanwhile, preventive measures should be considered in order to reduce children's exposure to pesticides at home.

Introduction

Although pesticides are essential for eradication of pests in agriculture and for public health, they are toxic chemicals and can affect children's health in a variety of settings, such as at home, in parks and gardens, and on school ground daily. When children play on the floor or ground/lawn where pesticides are commonly applied and put objects/hands into their mouths, they increase their chances of exposure to pesticides. Studies have shown that households with children are commonly found to use and store pesticide products.[1-3] The use of pesticides at childcare facilities,[4] athletic fields,[5] school ground[6] could all present potential exposures and health hazards to children.

Because children are still developing, their immune systems may provide less protection, and their enzymatic and metabolic systems may be less able to detoxify and excrete pesticides than those of adults. Therefore, they are more vulnerable to pesticides. Epidemiological studies also support that pesticide exposure can have greater impact on children's health than adults.[7,8] Children exposed to pesticides at homes or at school have experienced acute toxic effects on their respiratory, gastrointestinal, nervous, and endocrine systems, as well as other serious medical outcomes.[6,9,10] The concern of health effects associated with long-term low level exposure to pesticides in children is increasing in recent years, and leads to a substantial amount of epidemiological studies demonstrating the associations between pesticide exposures and childhood cancers.[11-16] However, most of these studies focused on parental occupational exposure or agricultural exposure. Based on a limited number of observational epidemiological studies, a few systematic reviews were

conducted in examining the association between residential pesticide exposure and childhood cancers, but these relationships were not clearly elucidated in these reviews as authors had included parental occupational exposure data or studies investigating multiple risk factors together which increases chance findings due to multiple statistical testing.[12-14]

The aim of our study was to perform a systemic review of the currently available epidemiologic evidence to estimate the relationship between residential (or non-occupational/non-agricultural) childhood pesticide exposure and childhood cancer in an effort to provide scientific evidence for prevention actions and make legislative decisions.

Methods

Data Source and Study Selection

We conducted a literature search in PubMed for papers published prior to February 2014. We used the combinations of the following key words to identify relevant papers: [residential, urban, indoor, house, home, household or school] AND [pesticide, insecticide, herbicide, or fungicide, organochlorine or organophosphorus] AND [children, childhood, youth, teenager, adolescent, toddler, infant, neonate, prenatal or postnatal] AND [cancer, tumor, malignancy, neoplasm, neuroblastoma, lymphoma, leukemia, sarcoma, astrocytoma, glioma, craniopharyngioma, ependymoma, rhabdomyosarcoma or retinoblastoma]. The search was limited to human studies and written in English. All abstracts were screened to determine the suitability for the review.

We included original epidemiological studies reporting non-occupational pesticides exposure and children's health. We used the following criteria to exclude papers from the meta-analysis. We excluded: 1) those not reporting original results

(such as review articles, ecologic studies, case reports); 2) toxicological studies; 3) studies conducted on occupational settings, hazardous waste sites, farms, or proximity to agricultural pesticides; 4) studies involving only adults or children with down's syndrome or without reporting children's health outcomes; 5) studies with only pesticides in general (no specific pesticide groups) or studies with a list of chemicals including pesticides; 6) studies without specific windows of exposure; or 7) duplicate studies including subjects already included in another more complete or more recent study examining a greater number of subjects.

Two authors of this paper (M.C and A.L.) independently retrieved and screened all the titles and abstracts of studies according to the predetermined selection criteria. We also manually screened references in the selected articles for additional relevant studies. The full texts of the studies with potential eligibility were obtained and assessed independently by the two authors (M.C. and A.L.) for final inclusion. Any discrepancies were resolved by consensus.

Data extraction

From each eligible study, 2 authors (M.C. and C.C) extracted information about the study design, the location, study period, study population and control characteristic, exposure assessment method, outcomes, and key findings. The same two authors independently extracted and tabulated the most relevant estimators, namely the odd ratio (OR) and the 95% confidence intervals (CIs). The OR and CIs are two commonly used estimators in most meta-analyses concentrating on identifying health risks associated with environmental chemical exposures.[12,13,15,17-20] The results were compared, and the consensus was obtained prior to the meta-analysis.

The data were sub-grouped and calculated after classification of the studies based on the pesticide categories, the exposure locations and the type of cancer in the following stratified meta-analyses:

- Pesticide category and exposure locations: home pesticide (studies including indoor pesticides), herbicides exposure, outdoor insecticides exposure
- Cancer types: acute leukemia, leukemia, lymphoma, hematopoietic cancers (leukemia and lymphoma), childhood brain tumor, all childhood cancers (including neuroblastoma, Wilms tumor, and soft tissue sarcoma)

Data from professional home treatment was calculated by performing a meta-analysis on data with professional home treatment together with parental home treatment or data for professional home treatments alone (if number of studies ≥2). Dose effect was also calculated by performing a separate meta-analysis by replacing data with data of highest frequency of pesticide uses.

Data Analysis

We performed the meta-analysis using the Comprehensive Meta Analysis version 2 (Biostat, Inc, 2007) in accordance with Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[21] The random effects model was used in this analysis, and random-effects summary of ORs and 95% CIs were estimated to provide an indicator of the overall strength of association between childhood pesticide exposure and childhood cancers, which is illustrated by forest plots. In the plots, the CI for each study is represented by a horizontal line and the estimate of summary OR by a box square. The box area is proportional to the weight which is the inverse of the variance of the effect estimate from each individual study in the meta-analysis. The diamond and

broken vertical line for type of cancer represent the subtotal summary estimate, with confidence interval given by its width. The null hypothesis is 1 and represent by the central vertical dash line from top to bottom of the plot. All statistical tests were two sided, and a *p*-value of < 0.05 was considered statistically significant.

- *Assessment of heterogeneity*

Since the current review includes limited number of studies, and the conventional statistical approach to evaluating heterogeneity using a chi-square test (Cochran's Q) has low power when there are few studies,[22] therefore I^2 statistic was used to quantify the amount of variation in results across studies that is due to heterogeneity. I^2 can be interpreted as a measure of the percentage of the total variation that can't be explained by chance.[22] An I^2 value of 25%, 50%, or 75% can be used approximately as low, moderate, or high degrees of heterogeneity.[22] A value of 0% indicates no observed heterogeneity, and the estimation from either fixed effects model or random effects model will be the same. The *p*-values for heterogeneity are based on the Q-statistic.

- *Publication bias*

Publication bias was tested with funnel plots and Egger's test.[23] The funnel plot was made by the natural logarithm of the estimate of ORs (lnORs) versus the standard error (1/SE) from all included individual studies in a meta-analysis. Funnel plot asymmetry, which can result from unpublished small studies without statistically significant effects, was tested using the linear regression method.[23]

- *Sensitivity analysis*

To determine the robustness as well as whether some of the selections have a major effect on the results of this meta-analysis, we conducted several sensitivity analyses by:

1) Removing the study with highest weight;
2) Removing the studies reporting extreme ORs (the highest and the lowest);
3) Removing hospital based studies (or performing a meta-analysis including only population based studies).
4) Removing extended exposure window or ill-defined pesticide category

Results

Study identification and characteristics:

Figure 1 describes study identification, screening and selection process. From the initial 267 articles identified from PubMed search, 191 were excluded based on their titles or abstracts, and 11 were excluded based on the full text. We further excluded 4 studies from the analysis because of duplicated population or study population located in a region with high agricultural pesticide use or insufficient data to enable the calculation.[24-27] No additional articles were identified from reviewing references cited in the included articles. A total of 16 articles meeting full inclusion criteria were eventually included in the meta-analysis.[28-43]

The characteristics of the studies used in the meta-analysis are shown in Table 1. All 16 studies are case-controlled studies, and were published between 1993 and 2012. The participation rates for most studies were ranging between 65% and 96% for case groups, and 61% and 99% for control groups. The sample sizes ranged from 45[32] to 1184 cases,[38] and the upper age limits of case groups were between 9 and 19 years.

Among these studies, 10 were associated with hematopoietic malignancies, 5 with childhood brain tumor (CBT), and 2 with Wilms tumor and neuroblastoma, including 4 studies reported data on more than one malignancy.[36-38,41]

The current meta-analysis was run separately for the two windows of exposure: prenatal and after birth until diagnosis of diseases, and after birth until diagnosis. Since the outcome from either window of exposure was similar (as shown in the supplement), the following results and discussion were focused on the window from prenatal and after birth until diagnosis.

Publication bias

We examined the main findings from all studies and included in an inverse funnel plot of log-transformed odds ratio versus SE. Although limited by the small number of studies included, there was no clear trend of publication bias (or asymmetry) from visual inspection of the plot with Egger's test *p*-values of 0.92, 0.10, and 0.26 of for home pesticides, herbicides and outdoor insecticide exposures, respectively.

Study synthesis

Table 2 summarizes the results of the sub-group meta-analyses and the assessment of heterogeneity. The results of 13 studies on home pesticide exposure, which was grouped by different types of childhood cancers and arrayed by different years of publication, are shown in Figure 2. Exposure to indoor insecticides during childhood was associated with a significant increase in risk of childhood leukemia (OR=1.47; 95% CI, 1.26-1.72; I^2=30%) and childhood lymphomas (OR=1.43; 95% CI, 1.15-1.78; I^2=0%). Further sub-group analysis by combining studies on acute leukemia (AL) yield elevated risks for exposure to both home pesticides (OR= 1.55; 95% CI, 1.38-

1.75) and indoor insecticides (OR= 1.59; 95% CI, 1.39-1.81) with significantly reduced heterogeneities (I^2 of 0%). Combining studies on leukemia and lymphoma, a statistically significant association between childhood hematopoietic malignancies and home pesticides (11 out of 12 data were from indoor insecticides) exposure during childhood was observed with low degree of heterogeneity (OR=1.46; 95% CI, 1.32-1.60; I^2 ≤5%). A positive but not statistically significant association between home pesticides exposure during childhood and CBT was observed (OR=1.22; 95% CI: 0.83-1.81; I^2 = 23%) and this association was further reduced after combined with professional home treatment (OR=1.11; 95% CI:0.87-1.42; I^2 = 5%).

We conducted sensitivity analysis (Table Supplement) on the results shown statistically significant associations to test if these results were influenced by one or two studies. Sensitivity analysis by removing highest weights, exclusion of extreme ORs, or deleting hospital/friends controls didn't change the statistically significant associations between home pesticide (or indoor insecticides) exposure and childhood AL/leukemia/lymphoma/childhood hematopoietic malignancies (shown in supplement Table 1). Heterogeneities were significantly reduced (most I^2 were 0%) after extreme ORs were removed in the sensitivity analyses. When we replaced the indoor pesticide data of Ma et al[37] with insecticides data in the re-run meta-analysis, the result was very similar, which was consistent with the statement by the authors that "there was a considerable overlap between the definition as well as the results between indoor pesticides and insecticides".

Sub-group analysis on dose and multiple agents effect yielded a statistically significant increased risk for childhood leukemia (OR=1.92; 95% CI, 1.27-2.89) and

hematopoietic malignancies (OR=2.04; 95% CI, 1.40-2.97). However, when the studies on professional home treatment were grouped together, the apparent significant increased risk for childhood leukemia became not statistically significant. Part of the reason could be due to the small number of studies included.

Combining all studies reporting childhood cancers (including neuroblastoma[31] and Wilms tumor[30]) and home pesticide childhood exposure yielded a meta-rate summary OR of 1.40 (95% CI: 1.28-1.52) with a low degree of heterogeneity (I^2 of 5%). Therefore, the results shows that there is a statistically significant risk of childhood cancers associated with exposures to home pesticide, especially indoor insecticides, during childhood.

Figure 3 shows the cancer risks for residential herbicides exposure during childhood. A statistically significant association between childhood leukemia (including AL) and exposure to herbicides during childhood (OR=1.25; 95% CI, 1.09-1.44, I^2=0%) was observed, and the sensitivity analysis confirmed the robustness of this association. The observed association with increase in risk of childhood lymphoma and child brain tumor became not statistically significant during the sensitivity analyses. When studies on all types of childhood cancers combined, including neuroblastoma[31] and Wilms tumor,[30] a statistically significant association with residential herbicide exposure was observed (OR=1.35; 95% CI:1.16-1.55; I^2 = 23%).

Lastly, we did not find any statistically significant association between exposure to outdoor insecticides or outdoor pesticides (data not shown) and any types of childhood cancers.

Discussion

In this meta-analysis, we examined 16 epidemiological studies on the possible association between residential pesticide exposure during childhood and childhood cancers. Overall, the results suggest that cancer risks are related to the type and the location of pesticide uses during childhood. Exposure to residential indoor insecticides but not outdoor insecticides during childhood was significantly associated with an increasing risk of childhood cancers including leukemia, AL, and lymphoma, but not CBT. Among the five studies reporting CBT outcomes in the analyses, four studies didn't provide specific exposure locations. This ambiguity between indoor and outdoor applications could dilute the true effects of residential pesticides, and therefore results in the association towards the null. Similarly, adding professional home treatment in hematopoietic cancers and CBT lowered the summary ORs could be also due to the ambiguity of exposure location. The most statistically significant summary ORs were observed in the association between childhood exposure to indoor insecticides and the risk of AL, and the risk of childhood hematopoietic malignancies increased with the frequency of use. This observation provides additional support to the positive exposure-response relationship between residential indoor insecticide uses and the increased risk for childhood hematopoietic malignancies. Exposure to herbicides was also associated with a slightly increased risk of childhood cancers in general, which include AL, leukemia, lymphoma and CBT, although statistical significance was only true to the association with AL and leukemia. The most statistically significant summary ORs were observed in the association between childhood exposure to herbicides and the risk of acute leukemia. However, due to the small number of studies included, more studies are needed to confirm this association with childhood herbicide exposures.

Results from the current analysis are in agreement with the main findings of two previously published studies which both observed significant association for insecticides and childhood leukemia.[13,14] Although these results were based on a small number of studies, the consistency of the main findings suggests that there is likely an increased risk of childhood leukemia associated with indoor insecticide exposure during childhood. We have observed a slightly increased risk of childhood leukemia associated with exposure to herbicides with no evidence of heterogeneity. This finding is also consistent with that reported by Van Maele-Fabry et al[14], but not by Turner et al[13], and both reported a high degree of heterogeneity (I^2 of 61% and 72%, respectively). Neither our study nor the study of Turner et al[13] observed any association between childhood leukemia and exposure to outdoor insecticides during childhood. Like Van Maele-Fabry et al,[14] we also didn't observe any association between childhood leukemia and outdoor pesticide exposure (data not shown). There was a third study reporting that pesticide use at home or in the garden was statistically associated with the increased risk of lymphoma, leukemia and CBT.[20] However, Vinson et al[20] did not provide information on specific pesticide categories or locations of pesticide uses in their analysis, and most of the study results were related to occupational exposure. Therefore, we could not directly compare our results to those reported by Vinson et al.[20]

Although most of the findings reported here are consistent to earlier studies, there are differences between our studies and theirs. First of all, unlike the studies of Van Maele-Fabry et al[14] and Turner et al[13], our study not only investigated the association of residential pesticide exposure during childhood and leukemia, but also of other types of cancers. Furthermore, we used different methodologies in our studies.

One main difference is that several studies included in the previous two meta-analyses were excluded from the current analysis. These were studies either conducted on occupational settings, involved only adults, only reported pesticides in general (no pesticide groups), or included pesticides and other chemicals. Another difference is that we identified studies from PubMed with papers written in English, a similar approach used in Van Maele-Fabry et al[14] but not in Turner et al[13] in which they searched literature from several databases with no language restriction (three studies written in non-English) and included unpublished studies (two PhD thesis). Although it is not possible to assess the magnitude of how the methodology differences would contribute to the findings of the meta-analysis among those studies, we believe that including only data from peer-reviewed studies would render the creditability of meta-analysis.

In addition to differences in study scope and study identification, there are also differences in stratification analyses. Both our study and Turner et al[13] used a random effect model, whereas Van Maele-Fabry et al[14] used both fix-effect model (if I^2 ≤25%) and random effect mode (if I^2 >25%). Although all three meta-analyses had taken into account exposure locations and pesticide categories when performing stratification analysis, Van Maele-Fabry et al[14] reported indoor and outdoor exposures with no information on which category of pesticide was examined. Stratification analyses based on categories of pesticide exposure were run in Van Maele-Fabry et al,[14] but no analysis was done on the exposure location (such as indoor or outdoor) for each category of pesticide exposure; therefore the true risk factors could be diluted. There were also no results from sensitivity analyses provided in Van Maele-Fabry et al.[14] Unlike Van Maele-Fabry et al's[14] report and our observation, Turner et al[13] reported

significant positive association between childhood leukemia and exposure to residential outdoor pesticide, but not outdoor insecticides nor herbicides. However, these results were inconsistent with each other since outdoor pesticides were most likely to be outdoor insecticides or herbicides. In the current meta-analysis, we divided studies into three sub-groups based on the pesticide use pattern, such as home pesticides, herbicides, and outdoor insecticide, and used random-effect model to estimate the summary ORs for each sub-group. In the home pesticide (mostly indoor insecticides) category, although some sub-group analyses were conducted using only limited number of studies (<5), the observed heterogeneity was relatively low (I^2 ≤13%) in these analyses. We also pooled studies to increase the accuracy of estimated summary ORs for hematopoietic malignancy and all cancers, and observed zero or low levels of heterogeneity. Similarly, there was no observed heterogeneity in the herbicide category, including estimated summary ORs for hematopoietic malignancy and all cancers. These results of zero or low heterogeneity for home pesticides and herbicide exposure indicated the consistency of studies included and suggested combining data is appropriate. However, the heterogeneity for outdoor insecticide exposure was high. Overall, these studies included in the current meta-analysis differed in study design, study population, and the exposure and timing of exposure. Therefore, the heterogeneity of the associations should be interpreted with caution.

Although meta-analysis is a useful tool to assess the causal relationship by combining results from different studies, the outcomes could be constrained by the limitations associated with the original studies. In the current analysis, the small numbers of studies included in the analysis represents a major limitation. This is due to

the fact that studies devoting to assessing pesticide exposures and childhood cancers are very rare. In addition, there are other limitations such as selection bias, recall bias and misclassification, and publication bias associated with this analysis that might render the applicability of the findings to the general population. Because of the potential selection bias associated with hospital or friend controls, we performed a sensitivity analysis by excluding Davis et al[32] and Menegaux et al[39] in each pesticide category to reinforce the associations. In order to reduce recall bias and misclassification, studies included in the current meta-analysis had used several strategies to reduce confounding factors and biases, such as restriction of entry to study of individuals with confounding factors, matching controls to have equal distribution of confounders, using standardized questionnaires and identical interviewing procedures for both cases and controls and also adjustment of the results. Publication bias refers to studies with less significant findings that may be less publishable than those with positive outcomes and therefore would not be available for meta-analyses. For example, one of the studies from the current analysis stated that "neither residential use of insecticides nor use of pesticides in the garden was found to be significantly more frequent in any group of cases with solid tumors compared with controls, therefore no quantitative data were provided".[38] Although the results from the current meta-analysis don't seem to be significantly influenced by the publication bias, this bias may not be completely excluded. The impact of exclusion of non-published data and studies in other languages than English was assessed by Van Maele-Fabry et al[14], in which rerun meta-analysis by including those non-published studies and studies in other languages than English didn't substantially modify the results.

Policy Implication Synthesis

The current meta-analysis has revealed the positive associations observed for home pesticide uses and childhood cancers, with a statistically significant association between indoor insecticide uses and childhood acute lymphoblastic leukemia (ALL). Although epidemiological research is relatively limited to allow adequate assessment of the causal relationship between pesticide uses in residential, school ground, or parks and cancer incidents in young children, the current scientific findings have indicated a positive association. While research community is working toward a better understanding of pesticide exposure and its cancer etiology in children, there are several reasons that warrant an immediate action on the public policy implementation to mitigate the possible adverse heath outcome.

First of all, the association of residential pesticide exposure and childhood cancers is significant enough that merits an exercise of public health precautionary principle. We need practical and effective interventions on reducing pesticide uses in the environment where children are often present. Not only because of its close proximity to children, pesticides used in indoor residential settings are tend to be in large quantity per area and not as easy to be dissipated as used in the outdoor environment. Promoting non-pesticide-base applications for indoor pest controls therefore make great health sense. The long-term benefits of protecting children's health from exposing to pesticides indoor will outweigh the short-term costs of adapting non-pesticide-base pest control practices.

Secondly, adapting non-pesticide-base pest control practices will likely eradicate the increasing resistance problems that are commonly associated with pesticides that are routinely being used in agricultural and residential settings. Once resistance is formed, more pesticides, both quantities and the numbers of pesticides, are needed to be applied to overcome the resistance problem. This vicious cycle only further worsens the resistant problem, and therefore prompts more pesticide uses.

Lastly, because of the climate pattern changes in recent years, the conditions will help to foster the survivals of many pests, weeds, and pathogens in the environment. West Nile virus infestation is just one of the many examples. Therefore, it is foreseeable

that overall pesticide uses in the society will only be increasing. While some pesticide uses for public health purposes are legitimate and likely needed, other usages, such as residential applications, are deemed unnecessary and should be eliminated, or at least significantly reduced in order to protect children's health.

It is highly relevant to the pesticide public policy by adapting the "Risk Cup" concept that US EPA has been used to governing the total acceptable risk to a given pesticide based on its Reference Dose (RfD) in the risk management of residential pesticide exposure among children. The RfD is the level of exposure to a specific pesticide that a person could receive every day over a 70-year period with bearing a long-term health effect. The analogy of a "risk cup" can be used to describe aggregate exposure estimates. The full cup represents the total RfD and each use of the pesticide contributes a specific amount of exposure that adds a finite amount of risk to the cup. In the event that the "Risk Cup" is full, meaning that the combined total of all estimated sources of exposure to the pesticide has reached 100% of the RfD, risk mitigation measures need to be implemented to avoid the development of adverse health effects. While the size of the "Risk Cup" will vary greatly among individuals, it is politically responsible to implement effective mitigation measures to ensure individuals' Risk Cups will never be full. The non-pesticide-base residential pesticide practice is the readily available mitigate measure that will serve the purpose of protecting children from exposing to "unnecessary" pesticides well.

REFERENCES

1. Adgate JL, Kukowski A, Stroebel C, Shubat PJ, Morrell S, Quackenboss JJ, et al. Pesticide storage and use patterns in Minnesota households with children. *J Expo Anal Environ Epidemiol.* 2000;10(2):159-167.
2. Bass JK, Ortega L, Rosales C, Petersen NJ, Philen RM. What's being used at home: a household pesticide survey. *Rev Panam Salud Publica.* 2001;9(3):138-144.
3. Guha N, Ward MH, Gunier R, Colt JS, Lea CS, Buffler PA, et al. Characterization of residential pesticide use and chemical formulations through self-report and household inventory: the Northern California Childhood Leukemia study. *Environ Health Perspect.* 2013;121(2):276-282.
4. Kim HH, Lim YW, Yang JY, Shin DC, Ham HS, Choi BS, et al. Health risk assessment of exposure to chlorpyrifos and dichlorvos in children at childcare facilities. *Sci Total Environ.* 2013;444:441-450.
5. Gilden R, Friedmann E, Sattler B, Squibb K, McPhaul K. Potential health effects related to pesticide use on athletic fields. *Public Health Nurs.* 2012;29(3):198-207.
6. Alarcon WA, Calvert GM, Blondell JM, Mehler LN, Sievert J, Propeck M, et al. Acute illnesses associated with pesticide exposure at schools. *JAMA.* 2005;294(4):455-465.
7. Faustman EM, Silbernagel SM, Fenske RA, Burbacher TM, Ponce RA. Mechanisms underlying Children's susceptibility to environmental toxicants. *Environ Health Perspect.* 2000;108 Suppl 1:13-21.
8. Sheets LP. A consideration of age-dependent differences in susceptibility to organophosphorus and pyrethroid insecticides. *Neurotoxicology.* 2000;21(1-2):57-63.
9. Landrigan PJ, Claudio L, Markowitz SB, Berkowitz GS, Brenner BL, Romero H, et al. Pesticides and inner-city children: exposures, risks, and prevention. *Environ Health Perspect.* 1999;107 Suppl 3:431-437.
10. Spann MF, Blondell JM, Hunting KL. Acute hazards to young children from residential pesticide exposures. *Am J Public Health.* 2000;90(6):971-973.
11. Infante-Rivard C, Weichenthal S. Pesticides and childhood cancer: an update of Zahm and Ward's 1998 review. *J Toxicol Environ Health B Crit Rev.* 2007;10(1-2):81-99.
12. Metayer C, Buffler PA. Residential exposures to pesticides and childhood leukaemia. *Radiat Prot Dosimetry.* 2008;132(2):212-219.
13. Turner MC, Wigle DT, Krewski D. Residential pesticides and childhood leukemia: a systematic review and meta-analysis. *Environ Health Perspect.* 2010;118(1):33-41.
14. Van Maele-Fabry G, Lantin AC, Hoet P, Lison D. Residential exposure to pesticides and childhood leukaemia: a systematic review and meta-analysis. *Environ Int.* 2011;37(1):280-291.
15. 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(10):1505-1513.
16. Zahm SH, Ward MH. Pesticides and childhood cancer. *Environ Health Perspect.* 1998;106 Suppl 3:893-908.

17. 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(2):207-214.
18. 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(10):1209-1226.
19. Van Maele-Fabry G, Duhayon S, Lison D. A systematic review of myeloid leukemias and occupational pesticide exposure. *Cancer Causes Control.* 2007;18(5):457-478.
20. Vinson F, Merhi M, Baldi I, Raynal H, Gamet-Payrastre L. Exposure to pesticides and risk of childhood cancer: a meta-analysis of recent epidemiological studies. *Occup Environ Med.* 2011;68(9):694-702.
21. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA.* 2000;283(15):2008-2012.
22. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ.* 2003;327(7414):557-560.
23. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ.* 1997;315(7109):629-634.
24. Meinert R, Kaatsch P, Kaletsch U, Krummenauer F, Miesner A, Michaelis J. Childhood leukaemia and exposure to pesticides: results of a case-control study in northern Germany. *Eur J Cancer.* 1996;32A(11):1943-1948.
25. Metayer C, Colt JS, Buffler PA, Reed HD, Selvin S, Crouse V, et al. Exposure to herbicides in house dust and risk of childhood acute lymphoblastic leukemia. *J Expo Sci Environ Epidemiol.* 2013;23(4):363-370.
26. Searles Nielsen S, Mueller BA, De Roos AJ, Viernes HM, Farin FM, Checkoway H. Risk of brain tumors in children and susceptibility to organophosphorus insecticides: the potential role of paraoxonase (PON1). *Environ Health Perspect.* 2005;113(7):909-913.
27. Soldin OP, Nsouli-Maktabi H, Genkinger JM, Loffredo CA, Ortega-Garcia JA, Colantino D, et al. Pediatric acute lymphoblastic leukemia and exposure to pesticides. *Ther Drug Monit.* 2009;31(4):495-501.
28. Bailey HD, Armstrong BK, de Klerk NH, Fritschi L, Attia J, Scott RJ, et al. Exposure to professional pest control treatments and the risk of childhood acute lymphoblastic leukemia. *Int J Cancer.* 2011;129(7):1678-1688.
29. Buckley JD, Meadows AT, Kadin ME, Le Beau MM, Siegel S, Robison LL. Pesticide exposures in children with non-Hodgkin lymphoma. *Cancer.* 2000;89(11):2315-2321.
30. Cooney MA, Daniels JL, Ross JA, Breslow NE, Pollock BH, Olshan AF. Household pesticides and the risk of Wilms tumor. *Environ Health Perspect.* 2007;115(1):134-137.
31. Daniels JL, Olshan AF, Teschke K, Hertz-Picciotto I, Savitz DA, Blatt J, et al. Residential pesticide exposure and neuroblastoma. *Epidemiology.* 2001;12(1):20-27.

32. Davis JR, Brownson RC, Garcia R, Bentz BJ, Turner A. Family pesticide use and childhood brain cancer. *Arch Environ Contam Toxicol.* 1993;24(1):87-92.
33. Ding G, Shi R, Gao Y, Zhang Y, Kamijima M, Sakai K, et al. Pyrethroid pesticide exposure and risk of childhood acute lymphocytic leukemia in Shanghai. *Environ Sci Technol.* 2012;46(24):13480-13487.
34. Greenop KR, Peters S, Bailey HD, Fritschi L, Attia J, Scott RJ, et al. Exposure to pesticides and the risk of childhood brain tumors. *Cancer Causes Control.* 2013;24(7):1269-1278.
35. Infante-Rivard C, Labuda D, Krajinovic M, Sinnett D. Risk of childhood leukemia associated with exposure to pesticides and with gene polymorphisms. *Epidemiology.* 1999;10(5):481-487.
36. Leiss JK, Savitz DA. Home pesticide use and childhood cancer: a case-control study. *Am J Public Health.* 1995;85(2):249-252.
37. Ma X, Buffler PA, Gunier RB, Dahl G, Smith MT, Reinier K, et al. Critical windows of exposure to household pesticides and risk of childhood leukemia. *Environ Health Perspect.* 2002;110(9):955-960.
38. Meinert R, Schuz J, Kaletsch U, Kaatsch P, Michaelis J. Leukemia and non-Hodgkin's lymphoma in childhood and exposure to pesticides: results of a register-based case-control study in Germany. *Am J Epidemiol.* 2000;151(7):639-646; discussion 647-650.
39. Menegaux F, Baruchel A, Bertrand Y, Lescoeur B, Leverger G, Nelken B, et al. Household exposure to pesticides and risk of childhood acute leukaemia. *Occup Environ Med.* 2006;63(2):131-134.
40. Pogoda JM, Preston-Martin S. Household pesticides and risk of pediatric brain tumors. *Environ Health Perspect.* 1997;105(11):1214-1220.
41. Rudant J, Menegaux F, Leverger G, Baruchel A, Nelken B, Bertrand Y, et al. Household exposure to pesticides and risk of childhood hematopoietic malignancies: The ESCALE study (SFCE). *Environ Health Perspect.* 2007;115(12):1787-1793.
42. Searles Nielsen S, McKean-Cowdin R, Farin FM, Holly EA, Preston-Martin S, Mueller BA. Childhood brain tumors, residential insecticide exposure, and pesticide metabolism genes. *Environ Health Perspect.* 2010;118(1):144-149.
43. Urayama KY, Wiencke JK, Buffler PA, Chokkalingam AP, Metayer C, Wiemels JL. MDR1 gene variants, indoor insecticide exposure, and the risk of childhood acute lymphoblastic leukemia. *Cancer Epidemiol Biomarkers Prev.* 2007;16(6):1172-1177.

Legends for Tables and Figures

Table 1. Overview of the case-control studies included in the meta-analysis.

Table 2. Meta-analysis using random-effects models for the relationship between childhood cancer and exposure to residential pesticides during childhood.

Figure 1. Flow diagram of included and excluded studies

Figure 2. Meta-analysis of the association between childhood cancers and exposure to home pesticides during childhood.

Figure 3. Meta-analysis of the association between childhood cancers and exposure to residential herbicides during childhood.

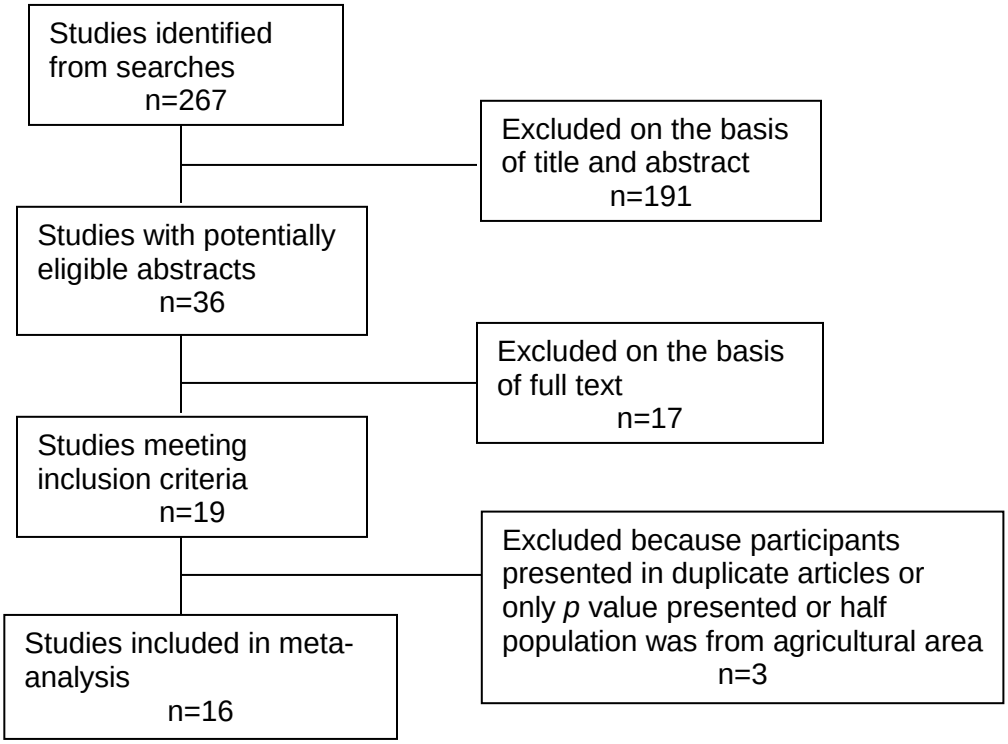
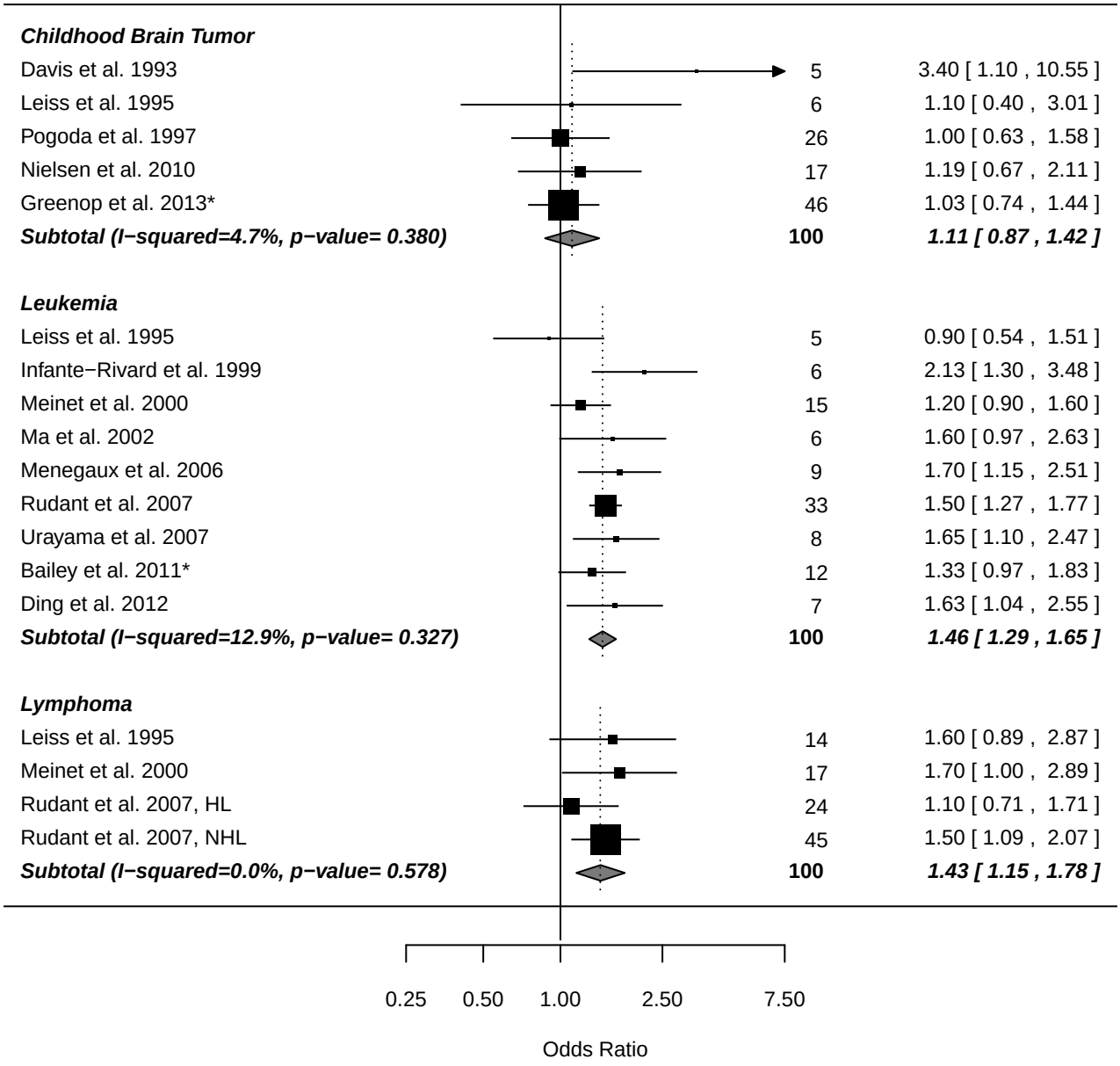


Figure 1. Flow diagram of included and excluded studies.


Study name
% Weight
Odds ratio [95% CI]
Childhood Brain Tumor
Davis et al. 1993 5 3.40 [1.10 , 10.55]
Leiss et al. 1995 6 1.10 [0.40 , 3.01]
Pogoda et al. 1997 26 1.00 [0.63 , 1.58]
Nielsen et al. 2010 17 1.19 [0.67 , 2.11]
Greenop et al. 2013* 46 1.03 [0.74 , 1.44]
Subtotal (I−squared=4.7%, p−value= 0.380) 100 1.11 [0.87 , 1.42]
Leukemia
Leiss et al. 1995 5 0.90 [0.54 , 1.51]
Infante−Rivard et al. 1999 6 2.13 [1.30 , 3.48]
Meinet et al. 2000 15 1.20 [0.90 , 1.60]
Ma et al. 2002 6 1.60 [0.97 , 2.63]
Menegaux et al. 2006 9 1.70 [1.15 , 2.51]
Rudant et al. 2007 33 1.50 [1.27 , 1.77]
Urayama et al. 2007 8 1.65 [1.10 , 2.47]
Bailey et al. 2011* 12 1.33 [0.97 , 1.83]
Ding et al. 2012 7 1.63 [1.04 , 2.55]
Subtotal (I−squared=12.9%, p−value= 0.327) 100 1.46 [1.29 , 1.65]
Lymphoma
Leiss et al. 1995 14 1.60 [0.89 , 2.87]
Meinet et al. 2000 17 1.70 [1.00 , 2.89]
Rudant et al. 2007, HL 24 1.10 [0.71 , 1.71]
Rudant et al. 2007, NHL 45 1.50 [1.09 , 2.07]
Subtotal (I−squared=0.0%, p−value= 0.578) 100 1.43 [1.15 , 1.78]
0.25
0.50
1.00
2.50
7.50
Odds Ratio

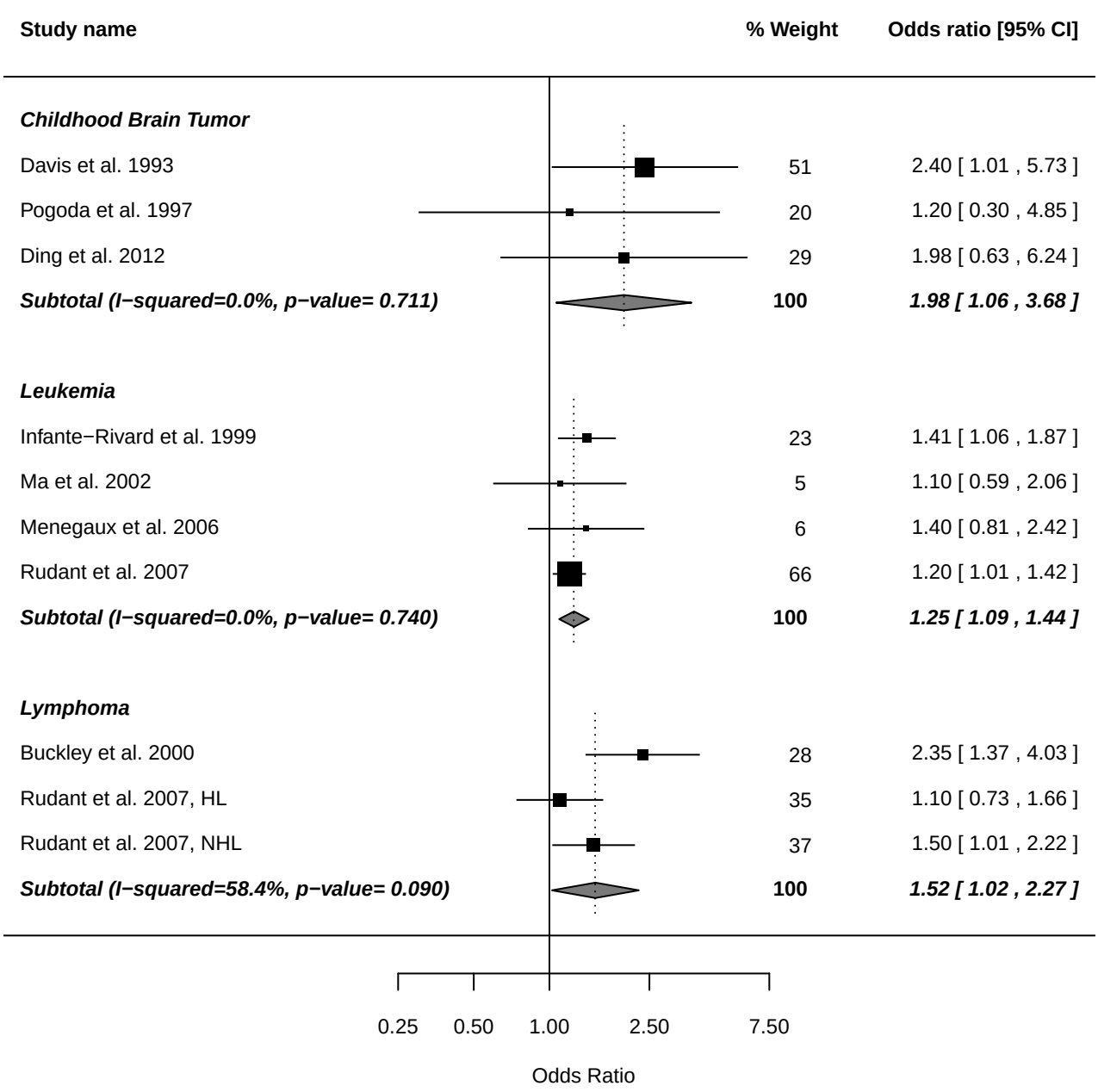

Study name
% Weight
Odds ratio [95% CI]
Childhood Brain Tumor
Davis et al. 1993
51
2.40 [1.01 , 5.73]
Pogoda et al. 1997
20
1.20 [0.30 , 4.85]
Ding et al. 2012
29
1.98 [0.63 , 6.24]
Subtotal (I−squared=0.0%, p−value= 0.711)
100
1.98 [1.06 , 3.68]
Leukemia
Infante−Rivard et al. 1999
23
1.41 [1.06 , 1.87]
Ma et al. 2002
5
1.10 [0.59 , 2.06]
Menegaux et al. 2006
6
1.40 [0.81 , 2.42]
Rudant et al. 2007
66
1.20 [1.01 , 1.42]
Subtotal (I−squared=0.0%, p−value= 0.740)
100
1.25 [1.09 , 1.44]
Lymphoma
Buckley et al. 2000
28
2.35 [1.37 , 4.03]
Rudant et al. 2007, HL
35
1.10 [0.73 , 1.66]
Rudant et al. 2007, NHL
37
1.50 [1.01 , 2.22]
Subtotal (I−squared=58.4%, p−value= 0.090)
100
1.52 [1.02 , 2.27]
0.25
0.50
1.00
2.50
7.50
Odds Ratio

Table 1. Overview of the case-control studies included in the meta-analysis.

Study	Sample size (case/control)	Age (years)	Study population/location and period	Exposure assessment	Cases	Control
Davis et al. (1993) USA	45/85	≤ 10	Patients in Missouri, diagnosed 1985-1989	Maternal phone interview	CBT	Non-cancer friends or other cancer matched with age and sex
Leiss et al. (1995) USA	252/222	< 15	Patients in Denver, 1976-1983	Parental interview	CBT, Leu, Lym, STS	Non-cancer population matched by sex, age, region
Pogoda et al. (1997) USA	224/218	≤ 19	Patients from west coast, 1984-1991	Maternal phone interview	CBT	Non-cancer population matched by sex, age, region
Infante-Rivard et al. (1999) Canada	491/491	≤ 9	Patients from metropolitan Montreal, diagnosed 1980-1993	Parental phone interview	ALL	Non-cancer population matched by age, sex, region
Meinet et al. (2000) Germany	1184,234, 940/2588	≤ 15	Patient from West Germany, diagnosed 1992-1994	Mail and parental phone interview	Leu, NHL	Non-cancer population matched by sex, age, region
Buckley et al. (2000) USA	268/268	≤ 20	Patients in US,1986-1990	Maternal phone interview	NHL	Non-cancer population matched by age, gender and race.
Daniel et al. (2001) USA	390/296	<19	Hospital patients in US and Canada,1992-1994	Parental phone interview	Neuroblastoma	Non-cancer population matched by age, region.
Ma et al. (2002) USA	162/162	≤14	Hospital patients in North California, 1995-1999	Maternal in-home personal Interview	ALL, Leu	Non-cancer population matched by sex, age, mother's race, region
Menegaux et al. (2006) France	280/288	< 15	Hospital patients in France, diagnosed 1995-1999	Maternal personal interview	AL	Hospital non-cancer children matched by age, sex, hospital, race
Rudant et al. (2007) France	1060/1681	< 15	Patients in France, diagnosed 2003-2004	Maternal phone interview	AL, HL, NHL	Non-cancer population matched by age, sex

Urayama et al. (2007) USA	294/369	< 15	Patients from northern and central California, diagnosed since 1995	In-home interviews with caretaker	ALL	Non-cancer children matched by age, sex, Hispanic status, maternal race, region
Cooney et al. (2007) USA	523/517	<16	Patients in US and Canada, 1999-2002	Maternal phone Interview	Wilms tumor	Non-cancer children matched by age and region
Nielsen et al. (2010) USA	201/285	≤10	Patients in US west coast, 1984-1991	Maternal in-person Interview	CBT	Non-cancer children matched by age and sex
Bailey et al. (2011) Australia	388/870	<15	Patients in Australia, 2003-2007	Parental questionnaires and phone interview	ALL	Non-cancer population matched by sex, age, region
Ding et al. (2012) China	176/180	≤14	Hospital patients in Shanghai China, 2010-2011	Maternal in-person interview and children urine collections	ALL	Non-cancer hospital children matched by sex and age
Greenop et al. (2013) Australia	288/917	≤14	Patients in Australia, 2005-2010	Maternal in-person interview	CBT	Non-cancer population matched by sex, age and region

AL-Acute leukemia; ALL-Acute lymphoblastic leukemia; CBT-Childhood brain tumor; HL-Hodgkin lymphoma, Leu-Leukemia; Lym-Lymphoma; NHL-non-Hodgkin lymphoma; STS- Soft tissue sarcoma

Table 2. Meta-analysis using random-effects models for the relationship between childhood cancer and exposure to residential pesticides during childhood.

Subgroups	Study N.	Summary		Heterogeneity	
		OR	95% CI	*p*	I^2
Home Pesticides [a-c]					
(A) Acute Leukemia	6	1.59	1.40-1.80	0.839	0
Add professional home treatment	7	1.55	1.38-1.75	0.794	0
Indoor insecticides	5	1.59	1.39-1.81	0.725	0
(B) Leukemia	8	1.48	1.29-1.70	0.267	20
Add professional home treatment	9	1.46	1.29-1.65	0.327	13
Dose and multiple agents effects[d]	3	1.92	1.27-2.89	0.959	0
Professional treatment only	3	2.04*	1.05-3.95	0.061	64
Indoor insecticides	7	1.47	1.26-1.72	0.197	30
(C) Lymphoma	4	1.43	1.15-1.78	0.578	0
(D) Hematopoietic Cancers	12	1.47	1.33-1.62	0.457	0
Add professional home treatment	13	1.46	1.32-1.60	0.513	0
Indoor insecticides	11	1.46	1.31-1.63	0.388	5
Dose and multiple agents effect[d]	4	2.04	1.40-2.97	0.894	0
(E) Childhood brain tumors[e,f]	4	1.22	0.83-1.81	0.275	23
Add professional home treatment	5	1.11	0.87-1.42	0.380	5
(F) All cancers[f-h]	20	1.40	1.28-1.52	0.390	5
Herbicide [b-c]					
(A) Acute Leukemia	4	1.26	1.10-1.44	0.777	0
(B) Leukemia	4	1.25	1.09-1.44	0.740	0
(C) Lymphoma	3	1.52*	1.02-2.27	0.090	58
(D) Hematopoietic Cancers	7	1.33	1.15-1.54	0.295	18
(E) Child brain tumors	3	1.98*	1.06-3.68	0.682	0
(F) All cancers[g-i]	12	1.35	1.16-1.55	0.221	23
Outdoor Insecticides					
(A) Leukemia	3	1.11	0.60-2.05	0.002	84
(B) Hematopoietic Cancers	5	1.09	0.75-1.58	0.007	71
(C) Child brain tumors	2	1.29	0.86-1.92	0.548	0
(D) All cancer[g,h]	8	1.14	0.89-1.45	0.028	55

* The Summary ORs became not statistically significant in the sensitivity analysis when Removing ill-defined herbicide or removing highest weight or extreme ORs.
- Hematopoietic Cancers include Leukemia and lymphoma.
- Study results with case numbers less than 3 are not included in the summary.

[a] In the study of Infante-Rivard C et al. 1999 where insecticides against different types of nuisance were reported, data of moths which had highest OR was used; [b] In the studies where results of different exposure windows in the same study were reported, the window away from birth were used: 2 year before diagnose to diagnose in Leiss JK et al. 1995; [c] In the study of Ma X et al. 2002, both ALL and

leukemia were reported, leukemia data was used in leukemia and all childhood cancers stratification and ALL data was used in AL stratification; [d] The data of >10 per year were used in Meinet R et al. 2000 and Meinet R et al. 2000Lym at the both exposure windows, and the data of >5 per year was used in Ma X et al. 2002; [e] For David JR 1993, both cancer-free controls and cancer controls were reported, cancer-free controls were used; For Nielsen SS et al. 2010, crude OR and 95% CI were calculated based on the data in the paper; [f] where more than one home pesticides usage were reported, home pesticides for nuisance pests were used; [g] Since the results were essentially the same during pregnancy and during childhood in Cooney MA et al. 2007, the data reported from pregnancy through childhood was treated as during childhood; [h] All cancers include neuroblastoma (Daniel JL et al. 2001) in outdoor insecticides, and neuroblastoma (Daniel JL et al. 2001) and wilms tumor (Cooney MA et al. 2007) and studies of professional home treatments in home pesticides; [i] In the study of Daniel JL et al. 2001, exposure window was since pregnancy through childhood.