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Home pesticide exposures and risk of childhood leukemia: Findings from the Childhood Leukemia International Consortium

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Abstract

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Some previous studies have suggested that home pesticide exposure before birth and during a child's early years may increase the risk of childhood leukemia. To further investigate this, we pooled individual level data from 12 case-control studies in the Childhood Leukemia International Consortium (CLIC). Exposure data were harmonized into compatible formats. Pooled analyses were undertaken using multivariable unconditional logistic regression. The odds ratio (ORs) for acute lymphoblastic leukaemia (ALL) associated with any pesticide exposure shortly before conception, during pregnancy and after birth were 1.39 (95% confidence interval (CI) 1.25, 1.55) (using (2,785 cases, 3635 controls), 1.43 (95% CI 1.32, 1.54) (5,055 cases, 7,370 controls) and 1.36 (95% CI 1.23, 1.51) (4,162 cases 5,179 controls), respectively. Corresponding ORs for risk of acute myeloid leukaemia (AML) were 1.49 (95% CI 1.02, 2.16) (173 cases, 1,789 controls), 1.55 (95% CI 1.21, 1.99) (344 cases, 4,666 controls) and 1.08 (95% CI 0.76, 1.53) (198 cases, 2,655 controls) respectively. There was little difference by type of pesticide used. The relative similarity in ORs between leukaemia types, time periods and pesticide types may be explained by similar exposure patterns and effects across the time periods in ALL and AML, participants' exposure to multiple pesticides, or recall bias. Although some recall bias is likely, until a better study design can be found to investigate associations between home pesticide use and childhood leukaemia in an equally large sample, it would appear prudent to limit the use of home pesticides before and during pregnancy, and during childhood.

Keywords

pesticide; acute lymphoblastic leukemia acute myeloid leukemia; childhood; pooled analysis; case-control study

Introduction

Childhood leukemia, the most common childhood malignancy, and its main sub-types, acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML), occur mainly in children under five years of age, suggesting a role for parental exposures before birth or for the child's exposure in early childhood in their etiology. Reports that pesticides could be risk factors for childhood leukemia first appeared over 30 years ago,[1] and since then they have been the focus of numerous case-control studies as summarized in the latest reviews.[2-4] However, because of the infrequency of childhood leukemia with an annual incidence rate of 30-50 per million for ALL and 4-8 per million for AML in developed countries,[5] individual studies rarely have sufficient statistical power to detect an effect, particularly for sub-types of leukemias.

To overcome this problem, we pooled original data from studies participating in the Childhood Leukemia International Consortium (CLIC), a multi-national collaboration of case-control studies of childhood leukemia.[6] The focus of these analyses was to investigate home pesticide exposure in relation to both ALL and AML. We have previously published findings of pooled analyses investigating parental occupational pesticide exposure and the risk of childhood leukemia using data from CLIC studies and found an association between maternal occupational exposure during pregnancy and the risk of AML and a less clear

association between paternal occupational exposure close to conception and the risk of ALL.[7]

The two most recently published meta-analyses of home pesticide exposure and the risk of childhood leukemia encompassed 13,[4] these were published in 2011 and 2010 respectively and included five studies[8-12] that are part of the current pooled analyses: four with ALL data,[8, 9, 11, 12] one with AML data,[12] and one with data for any childhood leukemia[10]. However, in both meta-analyses, the analyses of leukemia sub-types included data from fewer than six studies because the others lacked information on leukaemia subtype. Direct comparison between these meta-analyses is difficult due to differences in methods used and the results reported. Nevertheless, both reported elevated odds ratios (ORs) for ALL with exposure to insecticides and herbicides during pregnancy. For exposures after birth, both reported no association with herbicides but there was inconsistency with regard to insecticides exposure.

The aim of our analyses was to investigate whether home pesticide exposure in the time leading up to conception, during pregnancy or after the child's birth increased the risk of childhood ALL or AML. Pooling original individual-level data allowed us to better harmonize exposure information and categories and adjust for other factors, as well to create a far larger case samples than in the previous meta-analyses. We also investigated whether the relationship varied by immunophenotype or cytogenetic sub-type of ALL.

Methods

We included 12 CLIC studies (12 with ALL cases and nine with AML cases, which were conducted in North America, Europe and Australasia over a 30 year period) (Table 1), six of which have previously published findings related to home pesticide exposure.[8-13] Original data were requested from each study, including home or occupational pesticide exposures, matching variables, demographics, potential confounders and disease sub-types. A summary of study design and participant details, including inclusion criteria, has already been published.[6] Most studies recruited children up to and including the age of 14 years, except one that included children up to the age of 10 years (Italy). All were approved by the relevant institutional or regional ethics committees.

Exposure assessment

We included any CLIC study that had a measure of home pesticide exposure in any of three time periods: period leading up to the child's conception, during pregnancy and after the child's birth. The measures of home pesticide exposure in each included study are summarized in Table 1. Briefly, data on exposure before conception were available for six of the 12 included studies: three studies for exposure in the month before conception (Greece: 1993-1994 and 1996-97; Children's Oncology Group (COG)-E15); and two for three months before conception (Northern California Childhood Leukemia Study (NCCLS) and New Zealand). Data from the remaining study (Australia) related to exposure in the year before conception and were incompatible with the other studies; these data were therefore not pooled. With respect to exposure during pregnancy, ten studies had data available, while another (Italy) had data for exposure between the calendar years of conception and birth.

Finally for post-natal exposure, nine studies had data available, with seven (Australia, Canada, France (Adele), Germany, New Zealand, United Kingdom Childhood Cancer Study (UKCCS) and COG E-15) having data for exposure after the child's birth until the reference date (the date of diagnosis for the cases and the date of recruitment or questionnaire return for the controls); one (NCCLS) having had data for exposure until the child's third birthday or reference date whichever came first; and one for between the calendar years of birth and diagnosis (Italy).

The definition ‘home pesticide exposure’ varied across studies and, in some cases, by time period (Table 1). Exposure was defined as ‘pesticide’ in the data provided by three studies (Greece 1993-1994 and 1996-97 and New Zealand), while six had data for different types of pesticides from which an overall measure of home pesticide exposure could be derived (Canada, France (Adele and ESCALE), Italy, NCCLS and COG-E15). The remaining three studies only had data for ‘professional pest control treatments’ (Australia and Germany) and ‘house treatments for dry rot or wood worm’ (UKCCS).

Exposure was considered relevant in either parent before conception, the mother during pregnancy and the child after birth. For studies with information on household use in a specified time period (Australia, Canada and NCCLS), we assumed everyone living in the house was exposed. For the other studies, we used the relevant person(s)'s exposure data. We also conducted sub-group analyses in subsets of studies for different types of pest control products (household insecticides or miticides, pesticides used on pets or in their cages, insecticides or fungicides used on plants and trees, herbicides, professional pest control treatments, rodenticides, molluscicides and personal insect repellant) (see Supplementary Table 1 for availability of data by study); the trimester of exposure during pregnancy (New Zealand, COG-E15 and NCCLS); and each age at which professional pest control treatments were done until the age of three years (Australia and NCCLS).

Immunophenotype and cytogenetic classification of ALL

Information about ALL immunophenotype (B cell and T cell) was available for all studies. In addition, for B cell ALL cases, data for low hyperdiploidy (47-50 chromosomes) and high hyperdiploidy (51 or more chromosomes) which had been determined using conventional banding karyotypes or fluorescence *in situ* hybridization screening (FISH) were available for five studies (Australia, France (Adele and ESCALE), UKCCS and NCCLS). For four studies (Australia, France (ESCALE), UKCCS and NCCLS) data were available for *ETV6-Runx-1* gene fusion (cryptic t(12;21) translocations) in B cell ALL cases, determined by FISH or molecular detection of fusion transcripts and for 11q23/*MLL* rearrangement including either conventional cytogenetic identifying chromosome translocation involving the 11q23 region or *MLL* gene rearrangement by RT-PCR (*AF4/MLL*) or FISH-*MLL* break apart in ALL cases. Less common cytogenetic types were not included in our pooled analyses. The number of metaphases was not available in all studies, meaning that the karyotypes with no structural or numerical changes could not be considered normal karyotypes.

All studies routinely extracted cytogenetic data from medical records recorded at the time of the diagnosis for all cases. In addition, NCCLS had performed specific analyses at a central

laboratory from samples taken at the time of enrollment in the study. Before pooling the cytogenetic data, JC and experts in molecular biology (LZ, MPO) checked the consistency of CLIC data by conducting sex- and age-frequency analyses. In particular, there was no substantial heterogeneity between studies for the B cell cytogenetic abnormalities of interest (low hyperdiploidy, high hyperdiploidy, presence of *ETV6-Runx1*) or the presence of 11q23/*MLL* rearrangement, despite the assumed variations in methods across studies and time periods, and the prevalence of these cytogenetic abnormalities matched known distributions from clinical series[14, 1514, 15]

Statistical analyses

Two distinct analytic approaches were taken. Firstly, study specific ORs of exposure to home pesticides and risk of ALL and AML were estimated and included in meta-analyses so we could explore heterogeneity between studies. Secondly, individual data were pooled in a single dataset and the pooled ORs estimated. As the findings using both methods were similar, the Methods and Results of the meta-analytical approach are presented as Supporting Material (including Supplementary Figures 1-4: Forest plots showing individual and summary ORs).

Pooled analyses of individual data

Unconditional logistic regression (SAS version 9.4, SAS Institute Inc, Cary, NC, USA) was used to estimate pooled ORs and 95% confidence intervals (CIs) for home pesticide exposures for the following three time periods: in the 1-3 months before conception, during pregnancy and between the child's birth and reference date. All models included the child's age, sex, year of birth (grouped into three approximately equal time periods) and ethnicity (Caucasian, European or White versus the rest) and a variable denoting the study of origin. The following variables were considered *a priori* to be potential confounders and were tested to determine whether they met the empirical definition of confounding; (that is, independent association with both the exposure and outcome): birth order; birth weight (where available); mother's age and highest education of either parent (secondary education not completed, completed secondary education, and tertiary education); and study-specific matching variables (by allocating all the other studies the same dummy value for each variable). Of these, highest education of either parent was retained in all models and birth order was included in the analyses of AML. Sub-type analyses were undertaken for ALL immunophenotypes. We stratified analyses by child's sex, age at diagnosis (ALL: 0-1 years, 2-4 years, 5-9 years and 10 or more years; AML: 0-4 years, 5 or more years) and reference year group (in two groups so approximately half the cases were in each group (ALL: before 1997 or later, AML: before 2000 or later)). The analyses for exposures after birth were first run using all studies with data for any time period after birth and then rerun, restricting to studies with exposures up until the reference date. Where there were two or more studies with at least 30 cases with compatible data, sub-group analyses were also done by trimester of pregnancy, type of pesticide exposure, cytogenetic and FAB classification sub-types.

To assess whether risk varied among these periods, logistic regression models were also repeated using a three level exposure variable: exposure only before pregnancy, exposure

only during pregnancy and exposure during both time periods with the reference category of no exposure in either time period.

To account for exposure to multiple types of pesticides, logistic regression models were repeated in the subsets of studies with similar data, mutually adjusting for all types of pesticides in the same model. As children with Down syndrome have higher rates of ALL and AML than other children, analyses were repeated excluding these children. Analyses were also repeated adjusting for paternal occupational pesticide exposure around conception and maternal occupational pesticide exposure during pregnancy and using combined home and/or occupational pesticide exposure variables.

To assess the correlation between exposure to pesticides between time periods, the Spearman's rank correlation coefficient was estimated for each combination of time periods among all participants with these data.

Data for paternal smoking, which is a potential risk factor for childhood leukemia[16, 17] was not collected from individual studies, thus deterministic sensitivity analyses for uncontrolled confounders[18] were later performed for paternal smoking using the Episensi procedure in Stata version 13.1 (StataCorp LP, College Station Texas, USA, 2009).

Results

Some measure of home pesticide exposure was available for 12 studies with 7,956 ALL cases and 14,494 ALL controls, and for nine studies with 740 AML cases and 10,847 AML controls. The demographic characteristics and the availability of exposure data of the total pooled population are shown in Table 2 and those for individual studies in Supplementary Table 2. Because the availability of data for type of exposure and time period varied across studies, no single analysis contained data from all studies. For ALL, the largest subsets of data were used for the analyses of any home pesticide exposure and any professional pest control treatments during pregnancy, with data from over 5,000 ALL cases and 7,000 of their controls. For the AML analyses, the largest subset of data used was 468 cases and 7,531 controls for the analyses of any professional pest control treatments after birth. (Table 4). Using the three studies with data for all three time periods (5330 participants from three studies), the Spearman's correlation co-efficients were 0.52, 0.33 and 0.28 for any pesticide exposure before conception and during pregnancy, before conception and after birth, and during pregnancy and after birth, respectively (results not shown in tables). Among the five studies with data on exposure before and during pregnancy, 44.7% of these participants and 67.1% of those exposed in either time period were exposed to pesticides in both periods. Similarly among the three studies with data on exposure before and during pregnancy, and after birth, 46.3% of all participants and 52.2% of those exposed in any time period were exposed in all of them (results not shown in tables).

Pooled analyses of individual data

The pooled OR for any pesticide exposure in the 1-3 months before conception and risk of ALL was 1.39 (95% CI 1.25, 1.55), based on data from five studies (Table 3). There was

little difference when the analyses were stratified by immunophenotype, age at of diagnosis, sex or reference year group (Table 3).

The pooled OR for any pesticide exposure during pregnancy and ALL risk was 1.43 (95% CI 1.32, 1.54) based on data from nine studies, with little variation when stratified by immunophenotype, sex (Table 3) or trimester of pregnancy (among the ~2,500 cases and 3,000 controls with these data, results not shown). However, the OR varied by age at diagnosis (*p* value for interaction = 0.01) with the highest OR for the youngest age group; and the OR for those diagnosed in 1996 or later was slightly higher than those diagnosed earlier (reference year group interaction *p* value= <0.01) (Table 3). For those with exposure data for 1-3 months before pregnancy as well as for pregnancy, the ORs for the three mutually exclusive levels of exposure variable (only 1-3 months before pregnancy, only during pregnancy, during both time periods with 'no exposure in either' as the reference group) were: 1.22 (95% CI 0.94, 1.58), 1.04 (95% CI 0.88, 1.22), and 1.42 (95% CI 1.24, 1.61), respectively; the majority were exposed in both time periods (69.3% of cases and 64.9% of controls) (results not shown in tables).

Using data from six studies, the OR for exposure after birth and risk of ALL was 1.36 (95% CI 1.23, 1.51), with little variation by immunophenotype, child's age at diagnosis, or sex, but the OR appeared to be slightly higher in children diagnosed in 1996 or later (reference year group interaction *p* value= 0.02) (Table 3). When these analyses were restricted to those studies which recorded exposures up until the reference date, the OR was 1.31 (95% CI 1.17, 1.46) (results not shown in tables).

Across all time periods, the ORs for ALL associated with exposure to professional pest control treatments and other categories of pesticide use were consistent with the overall home pesticide exposure OR for that time period, apart from molluscides and, after birth, personal repellants (Table 3). Among those with data on pesticide type, the proportions of the exposed group who were exposed to more than one type of pesticide were, among cases, 45.1%, 48.6% and 60% before conception, during pregnancy and after birth respectively; and among controls, 40.3%, 48.2% and 55.2%, respectively. When the models were rerun mutually adjusting for multiple pesticides where this was possible, there was little change in the ORs (data not shown).

There were sufficient studies and cases to do analyses by cytogenetic sub-types for home pesticide and professional pest control treatment exposure during pregnancy and after birth. While the ORs appeared elevated for some of the cytogenetic sub-types (Table 4), the estimates were imprecise and none were significantly different from ORs from the analyses using all cases or all B cell cases from the same studies (data not shown).

The pooled OR for AML associated with any exposure to home pesticides in the 1-3 months before pregnancy was 1.49 (95% CI 1.02, 2.16) using data from four studies, and little difference was seen by age at diagnosis, sex or reference year group (Table 5).

Using data from seven studies, the OR for any exposure during pregnancy and the risk of AML was 1.55 (95% CI 1.21, 1.99) (Table 5) with little difference age group at diagnosis, sex, reference year group (Table 5) or by trimester of pregnancy (~150 cases and 4,000

control, data not shown). For those with exposure data for 1-3 months before pregnancy as well as for pregnancy, the ORs for the three mutually exclusive levels of exposure (only before pregnancy, only during pregnancy, during both time periods, with no exposure in either as the reference group) were: 1.77 (95% CI 0.78, 4.04); 1.18 (95% CI 0.63, 2.23), 1.56 (95% CI 1.02, 2.38) respectively; the majority were exposed in both time periods (76.6% of cases and 75.2% of controls) (results not shown in tables).

Using data from 4 studies, the OR for any home pesticide exposure after birth and the risk of AML was 1.08 (95% CI 0.76, 1.53). In the stratified analyses, there was no difference by age at diagnosis or sex, but the OR appeared higher among those diagnosed after 2000 (reference group interaction p value = 0.08) (Table 5). When these analyses were restricted to studies that included exposures up until the reference date, the OR was 0.97 (95% CI 0.61, 1.53), based on 87 cases (results not otherwise shown).

The ORs for AML associated with professional pest control treatments and other exposure categories were generally similar to the overall OR for home pesticide exposure during pregnancy and after birth (Table 5), but there were insufficient data to do all analyses for all time periods. Among those with data on pesticide type, the proportions of exposed cases who were exposed to more than one type of pesticide were 39.3% and 59.7% during pregnancy and after birth respectively, and among exposed controls these figures were 36.0% and 52.7%, respectively. When the models were rerun mutually adjusting for multiple pesticides where this was possible, there was little change in the ORs (data not shown).

When the analyses for both ALL and AML for all time periods were repeated excluding children with Down syndrome (43 ALL cases, two ALL controls, 17 AML cases, one AML control for the during pregnancy analyses, and less for other time periods), there was little change in the results. There was also little change when the analyses were adjusted for parents' occupational pesticide exposure or when the home and occupational exposure was combined into a single variable (data not shown).

The deterministic sensitivity analyses for paternal smoking as an uncontrolled confounder showed that adjustment for it would have made little difference on the ALL findings (Supplementary Table 6). While the magnitude of the association with AML was slightly lower, the overall conclusions remained the same (Supplementary Table 6).

Discussion

The findings of these pooled analyses are consistent with the existing evidence in the literature. We found that any pesticide exposure in the few months leading up to conception (using data from five studies), during pregnancy (nine studies) and after birth (six studies) was associated with an increased risk of childhood ALL, with little variation by time period, type of pesticide or among other sub-groups. We also found that any pesticide exposure in the few months leading up to conception (four studies) and during pregnancy (seven studies) increased the risk of childhood AML, but exposure after birth (four studies) did not. Using a larger sample of cases, our results are consistent with previous meta-analyses, although there

is considerable overlap in the studies included in our pooled study and the meta-analyses. In addition, by pooling individual level data, we were able to perform sub-group analyses that have not previously reported.

The term “pesticides” covers a large, heterogeneous group of chemicals. The active ingredients of each chemical may have different mutagenic, carcinogenic or immunotoxic properties and some individual pesticides have been classed as at least ‘probable or possible carcinogens’ by the International Agency for Research on Cancer.[19] In addition, it is biologically plausible that pesticide exposure could be associated with the risk of childhood leukemia. Exposure of the father prior to conception might result in germ cell damage, and it has been shown that maternal exposure during pregnancy can result in fetal exposure, as demonstrated by the presence of pesticide residuals in umbilical cord blood and meconium.[20] Children may be more susceptible than adults to the harmful effects of environmental toxins including pesticides because they have higher respiratory and metabolic rates than adults, and they tend to play close to the ground with frequent hand to mouth contact.[21] However, despite the evidence of potential carcinogenicity of some individual pesticides, the biological plausibility of an association, and the consistency with the literature, our findings raise some important issues, namely how to interpret the general lack of variation by time period, by broad type of pesticide and by leukemia type. It is improbable that there is the same relationship with all types of pesticides and for all times from before conception to after birth for ALL and for any time from before conception to birth for AML. We can articulate three alternative explanations for our findings.

Firstly, patterns of exposure may be too similar in the three time periods we examined to define the true ‘critical’ period(s) for exposure, if there is truly an association. The correlation between exposure before conception and during pregnancy was strong, with some correlation, albeit weaker, between other combinations of time periods. Only five studies had comparable data for before and during pregnancy and three studies had data for all three time periods, and among those exposed at any time, the majority had been exposed in all time periods, which may partially explain the lack of variability in risk between time periods. Thus, we cannot narrow down the true critical period(s).

Secondly, the lack of variation by broad type of pesticide may be due to participants’ exposure to multiple types of pesticide. We developed eight broad categories of pesticides, based on the available data, and many people were exposed to more than one type. As only one study had data for all eight types, we could not include all types in one logistic regression model, which would have enabled us to disentangle the effects of one type from another.

Finally, we cannot rule out recall bias as all studies relied on self-report. Pesticide exposure relies solely on parental recall about a time period of up to 16 years before data collection for parents of older children, so there is likely to be a degree of measurement error. Of the twelve studies, interviews were conducted by trained interviewers, either face to face (seven studies) or by telephone (three studies), while the remaining two studies used self-administered questionnaires, followed by telephone interviews. While all studies used structured surveys to minimize bias, this may not have prevented case parents potentially

thinking more deeply about past exposures, and therefore reporting them more frequently.[22] The NCCLS found that the level of reproducibility in a second interview was similar among cases and controls, suggesting that recall bias was not a major issue in at least that study.[23] However, the first reports linking pesticides to leukemia appeared over 30 years ago[1] and a basic search of the internet yields thousands of references to this topic. Our findings which suggest a higher risk in the later years may reflect a growing awareness among case parents over time, resulting in increasing levels of recall bias. Often when a risk of disease is only elevated for a particular time period or among a sub-set of cases, it is seen as evidence against recall bias being present in a study, but this does not apply for our study, as the only analyses for which we found no association was for exposure after birth for AML and for a exposure categories. Ideally an exposure assessment method other than self-report should be used such as biomarkers, but the question remains how to quantify *in utero* exposures retrospectively as there are few opportunities to study rare diseases prospectively. The NCCLS has used residential dust samples to quantify past pesticide exposures, but these measurements may lack temporal specificity (e.g., they are unable to distinguish *in utero* exposure from early-life exposure) and they are only valid for families with residential stability.[24]

The major strength of this current investigation was the large sample sizes, especially for any pesticide exposures during pregnancy. While three [8, 9, 12] of the studies included in the pooled analyses of exposure during pregnancy have previously published their findings in relation to ALL, the other six studies had not. In addition, we were able to include nearly 900 more cases from Canada and NCCLS than were available for the previous reports. Of the seven studies we included in the AML analyses of pesticide exposure during pregnancy, only one[12] had previously been published. The access to the original data allowed us to harmonize other information such as immunophenotype and cytogenetic sub-types as well as exposure data, which has not previously been done.

Apart from the limitations already discussed, the major weakness is the crude measure of exposure, which lacks details about specific pesticides used. However, we were limited by the details collected in the original studies, which generally asked about target pests as it was thought that parents would recall these better. As can be seen in Table 1, there was a wide variation in the prevalence of pesticide exposure amongst the controls across studies, e.g. 0-68% during pregnancy. In general, pesticide exposure was reported more frequently in North American studies than in European ones, and the prevalence appeared to rise with the number of pesticide types that parents were asked about in the original questionnaires. By contrast the prevalence of pesticide use did not appear to vary by calendar period when the studies were conducted. From the available data, it is not possible to judge whether the differences reflect true differences in pesticide exposure across studies, or differences in the way questions about pesticide were asked. However, the data were pooled despite the heterogeneity in prevalence of use.

In conclusion, while these pooled analyses support the existing evidence of an association between home pesticides and the risk of childhood ALL and AML, we cannot rule out recall bias as at least a partial explanation for these findings. In addition, we were unable to identify with any certainty the critical time period(s) of exposure, or disentangle the

potential effects of individual types of pesticides. Despite the possibility of recall bias, until a better study design can be found to investigate these potential associations in an equally large case sample, it would appear prudent to recommend that parents (and those contemplating pregnancy) should limit pesticide exposure in the home during the year before birth and the child's early years.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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The New Zealand Childhood Cancer Study was co-ordinated at the University of Otago, where the study team included JD Dockerty, GP Herbison (who helped prepare data for this pooled analysis), DCG Skegg and JM Elwood. The names of the interviewers, secretaries, research assistants, clinicians, pathologists and cancer registry staff who contributed are listed in earlier publications from the NZ study.

The UKCCS was conducted by 12 teams of investigators (ten clinical and epidemiological and two biological) based in university departments, research institutes, and the National Health Service in Scotland. Its work is coordinated by a management committee. Further information can be found on the web-site www.ukccs.org.

COG: The E15 cohort of the Children's Oncology Group was identified by CCG (Children's Cancer Group) principle and affiliate member institutions. Further information can be found on the web-site: http://www.curesearch.org/.

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Abbreviations

ALL	acute lymphoblastic leukemia
Aus-ALL	Australian Study of Causes of Acute Lymphoblastic Leukaemia in Children
CI	Confidence interval
CLIC	Childhood Leukemia International Consortium
COG	Childhood Oncology Group (Children's Cancer Group)
ESCALE	Epidemiological Study on Childhood Cancer and Leukemia

GCCR	German Childhood Cancer Registry
NARECHEM	Nationwide Registration for Childhood Haematological Malignancies
NCCLS	Northern California Childhood Leukemia Study (USA)
NZCCS	New Zealand Childhood Cancer Study.
OR	Odds ratio
RDD	random digit dialing
SETIL	Studio sulla Eziologia dei Tumori Infantali Linfoemopoietici
UKCCS	United Kingdom Childhood Cancer Study

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Novelty and impact statement

To investigate whether home pesticide exposure increases the risk of childhood leukemia, we assembled the largest sample size to date, especially for acute myeloid leukemia (AML) and sub-types of acute lymphoblastic leukemia (ALL), by pooling individual level exposure data from 12 case-control studies. Our findings of increased risk for both ALL and AML suggest that it would be prudent for parents to limit the use of home pesticides before and after a child's birth.

Table 1

Selected characteristics and definitions of home pesticide exposure in the studies in the CLIC pooled analyses of home pesticide exposure and the risk of childhood leukemia

Country, Study (years of case accrual)	Cases	Controls					Data collection method	Time period	Definition of exposure	Prevalence amongst Controls
	Source	Participation[1]	N	Source	Participation[1]	N				
Australia, Aus-ALL (2003-2007)	Hospitals (nationwide)	75%	ALL 388	RDD	64% of agreed controls	870	Self-administered questionnaire mailed to mother with follow-up computer assisted telephone interview.	During pregnancy	Any professional pest control treatment	11.0
								After birth until reference date[2]	Any professional pest control treatment	30.9
Canada, Quebec (1980-2000)	Hospitals (province wide)	93%	ALL 790	Health Insurance file population-based registry (province-wide)	86%	790	Telephone interview with parents using structured questionnaire	In the month before or during pregnancy	Any pesticides defined as any household use of the following: ■ Personal repellants (mother) ■ Professional pest control treatment ■ Outdoor sprays or vaporizers or products to target ■ Ants, cockroaches, flies, bees, wasps ■ Moths ■ Mites/spiders ■ Rodents ■ Mosquitoes ■ Termites ■ Snails/slugs ■ Herbicides ■ House plant insects ■ Tree disease	57.5
									Professional pest control treatment	3.5
								After birth until reference date[2]	Any pesticides defined as any household use of the following: ■ Personal repellants (child) ■ Outdoor sprays or vaporizers or products to target ■ Ants, cockroaches, flies, bees, wasps ■ Moths ■ Mites/spiders ■ Rodents ■ Mosquitoes ■ Termites ■ Snails/slugs ■ Herbicides ■ House plant insects ■ Tree disease	81.6

Country, Study (years of case accrual)	Cases	Controls					Data collection method	Time period	Definition of exposure	Prevalence amongst Controls
	Source	Participation[1]	N	Source	Participation[1]	N				
France, ADELE (1993-1999)	Hospitals	95%	ALL: 240 AML: 36	Hospitals (same as cases)	99%	288	Face to face interview with mother using structured questionnaire	During pregnancy	Maternal use of ■ Insecticides in the home ■ Garden insecticides ■ Garden fungicides ■ Garden herbicides	22.9
								After birth until reference date[2]	Maternal use of ■ Insecticides in the home ■ Garden insecticides ■ Garden fungicides ■ Garden herbicides	39.9
France ESCALE (2003-2004)	Population-based cancer registry (nationwide)	91%	ALL: 648 AML: 101	Population quotas by age, sex, region (nationwide)	71%	1,681	Telephone interview with mother using structured questionnaire	During pregnancy	Maternal use of ■ Insecticides in the home ■ Crop insecticides ■ Pet insecticides ■ Fungicides ■ Herbicides	37.9
Germany, GCCR (1988-1994)	Population-based cancer registry (nationwide)	82%	ALL: 751 AML: 130	Population-based registry (community based but complete nationwide coverage)	71%	2,458	Self-administered questionnaire mailed to parents with separate follow-up telephone interviews with both parents	After birth until reference date[2]	Any professional pest control treatment	1.9
Greece, NARECHEM (1993-94)	Nationwide hospital cancer registry	100%	ALL; 140 AML: 13	Hospital	96%	300	Face to face interview with guardian using structured questionnaire	In the month before conception	Mother exposed to pesticides in the residence	1.0
								During pregnancy	Mother exposed to pesticides in the residence	3.0
Greece, NARECHEM (1996-97)	Nationwide hospital cancer registry	83%	ALL 86 AML 13	Hospital	96%	99	Face to face interview with guardian using structured questionnaire	In the month before conception	Mother or father exposed to pesticides in the residence	0.0
								During pregnancy	Mother exposed to pesticides in the residence	0.0
Italy, SETIL (1998-2001)	Nationwide clinical database	91%	ALL: 601 AML: 32	Population-based National Health Service Registry	69%	1,044	Face to face interviews with both parents using structured questionnaires for each dwelling lived in from one year before child's birth until reference date. Information collected about years in which each pesticide was used collected.	Between the calendar years of conception and birth	Any pesticides defined as any household use of the following:: ■ Insecticides, herbicides in the garden or vegetable garden ■ Pesticides for house plants ■ Insecticides for ants, cockroaches or similar ■ Insecticides for flies or mosquitoes ■ Insecticides for pets or their cages	56.3
									Any professional pest control treatment	2.2

Country, Study (years of case accrual)	Cases	Controls					Data collection method	Time period	Definition of exposure	Prevalence amongst Controls
	Source	Participation[1]	N	Source	Participation[1]	N				
								Between the calendar years of birth and diagnosis	Any pesticides defined as any household use of the following:: ■ Insecticides, herbicides in the garden or vegetable garden ■ Pesticides for house plants ■ Insecticides for ants, cockroaches or similar ■ Insecticides for flies or mosquitoes ■ Professional pest control ■ Insecticides for pets or their cages	65.7
									Any professional pest control treatment	4.0
New Zealand, NZCCS (1990-1993)	Registry (nationwide)	92%	ALL 97 AML 22	Birth registry (nationwide)	69%	303	Face to face interview with mother using structured questionnaire	In three months before conception	Mother exposed to pesticides around home	45.3
								During pregnancy	Mother exposed to pesticides around home	64.4
								After birth until reference date[2]	Child ever exposed to pesticides around home	49.7
UK, UKCCS (1991-1996)	Population-based tailored referral systems	93%	ALL: 1,461 AML: 248	GP registries (nationwide)	64%	3,448	Separate face to face interviews with both parents using structured questionnaire; if not possible, telephone interview	During pregnancy	Any professional pest control treatment of the house for woodworm/dry rot	1.2
								After birth until reference date[2]	Any professional pest control treatment of the house for woodworm/dry rot	10.2
US, COG-E15 (1989-1993)	Children's Cancer Group clinical trials	87%	ALL 1,914	RDD	70%	1,987	Separate telephone interviews with both parents using structured questionnaires	In the month before conception	Mother or father had any contact with pesticides defined as the use of any of the following: ■ Any professional pest control treatment or Products to control ■ Ants, cockroaches flies bees ■ Moths ■ Spiders or mites ■ Rodents or gophers ■ Fleas or ticks ■ Termites ■ Slugs or snails ■ Weeds ■ Plant/tree insect or diseases	47.9
									Any professional pest control treatment	5.7

Country, Study (years of case accrual)	Cases	Controls					Data collection method	Time period	Definition of exposure	Prevalence amongst Controls
	Source	Participation[1]	N	Source	Participation[1]	N				
								During pregnancy	Mother had any contact with pesticides defined as the use of any of the following: Products to control ■ Ants, cockroaches flies bees ■ Moths ■ Spiders or mites ■ Rodents or gophers ■ Fleas or ticks ■ Termites ■ Slugs or snails ■ Weeds ■ Plant/tree insect or diseases	68.3
									Any professional pest control treatment	10.2
								After birth until reference date[2]	Child had any contact with pesticides defined as the use of any of the following: Products to control ■ Ants, cockroaches flies bees ■ Moths ■ Spiders or mites ■ Rodents or gophers ■ Fleas or ticks ■ Termites ■ Slugs or snails ■ Weeds ■ Plant/tree insect or diseases	77.2
US, NCCLS (1995-2008)	Hospitals	86%	ALL 840 AML 145	Birth registry (state wide)	68%	1,226	Face to face interview with primary caregiver, usually mother, using structured questionnaire	In the three months before conception	Any pesticide as defined as any household use of the following: ■ Any professional lawn service ■ Indoor fogger ■ Any professional pest control treatment ■ Personal repellants for ticks or mosquitoes (mother or father) or Products to control ■ Ant, fly or cockroaches ■ Flea, ticks (collar, soap, spray, powder, dust or other skin application) ■ Plant/tree insect or disease ■ Rat, mouse, gopher or mole ■ Slug or snail bait ■ Weeds	61.5
									Any professional pest control treatment	11.8
								During pregnancy	Any pesticide as defined as any household use of the following:	66.8

Country, Study (years of case accrual)	Cases	Controls				Data collection method	Time period	Definition of exposure	Prevalence amongst Controls
	Source	Participation[1]	N	Source	Participation[1]	N			
								■ Any professional lawn service ■ Indoor fogger ■ Any professional pest control treatment ■ Personal repellants for ticks or mosquitoes (mother) or Products to control ■ Ant, fly or cockroaches ■ Flea, ticks (collar, soap, spray, powder, dust or other skin application) ■ Plant/tree insect or disease ■ Rat, mouse, gopher or mole ■ Slug or snail bait ■ Weeds	
								Any professional pest control treatment	13.2
							After birth until the child' 3rd birthday	Any pesticide as defined as any household use of the following: ■ Any professional lawn service ■ Indoor fogger ■ Any professional pest control treatment ■ Personal repellants for ticks or mosquitoes (child) or Products to control ■ Ant, fly or cockroaches ■ Flea, ticks (collar, soap, spray, powder, dust or other skin application) ■ Plant/tree insect or disease ■ Rat, mouse, gopher or mole ■ Slug or nail bait ■ Weeds	84.8
								Any professional pest control treatment	27.6

RDD: random digit dialing

[1]Participation fractions are based on information available from published studies or obtained directly from study personnel. Definition of the participation fraction may vary across studies.

[2]Date of diagnosis for cases and the date of recruitment or questionnaire return for controls.

Table 2

Key demographic characteristics of participants in the 12 studies in the CLIC pooled analyses of home pesticide exposure and the risk of leukemia in the offspring

	ALL (12 studies)				AML (9 studies)			
	Case (n= 7,956)		Control[1] (n = 14,494)		Case (n= 740)		Control[2] (n= 10,847)	
	n	%	n	%	n	%	n	%
Sex								
Boy	4,457	*55.7*	8,066	*55.7*	401	*54.2*	6,073	*56.0*
Girl	3,499	*44.3*	6,428	*44.3*	339	*45.8*	4,774	*44.0*
Child's age (years)[3]								
0-1	867	*10.9*	2,149	*14.8*	220	*29.7*	1,724	*15.9*
2-4	3,731	*46.9*	5,764	*39.8*	138	*18.6*	4,101	*37.8*
5-9	2,319	*29.1*	4,225	*29.1*	180	*24.3*	3,112	*28.7*
10-14	1,038	*13.0*	2,326	*16.0*	200	*27.0*	1,906	*17.6*
15-16	1	*0.0*	30	*0.2*	2	*0.3*	4	*0.0*
Child's year of birth								
1970-1987	2,824	*35.5*	4,692	*32.4*	234	*31.6*	2,812	*25.9*
1988-1996	3,676	*46.2*	6,944	*47.9*	364	*49.2*	5,861	*54.0*
1997-2007	1,456	*18.3*	2,858	*19.7*	142	*19.2*	2,174	*20.0*
Child's reference year[3]								
1980-1992	2,872	*36.1*	3,924	*27.1*	90	*12.2*	1,520	*14.0*
1993-1997	2,533	*31.8*	5,578	*38.5*	388	*52.4*	5,343	*49.3*
1998-2008	2,551	*32.1*	4,992	*34.4*	262	*35.4*	3,984	*36.7*
Birth order								
1st	3,648	*45.9*	6,456	*44.5*	323	*43.6*	4,791	*44.2*
2nd	2,706	*34.0*	5,067	*35.0*	246	*33.2*	3,849	*35.5*
3rd or more	1,565	*19.7*	2,920	*20.1*	162	*21.9*	2,156	*19.9*
Missing	37	*0.5*	51	*0.4*	9	*1.2*	51	*0.5*
Mother's age at child's birth								
<25 years	2,222	*27.9*	3,563	*24.6*	222	*30.0*	2,596	*23.9*
25-34 years	4,837	*60.8*	9,224	*63.6*	431	*58.2*	6,930	*63.9*
>34 years	876	*11.0*	1,682	*11.6*	83	*11.2*	1,296	*11.9*
Missing	21	*0.3*	25	*0.2*	4	*0.5*	25	*0.2*
Child has Down Syndrome								
Yes	97	*1.2*	6	*0.0*	39	*5.3*	3	*0.0*
Highest level of education of either parent								
Did not finish secondary education	1,409	*17.7*	2,491	*17.2*	173	*23.4*	2,226	*20.5*
Completed secondary education	3,312	*41.6*	5,694	*39.3*	274	*37.0*	3,985	*36.7*
Tertiary education	3,186	*40.0*	6,176	*42.6*	280	*37.8*	4,503	*41.5*
Missing	49	*0.6*	133	*0.9*	13	*1.8*	133	*1.2*

	ALL (12 studies)				AML (9 studies)			
	Case (n= 7,956)		Control[1] (n = 14,494)		Case (n= 740)		Control[2] (n= 10,847)	
	n	%	n	%	n	%	n	%
Ethnicity								
White/Caucasian/European	6,672	*83.9*	12,797	*88.3*	590	*79.7*	9,507	*87.6*
Other	1,248	*15.7*	1,615	*11.1*	145	*19.6*	1,295	*11.9*
Indeterminate	17	*0.2*	39	*0.3*	0	*0.0*	2	*0.0*
Missing	19	*0.2*	43	*0.3*	5	*0.7*	43	*0.4*
Summary pesticide exposure data before conception	2,785	*35.0*	3,635	*25.1*	173	*23.4*	1,789	*16.5*
Any professional pest control exposure data in the 1-3 months before pregnancy	2660	*33.4*	3120	*21.53*	Not shown as only data from 1 study			
Summary pesticide exposure data during pregnancy	5,055	*63.5*	7,370	*50.8*	345	*46.7*	4,664	*43.0*
Any professional pest control exposure data during pregnancy	5,660	*71.1*	8,938	*61.7*	388	*52.4*	5,322	*49.1*
Summary pesticide exposure data after birth	4,162	*52.3*	5,179	*35.7*	198	*26.8*	2,655	*24.5*
Any professional pest control exposure data after birth	3,611	*45.4*	8,388	*57.9*	468	*63.2*	7,531	*69.4*

[1] Includes controls from all studies with ALL cases (that is, all studies).

[2] Includes controls from all studies with AML cases (that is, all studies except Australia, Canada, and COG-E15).

[3] Age groups and reference years are based on the child's age at the censoring date. For case, this was the date at diagnosis and for controls, it was the date that the study investigators nominated (either the date of recruitment or the date of the questionnaire return).

Table 3

Pooled ORs (95% CI) for the association between home pesticide exposure and the risk of ALL in the offspring: Overall and by subgroups

	Within 1-3 months before conception (5 studies[1], unless otherwise indicated)			During pregnancy (9 studies[2], unless otherwise indicated)			After birth (6 studies[3], unless otherwise indicated)		
	Total N Case/Controls	% exposed	OR[4,5] (95% CI)	Total N Case/Controls	% exposed	OR[4,5] (95% CI)	Total N Case/Controls	% exposed	OR[4,5] (95% CI)
Any pesticide exposure									
All participants with relevant data	2,785/3,635	53.9/46.4	1.39 (1.25, 1.55)	5,055/7,370	63.0/53.2	1.43 (1.32, 1.54)	4,162/5,179	79.3/73.7	1.36 (1.23,1.51)
Missing values	292/280			300/339			258/368		
Immunophenotype									
B-lineage cases	1,896/3,635	53.3/46.4	1.41 (1.25, 1.59)	3,779/7,370	62.5/53.2	1.47 (1.35, 1.61)	3,020/5,179	79.0/73.7	1.35 (1.21, 1.52)
T-lineage cases	250/3,635	52.4/46.4	1.47 (1.10, 1.95)	514/7,370	61.7/53.2	1.42 (1.16, 1.74)	421/5179	79.8/73.7	1.43 (1.10, 1.85)
Age at diagnosis									
0-1 years	303/498	53.5/47.2	1.44 (1.05, 1.97)	574/1,157	67.1/49.4	1.87 (1.48, 2.37)	428/641	67.8/62.2	1.22 (0.91, 1.62)
2-4 years	1,275/1,503	55.5/47.1	1.49 (1.27, 1.75)	2,374/2,940	63.4/55.2	1.43 (1.27, 1.61)	2,005/2,309	77.7/73.9	1.30 (1.12, 1.51)
5-9 years	796/1,062	51.5/47.9	1.14 (0.93, 1.39)	1,496/2,180	60.4/53.6	1.24 (1.07, 1.43)	1,249/1,587	82.6/76.1	1.43 (1.18, 1.74)
10 or more years	411/572	54.0/41.1	1.66 (1.25, 2.21)	611/1,093	64.2/51.1	1.59 (1.27, 2.00)	480/642	87.7/78.7	1.81 (1.27, 2.58)
			Interaction *p* value = 0.70			Interaction *p* value = 0.01			Interaction *p* value = 0.10
Sex									
Girls	1,239/1,638	54.7/46.9	1.41 (1.20, 1.65)	2,251/3,272	64.7/53.6	1.52 (1.35, 1.71)	1,816/2,300	80.1/73.8	1.38 (1.18, 1.61)
Boys	1,546/1,997	53.3/46.0	1.38 (1.19, 1.59)	2,804/4,098	61.7/52.8	1.35 (1.22, 1.51)	2,346/2,879	78.7/73.7	1.35 (1.17, 1.54)
			Interaction *p* value = 0.91			Interaction *p* value = 0.20			Interaction *p* value = 0.73
Child's reference year[6]									
Before 1997	2,059/2,507	51.6/41.2	1.47 (1.30, 1.66)	2,934/3,284	63.9/57.4	1.33 (1.19, 1.49)	2,665/2,767	78.3/73.8	1.32 (1.15, 1.50)
1997 or later	726/1,128	60.5/58.0	1.20 (0.98, 1.46)	2,121/4,086	61.9/49.8	1.50 (1.34, 1.68)	1,497/2,412	81.0/73.7	1.38 (1.17, 1.64)
			Interaction *p* value = 0.28			Interaction *p* value = <0.01			Interaction *p* value = 0.02
Exposure to									
Professional pest control treatments	2,660/3,120[7]	9.2/8.0	1.24 (1.03, 1.50)	5,660/8,938[8]	8.2/6.1	1.19 (1.04, 1.36)	3,611/8,388[9]	15.4/11.3	1.28 (1.14, 1.45)
Household insecticide/miticide	2,529/3,027[7]	30.3/24.9	1.34 (1.19, 1.51)	4,792/6,732[10]	45.5/38.9	1.28 (1.18, 1.38)	4,032/4,832[11]	60.0/55.8	1.23 (1.12, 1.34)
Pesticide used on pets	2,586/3,055[7]	21.0/18.9	1.17 (1.02, 1.34)	3,841/5,763[13]	19.9/16.6	1.15 (1.03, 1.29)	3,050/3,768[14]	31.7/27.8	1.15 (1.03, 1.29)

	Within 1-3 months before conception (5 studies[1], unless otherwise indicated)			During pregnancy (9 studies[2], unless otherwise indicated)			After birth (6 studies[3], unless otherwise indicated)		
	Total N Case/Controls	**% exposed**	**OR[4,5] (95% CI)**	**Total N Case/Controls**	**% exposed**	**OR[4,5] (95% CI)**	**Total N Case/Controls**	**% exposed**	**OR[4,5] (95% CI)**
Insecticide or fungicide used on plants or trees	2,699/3,166[7]	4.6/3.3	1.49 (1.14, 1.95)	4,938/6,879[10]	9.8/7.5	1.26 (1.11, 1.44)	4,006/4,786[11]	20.0/15.4	1.41 (1.26, 1.59)
Herbicide	2,659/3,135[7]	11.7/11.9	1.23 (1.04, 1.45)	4,938/6,879[10]	15.4/11.0	1.34 (1.19, 1.50)	4,066/4,878[11]	30.2/25.5	1.34 (1.21, 1.48)
Rodenticide	2686/3,150[7]	6.3/4.5	1.39 (1.10, 1.76)	3,492/3,963[14]	7.1/5.0	1.42 (1.17, 1.73)	3,251/3,547[14]	10.5/8.5	1.32 (1.12, 1.56)
Molluscicide	2,715/3,178[7]	3.0/3.7	1.06 (0.79, 1.43)	3,511/3,968[14]	3.5/4.3	1.01 (0.79, 1.28)	3,256/3,567[14]	6.5/7.9	1.06 (0.87, 1.30)
Personal insect repellant	Not shown as only 1 study had data			1,603/1,980[15]	12.9/9.3	1.42 (1.15, 1.77)	1,431/1,739[15]	29.5/27.7	1.02 (0.86, 1.20)

[1] Greece (NARECHEM 1993-1994 and 1996-1997), New Zealand, US (COG-E15 and NCCLS).

[2] Canada, France (Adele and ESCALE), Italy, Greece (NARECHEM 1993-1994 and 1996-1997), New Zealand, US (COG-E15 and NCCLS).

[3] Canada, France (Adele), Italy, New Zealand, US (COG-E15 & NCCLS).

[4] The reference group was those with no pesticide exposure in that time period.

[5] Adjusted for age, sex, birth year group, study, ethnicity and highest level of education of either parent.

[6] Reference years are based on the child's age at the censoring date. For case, this was the date at diagnosis and for controls, it was the date that the study investigators nominated (either the date of recruitment or the date of the questionnaire return).

[7] Data available from two studies (US (COG-E15 and NCCLS)).

[8] Data available from six studies (Australia, Canada, Italy, UKCCS, US (COG-E15 and NCCLS)).

[9] Data available from five studies (Australia, Germany, Italy, UKCCS, US (NCCLS)).

[10] Data available from six studies (Canada, France (Adele and ESCALE) Italy, US (COG-E15 and NCCLS)).

[11] Data available from five studies (Canada, France (Adele) Italy, US (COG-E15 and NCCLS)).

[12] Data available from four studies (France (ESCALE) Italy, US (COG-E15 and NCCLS)).

[13] Data available from three studies (Italy, US (COG-E15 and NCCLS)).

[14] Data available from three studies (Canada, US (COG-E15 and NCCLS)).

[15] Data available from two studies (Canada, US (NCCLS)).

Table 4

Pooled OR (95% CI) for the association between home pesticide exposure and the risk of ALL in the offspring by cytogenetic subtype

	During pregnancy				After birth			
	No of studies	Total N Case/Controls	% exposed	OR[1,2], (95% CI)	No of studies	Total N Case/Controls	% exposed	OR[1,2], (95% CI)
Any pesticide exposure								
B cell ALL low hyperdiploidy	3[3]	150/3,022	64.0/47.1	1.77 (1.22,2.56)	2[4]	107/1,387	88.8/75.7	2.15 (1.26,3.64)
B cell ALL high hyperdiploidy	3[3]	361/3,022	61.8/47.1	1.82 (1.43,2.31)	2[4]	224/1,387	81.7/75.7	1.32 (0.98,1.79)
B cell ALL *ETV6-Runx1* t(12;21)	2[5]	219/2,743	63.3/49.6	1.67 (1.23,2.26)	1[6]			
Any MLL arrangement	2[5]	30/2,743	70.0/49.6	2.12 (0.90,5.00)	1[6]			
Any professional pest control treatment								
B cell ALL low hyperdiploidy	3[7]	183/5,193	8.2/5.6	1.02 (0.58,1.79)	3[7]	166/5,040	22.3/17.1	1.13 (0.76,1.67)
B cell ALL high hyperdiploidy	3[7]	542/5,193	8.7/5.6	1.32 (0.95,1.85)	3[7]	530/5,040	22.6/17.1	1.33 (1.06,1.67)
B cell ALL *ETV6-Runx1* t(12;21)	3[7]	293/5,193	10.9/5.6	1.47 (0.98,2.21)	3[7]	287/5,040	26.1/17.1	1.42 (1.06,1.89)
Any MLL arrangement	3[7]	79/5,193	6.3/5.6	0.95 (0.37,2.44)	3[7]	62/5,040	9.7/17.1	0.58 (0.26,1.31)

[1] The reference group was those with no exposure in that time period.

[2] Adjusted for age, sex, birth year group, study, ethnicity and highest level of education of either parent

[3] France (ADELE and ESCALE), NCCLS

[4] France (ADELE), NCCLS

[5] France (ESCALE), NCCLS

[6] Data not shown as only 1 study (NCCLS)

[7] Australia, UKCCS, NCCLS

Table 5

Pooled OR (95% CI) for the association between home pesticide exposure and the risk of AML in the offspring: Overall and by subgroups

	Within 1-3 months before conception (4 studies[1], unless otherwise indicated)			During pregnancy (7 studies[2], unless otherwise indicated)			After birth (4 studies[3], unless otherwise indicated)		
	Total N Case/Controls	**% exposed**	**OR[4,5] (95% CI)**	**Total N Case/Controls**	**% exposed**	**OR[4,5] (95% CI)**	**Total N Case/Controls**	**% exposed**	**OR[4,5](95% CI)**
Any pesticide exposure									
All participants with relevant data	173/1,789	52.6/45.2	1.49 (1.02, 2.16)	345/4,666	55.9/46.2	1.55 (1.21, 1.99)	198/2,655	70.2/69.1	1.08 (0.76, 1.53)
Missing values	20/139			17/275			11/115		
Age at diagnosis									
0-4 years	82/953	54.9/47.7	1.53 (0.86, 2.70)	170/2,501	58.8/46.2	2.08 (1.44, 3.02)	80/1,486	66.3/67.8	1.10 (0.59, 2.03)
5 or more years	91/836	50.5/42.3	1.40 (0.83, 2.36)	175/2,165	53.1/46.3	1.26 (0.88, 1.78)	118/1,169	72.9/70.7	1.15 (0.72, 1.83)
			Interaction *p* value = 0.93			Interaction *p* value = 0.39			Interaction *p* value = 0.31
Sex									
Girls	78/783	51.3/46.5	1.15 (0.66, 1.99)	159/2,068	54.7/47.3	1.37 (0.95, 1.97)	91/1,176	71.4/68.4	1.11 (0.66, 1.88)
Boys	95/1,006	53.7/44.2	1.77 (1.06, 2.98)	186/2,598	57.0/45.4	1.72 (1.22, 2.43)	107/1,479	69.2/69.7	0.99 (0.61, 1.61)
			Interaction *p* value = 0.65			Interaction *p* value = 0.62			Interaction *p* value = 0.67
Child's reference year[6]									
Before 2001	93/1,052	40.9/33.7	1.36 (0.79,2.31)	155/2,025	43.9/43.7	1.13 (0.77, 1.68)	115/1,618	56.5/61.7	0.82 (0.54, 1.25)
2001 or later	80/737	66.3/61.6	1.49 (0.88, 2.54)	190/2,641	65.8/48.2	1.90 (1.37, 2.64)	83/1,037	89.2/80.6	2.09 (1.00, 4.39)
			Interaction *p* value = 0.35			Interaction *p* value = 0.52			Interaction *p* value = 0.08
Exposure to	Data not shown as only 1 study had data								
Professional pest control treatments				388/5,322[7]	6.4/4.1	1.26 (0.79, 2.00)	468/7,531[8]	13.5/9.1	1.26 (0.94, 1.69)
Household insecticide/miticide				294/4,022[9]	44.2/36.3	1.55 (1.21, 2.00)	167/2,318[10]	58.7/56.2	1.31 (0.93, 1.84)
Pesticide used on pets				266/3,802[11]	19.2/11.8	1.51 (1.07, 2.12)	126/1,994[12]	25.4/19.3	1.25 (0.79, 1.96)
Insecticide or fungicide used on plants or trees				302/4,118[9]	4.3/5.7	0.94 (0.53, 1.69)	157/2,241[10]	13.4/12.2	1.16 (0.70, 1.92)
Herbicide				304/4,136[9]	11.5/10.0	0.84 (0.56, 1.26)	172/2,344[10]	25.0/22.7	0.78 (0.52, 1.19)

[1] Greece (NARECHEM 1993-1994 and 1996-1997), New Zealand, US (NCCLS).

[2] France (Adele and ESCALE), Greece (NARECHEM 1993-1994 and 1996-1997), Italy, New Zealand, US (NCCLS).

[3] France (Adele), Italy, New Zealand, US (NCCLS).

[4] The reference group was those with no pesticide exposure in that time period.

[5] Adjusted for age, sex, birth year group, study, ethnicity, birth order and highest level of education of either parent.

[6] Reference years are based on the child's age at the censoring date. For case, this was the date at diagnosis and for controls, it was the date that the study investigators nominated (either the date of recruitment or the date of the questionnaire return).

[7] Data available from three studies (Italy, UKCCS, US (NCCLS)).

[8] Data available from four studies (Germany, Italy, UKCCS, US (NCCLS)).

[9] Data available from four studies (France (Adele and ESCALE), Italy, US (NCCLS)).

[10] Data available from three studies (France (Adele), Italy, US (NCCLS)).

[11] Data available from three studies (France (ESCALE), Italy, US (NCCLS)).

[12] Data available from two studies (Italy, US (NCCLS)).