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

Short title: Pooled analyses of home pesticide exposure and risk of childhood leukemia (63 characters)

Authors:

Helen D Bailey[1], Claire Infante-Rivard[2], Catherine Metayer[3], Jacqueline Clavel[4-6], Tracy Lightfoot[7], Peter Kaatsch[8], Eve Roman[7], Corrado Magnani[9], Logan G Spector[10,11], Eleni Petridou[12], Elizabeth Milne[13], John D Dockerty[14], Lucia Miligi[15], Bruce K Armstrong[16,17] Jérémie Rudant[4-6], Lin Fritschi[18,] Jill Simpson[7], Luoping Zhang[3], Roberto Rondelli[19], Margarita Baka[20], Laurent Orsi[4,5], Maria Moschovi[21], Alice Y Kang[3], Joachim Schüz[1]

Address for correspondence: Joachim Schüz, Section of Environment and Radiation, International Agency for Research on Cancer, 150 cours Albert Thomas, Lyon 69372 Cedex 08, France. Telephone: [+33] (0)4 72 73 8441. Fax: [+33] (0)4 72 73 8320 Email: SchuzJ@iarc.fr

Authorship: All authors are principal investigators, co-investigators or designated collaborators of participating CLIC studies

Author affiliations

[1]International Agency for Research on Cancer (IARC), Section of Environment and Radiation, Lyon, France

[2]Department of Epidemiology, Biostatistics, and Occupational Health, Faculty of Medicine, McGill University, Canada

[3]University of California, Berkeley, School of Public Health, Berkeley, United States

[4]Inserm U1153, Epidemiology and Biostatistics Sorbonne Paris Cité Center (CRESS), Epidemiology of childhood and adolescent cancers team (EPICEA), Villejuif, France

[5]Paris-Descartes University, UMRS-1153, Epidemiology and Biostatistics Sorbonne Paris Cité Center (CRESS), Paris, France

[6]RNHE - National Registry of Childhood cancers, Villejuif, France

[7]Department of Health Sciences, University of York, York, United Kingdom

[8]German Childhood Cancer Registry (GCCR) at the Institute for Medical Biostatistics, Epidemiology and Informatics, University Medical Centre, Johannes Gutenberg University Mainz, Germany

[9]Dipartimento di Medicina Traslazionale – Universita` del Piemonte Orientale, AOU Maggiore della Carita` e CPO – Piemonte, Novara, Italy

[10]Division of Epidemiology Clinical Research, University of Minnesota, Minneapolis, United States

[11]Department of Pediatrics and Masonic Cancer Center, University of Minnesota, Minneapolis, United States

[12]Department of Hygiene, Epidemiology and Medical Statistics, National and Kapodistrian University of Athens, Medical School, Athens, Greece

[13]Telethon Kids Institute, University of Western Australia, Perth, Australia

[14]Dean's Department and Department of Preventive and Social Medicine, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand

[15]ISPO-Cancer Prevention and Research Institute, Occupational and Environmental Epidemiology Unit, Florence, Italy

[16] Sydney School of Public Health, University of Sydney, New South Wales, Australia

[17]Sax Institute, Ultimo, NSW, Australia.

[18]Curtin University, School of Public Health, Perth, Australia

[19]Paediatric Haematology -Oncology, Lalla Seràgnoli, Policlinico Sant'Orsola Malpighi Bologna Italy

[20]Department of Pediatric Hematology-Oncology, ''Pan.&Agl. Kyriakou'' Children's Hospital, Athens, Greece

[21]Hematology-Oncology Unit, First Department of Pediatrics, Athens University Medical School, ''Aghia Sophia'' General Children's Hospital, Athens, Greece

Funding

The authors declare that they have no conflict of interest. The work reported in this paper by Helen Bailey was undertaken during the tenure of a Postdoctoral Fellowship from the International Agency for Research on Cancer, partially supported by the European Commission FP7 Marie Curie Actions, - People- Co-funding of regional, national and international programmes (COFUND). The CLIC administration, annual meetings, and pooled analyses are partially supported by the National Cancer Institute, NCI, USA (grant R03CA132172), National Institute of Environmental Health Sciences, NIEHS, USA (grants P01 ES018172, 2R01ES009137-13, 1R13CA174342-01; 1R13 ES024632-01 and R13 ES021145-01), the Environmental Protection Agency, EPA, USEPA, USA (grant RD83451101), Alex's Lemonade Stand Foundation; Grant number: 20140461 and the Children with Cancer, CwC, UK (Award No. 2010/097).

Aus-ALL was supported by the Australian National Health and Medical Research Council (Grant ID 254539).

The Canadian study was funded by The National Cancer Institute of Canada; Grant numbers: #014113, #010735-CERN #RFA0405; The Medical Research Council of Canada; Grant number: MOP 37951; The Fonds de la recherche en santé du Québec; Grant number: #981141; The Bureau of Chronic Disease Epidemiology, Canada; Health and Welfare Canada; The Leukemia Research Fund of Canada; and the National Health and Research Development Program, Ottawa.

ADELE Grant sponsors: INSERM, the French Ministère de l'Environnement, the Association pour la Recherche contre le Cancer, the Fondation de France, the Fondation Jeanne Liot, the Fondation Weisbrem-Berenson, the Ligue Contre le Cancer du Val de Marne, the Ligue Nationale Contre le Cancer.

ESCALE Grant sponsors: INSERM, the Fondation de France, the Association pour la Recherche sur le Cancer (ARC), the Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS), the AgenceFrançaise de Sécurité Sanitaire de l'Environnement et du Travail (AFSSET), the association Cent pour sang la vie, the Institut National du Cancer (INCa), the Agence Nationale de la Recherche (ANR), the Cancéropôle Ile-de-France;

The German study (GCCR) was supported by a grant from the Federal Ministry of the Environment, Nuclear Safety and Nature Preservation.

NARECHEM, is supported in part by the National and Kapodistrian University, Athens, Greece.

The SETIL study was financially supported by research grants received by AIRC (Italian Association on Research on Cancer), MIUR (Ministry for Instruction, University and Research), Ministry of Health, Ministry of Labour, Piedmont Region.

The New Zealand Childhood Cancer Study was funded by the Health Research Council of NZ, the NZ Lottery Grants Board, the Otago Medical School (Faculty Bequest Funds), the Cancer Society of NZ, the Otago Medical Research Foundation, and the A.B. de Lautour Charitable Trust.

The Northern California Childhood Leukemia Study (NCCLS) is supported by the National Institutes of Health (NIH), USA (grants P01 ES018172, R01 ES09137, and P42-ES04705), Environmental Protection Agency (USEPA), USA (grant RD83451101), and the CHILDREN with CANCER (CwC), UK (former Children with Leukaemia) for data collection. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH, USEPA, or the CwC.

Article category: research article epidemiology

Key words: pesticide; acute lymphoblastic leukemia acute myeloid leukemia; childhood; pooled analysis, case-control study;

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

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.

Abstract

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.

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[3] and 15 studies[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.

The United Kingdom Childhood Cancer Study (UKCCS) is sponsored and administered by Leukaemia and Lymphoma Research. The researchers are independent from the funders.

COG: The E15 cohorts of the Children's Oncology Group were funded by National Institutes of Health (NIH), USA (Grant R01CA048051) and The Children's Cancer Research Fund, Minneapolis, MN

Acknowledgements

We would like to thank Dr Maria S Pombo-de-Oliveira, Instituto Nacional de Câncer (INCA) who was one of experts in molecular biology who reviewed the consistency of CLIC cytogenetic data. We would like to thank our dear colleague and friend, Patricia Buffler, who passed away before the submission of this manuscript. She was a founding member and Chair of CLIC as well as the driving force behind the NCCLS. She provided unconditional support to finding the causes of childhood leukemia, and her scientific leadership and guiding forces within CLIC will be remembered.

The Aus-ALL consortium conducted the study and the Telethon Institute for Child Health Research (TICHR), University of Western Australia, was the coordinating centre. Bruce Armstrong (Sydney School of Public Health), Elizabeth Milne (TICHR), Frank van Bockxmeer (Royal Perth Hospital), Michelle Haber (Children's Cancer Institute Australia), Rodney Scott (University of Newcastle), John Attia (University of Newcastle), Murray Norris (Children's Cancer Institute Australia), Carol Bower (TICHR), Nicholas de Klerk (TICHR), Lin Fritschi (WA Institute for Medical Research, WAIMR), Ursula Kees (TICHR), Margaret Miller (Edith Cowan University), Judith Thompson (WA Cancer Registry) were the research investigators, Helen Bailey (TICHR)

was the project coordinator and Alison Reid (WAIMR) performed the occupational analyses. The clinical Investigators were: Frank Alvaro (John Hunter Hospital, Newcastle); Catherine Cole (Princess Margaret Hospital for Children, Perth); Luciano Dalla Pozza (Children's Hospital at Westmead, Sydney); John Daubenton (Royal Hobart Hospital, Hobart); Peter Downie (Monash Medical Centre, Melbourne); Liane Lockwood, (Royal Children's Hospital, Brisbane); Maria Kirby (Women's and Children's Hospital, Adelaide); Glenn Marshall (Sydney Children's Hospital, Sydney); Elizabeth Smibert (Royal Children's Hospital, Melbourne); Ram Suppiah, (previously Mater Children's Hospital, Brisbane).

GCCR: The German study was conducted by the nationwide German Childhood Cancer Registry (GCCR) at the Institute of Medical Biostatistics, Epidemiology and Informatics at the Johannes Gutenberg-University Mainz; researchers involved were Drs Jörg Michaelis (head), Peter Kaatsch, Uwe Kaletsch, Rolf Meinert, Anke Miesner and Joachim Schüz.

NARECHEM Greek Pediatric Hematology Oncology Clinicians: Margarita Baka MD: Department of Pediatric Hematology –Oncology, "Pan.&Agl. Kyriakou" Children's Hospital, Athens, Greece, Thivon & Levadeias, Goudi; Maria Moschovi MD: Hematology-Oncology Unit, First Department of Pediatrics, Athens University Medical School, "Aghia Sophia" General Children's Hospital, Athens, Greece, Thivon & Papadiamantopoulou, Goudi, 11527 Athens, Greece; Sophia Polychronopoulou MD: Department of Pediatric Hematology-Oncology, "Aghia Sophia" General Children's Hospital, Athens, Greece, Thivon & Papadiamantopoulou, Goudi, 11527 Athens, Greece; Emmanuel Hatzipantelis MD, PhD: Pediatric Hematology Oncology Unit, 2nd Pediatric

Department of Aristotle University, AHEPA General Hospital, Thessaloniki, Greece, 1 St. Kyriakidi, 54636 Thessaloniki, Greece; Vassiliki Sidi MD: Pediatric Oncology Department, Hippokration Hospital, Thessaloniki, Greece ; Eftychia Stiakaki MD: Department of Pediatric Hematology-Oncology, University Hospital of Heraklion, Heraklion, Greece; Nick Dessypris, MSc, PhD and Evanthia Bouka, MPH: Department of Hygiene, Epidemiology and Medical Statistics, Athens University Medical School, 11527 Athens, Greece.

The SETIL (Italian Multicentric Epidemiological Study on Risk Factors of Childhood Leukaemia, Non Hodgkin Lymphoma and Neuroblastoma) Working Group:

Corrado Magnani and Alessandra Ranucci (Cancer Epidemiology Unit, CPO Piedmont Novara); Lucia Miligi, Alessandra Benvenuti, Patrizia Legittimo and Angela Veraldi (Occupational and Environmental Unit ,ISPO, Firenze); Antonio Acquaviva (AOU Siena); Maurizio Aricò, Alma Lippi and Gabriella Bernini (AOU Meyer, Firenze); Giorgio Assennato (ARPA, Bari); Stefania Varotto and Paola Zambon (Università di Padova); Pierfranco Biddau and Roberto Targhetta (Ospedale Microcitemico, Cagliari); Luigi Bisanti and Giuseppe Sampietro (ASL di Milano); Francesco Bochicchio, Susanna Lagorio, Cristina Nuccetelli, Alessandro Polichetti and Serena Risica, (ISS, Roma); Santina Cannizzaro and Lorenzo Gafà (LILT, Ragusa); Egidio Celentano (ARSan, Napoli); Pierluigi Cocco (Università di Cagliari); Marina Cuttini (IRCCS Burlo Garofolo, Trieste); Francesco Forastiere,Ursula Kirchmayer and Paola Michelozzi (Dipartimento Epidemiologia Regione Lazio, Roma); Erni Guarino (INT Napoli); Riccardo Haupt (Istituto Giannina Gaslini, Genova); Franco Locatelli (Università di Pavia and AO Bambin Gesù, Roma); Lia Lidia Luzzatto (ASL 1 , Torino); Giuseppe Masera (Università

Milano Bicocca, Monza); Pia Massaglia (Università di Torino); Stefano Mattioli and Andrea Pession (Università di Bologna); Domenico Franco Merlo and Vittorio Bocchini (IST, Genova); Liliana Minelli and Manuela Chiavarini (Università degli Studi di Perugia);Margherita Nardi (AOU Pisa); Paola Mosciatti and Franco Pannelli (Università di Camerino);Vincenzo Poggi (AORN Santobono – Pausilipon, Napoli);Alessandro Pulsoni (Sapienza University, Roma); Carmelo Rizzari (AO San Gerardo, Monza); Roberto Rondelli (Policlinico S.Orsola, Bologna); Gino Schilirò (Università di Catania); Alberto Salvan (IASI-CNR, Roma); Maria Valeria Torregrossa and Rosaria Maria Valenti, (Università degli Studi di Palermo);Alessandra Greco, Gian Luca DeSalvo and Daniele Monetti (IOV-IRCCS, Padova); Claudia Galassi (San Giovanni Battista Hospital, Torino); Veronica Casotto (IRCCS Burlo Garofolo, Trieste); Gigliola de Nichilo (ASL BT, SPRESAL Barletta); Alberto Cappelli, (Accademia dei Georgofili, Florence).

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/.

The NCCLS thanks the families for their participation and the clinical investigators at the following collaborating hospitals for help in recruiting patients: University of California Davis Medical Center (Dr. J. Ducore), University of California San Francisco (Drs. M. Loh and K. Matthay), Children's Hospital of Central California (Dr. V. Crouse), Lucile Packard Children's Hospital (Dr. G. Dahl), Children's Hospital Oakland (Dr. J. Feusner), Kaiser Permanente Roseville (former Sacramento; Drs. K. Jolly and V. Kiley), Kaiser Permanente Santa Clara (Drs. C. Russo, A. Wong, and D. Taggart), Kaiser Permanente San Francisco (Dr. K. Leung), and Kaiser Permanente Oakland (Drs. D. Kronish and S. Month). Finally, the NCCLS thanks the entire study staff and former University of California, Berkeley Survey Research Center for their effort and dedication.

The French authors would like to thank all of the Société Française de lutte contre les Cancers de l'Enfant et de l'Adolescent (SFCE) principal investigators: André Baruchel (Hôpital Saint-Louis/Hôpital Robert Debré, Paris), Claire Berger (Centre Hospitalier Universitaire, Saint-Etienne), Christophe Bergeron (Centre Léon Bérard, Lyon), Jean-Louis Bernard (Hôpital La Timone, Marseille), Yves Bertrand (Hôpital Debrousse, Lyon), Pierre Bordigoni (Centre Hospitalier Universitaire, Nancy), Patrick Boutard (Centre Hospitalier Régional Universitaire, Caen), Gérard Couillault (Hôpital d'Enfants, Dijon), Christophe Piguet (Centre Hospitalier Régional Universitaire, Limoges), Anne-Sophie Defachelles (Centre Oscar Lambret, Lille), François Demeocq (Hôpital Hôtel-Dieu, Clermont-Ferrand), Alain Fischer (Hôpital des Enfants Malades,

Paris), Virginie Gandemer (Centre Hospitalier Universitaire – Hôpital Sud, Rennes), Dominique Valteau-Couanet (Institut Gustave Roussy, Villejuif), Jean-Pierre Lamagnere (Centre Gatien de Clocheville, Tours), Françoise Lapierre (Centre Hospitalier Universitaire Jean Bernard, Poitiers), Guy Leverger (Hôpital Armand-Trousseau, Paris), Patrick Lutz (Hôpital de Hautepierre, Strasbourg), Geneviève Margueritte (Hôpital Arnaud de Villeneuve, Montpellier), Françoise Mechinaud (Hôpital Mère et Enfants, Nantes), Gérard Michel (Hôpital La Timone, Marseille), Frédéric Millot (Centre Hospitalier Universitaire Jean Bernard, Poitiers), Martine Münzer (American Memorial Hospital, Reims), Brigitte Nelken (Hôpital Jeanne de Flandre, Lille), Hélène Pacquement (Institut Curie, Paris), Brigitte Pautard (Centre Hospitalier Universitaire, Amiens), Stéphane Ducassou (Hôpital Pellegrin Tripode, Bordeaux), Alain Pierre-Kahn (Hôpital Enfants Malades, Paris), Emmanuel Plouvier (Centre Hospitalier Régional, Besançon), Xavier Rialland (Centre Hospitalier Universitaire, Angers), Alain Robert (Hôpital des Enfants, Toulouse), Hervé Rubie (Hôpital des Enfants, Toulouse), Stéphanie Haouy (Hôpital Arnaud de Villeneuve, Montpellier), Christine Soler (Fondation Lenval, Nice), and Jean-Pierre Vannier (Hôpital Charles Nicolle, Rouen).

The Canada, Québec Study was conducted in the province over a twenty year period in all university-affiliated pediatric centers hospitals designated to diagnose and treat pediatric cancers, under the direction of Claire Infante-Rivard. Main support collaborators were Alexandre Cusson, Marcelle Petitclerc and Denyse Hamer. We thank all families for their generous participation

1. Zahm SH, Ward MH. Pesticides and childhood cancer. Environmental Health Perspectives 1998;106:893-908.

2. Infante-Rivard C, Weichenthal S. Pesticides and childhood cancer: an update of Zahm and Ward's 1998 review. Journal of Toxicology and Environmental Health.Part B, Critical Reviews 2007;10:81-99.

3. Turner MC, Wigle DT, Krewski D. Residential pesticides and childhood leukemia: a systematic review and meta-analysis. Environmental Health Perspectives 2010;118:33-41.

4. Van Maele-Fabry G, Lantin AC, Hoet P, Lison D. Residential exposure to pesticides and childhood leukaemia: A systematic review and meta-analysis. Environment International 2011;37:280-91.

5. Little J. Epidemiology of Childhood Cancered. Lyon, France: International Agency for Research on Cancer, World Health Organisation, 1999.

6. Metayer C, Milne E, Clavel J, Infante-Rivard C, Petridou E, Taylor M, Schuz J, Spector LG, Dockerty JD, Magnani C, Pombo-de-Oliveira MS, Sinnett D, et al. The Childhood Leukemia International Consortium. Cancer Epidemiol 2013;37:336-47.

7. Bailey HD, Fritschi L, Infante-Rivard C, Glass DC, Miligi L, Dockerty JD, Lightfoot T, Clavel J, Roman E, Spector LG, Kaatsch P, Metayer C, et al. Parental occupational pesticide exposure and the risk of childhood leukemia in the offspring: Findings from the childhood leukemia international consortium. Int.J Cancer 2014;135:2157-72.

8. Infante-Rivard C, Labuda D, Krajinovic M, Sinnett D. Risk of childhood leukemia associated with exposure to pesticides and with gene polymorphisms. Epidemiology 1999;10:481-87.

9. Ma X, Buffler PA, Gunier RB, Dahl G, Smith MT, Reinier K, Reynolds P. Critical windows of exposure to household pesticides and risk of childhood leukemia. Environmental Health Perspectives 2002;110:955-60.

10. 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. European Journal of Cancer 1996;32A:1943-48.

11. Menegaux F, Baruchel A, Bertrand Y, Lescoeur B, Leverger G, Nelken B, Sommelet D, Hemon D, Clavel J. Household exposure to pesticides and risk of childhood acute leukaemia. Occupational and Environmental Medicine 2006;63:131-34.

12. Rudant J, Menegaux F, Leverger G, Baruchel A, Nelken B, Bertrand Y, Patte C, Pacquement H, Verite C, Robert A, Michel G, Margueritte G, et al. Household exposure to pesticides and risk of childhood hematopoietic malignancies: The ESCALE study (SFCE). Environmental Health Perspectives 2007;115:1787-93.

13. Bailey HD, Armstrong BK, de Klerk NH, Fritschi L, Attia J, Scott RJ, Smibert E, Milne E, for the Aus-ALL Consortium. Exposure to professional pest control treatments and the risk of childhood acute lymphoblastic leukemia. International Journal of Cancer 2011;129:1678-88.

14. Aldrich MC, Zhang L, Wiemels JL, Ma X, Loh ML, Metayer C, Selvin S, Feusner J, Smith MT, Buffler PA. Cytogenetics of Hispanic and White children with acute lymphoblastic leukemia in California. Cancer Epidemiol.Biomarkers Prev. 2006;15:578-81.

Formatted: French (France)

15. Harrison CJ, Haas O, Harbott J, Biondi A, Stanulla M, Trka J, Izraeli S. Detection of prognostically relevant genetic abnormalities in childhood B-cell precursor acute lymphoblastic leukaemia: recommendations from the Biology and Diagnosis Committee of the International Berlin-Frankfurt-Munster study group. Br.J.Haematol. 2010;151:132-42.

16. Mattioli S, Farioli A, Legittimo P, Miligi L, Benvenuti A, Ranucci A, Salvan A, Rondelli R, Magnani C. Tobacco Smoke and Risk of Childhood Acute Non-Lymphocytic Leukemia: Findings from the SETIL Study. PLoS.One. 2014;9:e111028.

17. Farioli A, Legittimo P, Mattioli S, Miligi L, Benvenuti A, Ranucci A, Salvan A, Rondelli R, Conter V, Magnani C. Tobacco smoke and risk of childhood acute lymphoblastic leukemia: findings from the SETIL case-control study. Cancer Causes Control 2014;25:683-92.

18. Orsini N, Bellocco R, M. B, Wolk A, Greenland S. A tool for deterministic and probabilistic sensitivity analysis of epdemiological studies. The Stata Journal 2008;8:29-48.

19. International Agency for Research on Cancer. Occupational exposures in insecticide application, and some pesticides. IARC Monographs in the evaluation of carcinogenic risks in humans vol.53, vol. 53: International Agency for Research on Cancer, 1991.

20. Ostrea EM, Bielawski DM, Posecion NC, Corrion M, Villanueva-Uy E, Bernardo RC, Jin Y, Janisse JJ, Ager JW. Combined analysis of prenatal (maternal hair and blood) and neonatal (infant hair, cord blood and meconium) matrices to detect fetal exposure to environmental pesticides. Environmental Research 2009;109:116-22.

21. Moya J, Bearer CF, Etzel RA. Children's behavior and physiology and how it affects exposure to environmental contaminants. Pediatrics 2004;113:996-1006.

22. Schuz J, Spector LG, Ross JA. Bias in studies of parental self-reported occupational exposure and childhood cancer. American Journal of Epidemiology 2003;158:710-16.

23. Slusky DA, Metayer C, Aldrich MC, Ward MH, Lea CS, Selvin S, Buffler PA. Reliability of maternal-reports regarding the use of household pesticides: Experience from a case-control study of childhood leukemia. Cancer Epidemiol 2012;36:375-80.

24. Metayer C, Colt JS, Buffler PA, Reed HD, Selvin S, Crouse V, Ward MH. Exposure to herbicides in house dust and risk of childhood acute lymphoblastic leukemia. J Expo.Sci.Environ Epidemiol 2013;23:363-70.

Supplementary Table 6: Deterministic sensitivity analyses for paternal smoking as an uncontrolled confounder in the investigations of the association between home pesticide exposure and childhood leukemia

		ALL			AML		
Estimates of prevalence of paternal smoking[1]		Estimate of Relative risk relating paternal smoking to childhood leukemia[2]	OR (95% CI)	% Bias	Estimate of Relative risk relating paternal smoking to childhood leukemia[2]	OR (95% CI)	% Bias
Pesticide							
Exposed	Non-exposed						
Before pregnancy							
			Adjusted[3] 1.38 (1.25, 1.55)			Adjusted[4] 1.49, (1.02, 2.16)	
			Crude 1.35 (1.22, 1.49)			Crude 1.34 (0.98, 1.84)	
			External adjusted[5,6]			External adjusted[5,6]	
0.65	0.55	1.1	1.34 (1.21, 1.48)	1	1.5	1.29 (0.94, 1.77)	4
0.70	0.50	1.1	1.33 (1.20, 1.47)	2	1.5	1.24 (0.91, 1.70)	8
0.75	0.45	1.1	1.31 (1.19, 1.45)	3	1.5	1.20, (0.88, 1.64)	12
0.65	0.55	1.15	1.33 (1.20,1.47)	1	2	1.26 (0.92, 1.72)	6
0.70	0.50	1.15	1.32(1.20, 1.46)	3	2	1.19 (0.87, 1.63)	13
0.75	0.45	1.15	1.30 (1.18, 1.44)	4	2	1.11 (0.81, 1.52)	21
0.65	0.55	1.2	1.33 (1.20, 1.47)	2	2.5	1.24 (0.91, 1.70)	8
0.70	0.50	1.2	1.30 (1.18. 1.44)	4	2.5	1.15 (0.84, 1.57)	17
0.75	0.45	1.2	1.28 (1.16, 1.41)	6	2.5	1.06 (0.77, 1.45)	27
During pregnancy							
			Adjusted[1] 1.43 (1.32, 1.54)			Adjusted[2] 1.55 (1.21, 1.99)	
			Crude 1.50 (1.40, 1.62)			Crude 1.48 (1.18, 1.84)	
			External adjusted[5,6]			External adjusted[5,6]	
0.65	0.55	1.1	1.49 (1.38, 1.60)	1	1.5	1.40 (1.13, 1.74)	6
0.70	0.50	1.1	1.47 (1.37, 1.58)	2	1.5	1.32 (1.06, 1.64)	11
0.75	0.45	1.1	1.46 (1.36, 1.57)	3	1.5	1.25 (1.01, 1.54)	18
0.65	0.55	1.15	1.48 (1.38, 1.59)	1	2	1.36 (1.10, 1.69)	8
0.70	0.50	1.15	1.46 (1.36, 1.57)	3	2	1.30 (1.05, 1.61)	13
0.75	0.45	1.15	1.44 (1.34, 1.55)	4	2	1.22 (0.99, 1.51)	21
0.65	0.55	1.2	1.47 (1.37, 1.58)	2	2.5	1.39 (1.15, 1.72)	6

		ALL			AML		
Estimates of prevalence of paternal smoking[1]		Estimate of Relative risk relating paternal smoking to childhood leukemia[2]	OR (95% CI)	% Bias	Estimate of Relative risk relating paternal smoking to childhood leukemia[2]	OR (95% CI)	% Bias
0.70	0.50	1.2	1.45 (1.35, 1.56)	4	2.5	1.26 (1.02, 1.56)	17
0.75	0.45	1.2	1.42 (1.32, 1.53)	6	2.5	1.16 (0.94, 1.43)	27
After birth							
			Adjusted[3] 1.36 (1.23, 1.51)			Adjusted[4] 1.08 (0.76, 1.53)	
			Crude 1.36 (1.24, 1.50)			Crude 1.05 (0.77, 1.44)	
			External adjusted[5,6]			External adjusted[5,6]	
0.65	0.55	1.1	1.35 (1.22, 1.49)	1	1.5	1.00 (0.81, 1.24))	6
0.70	0.50	1.1	1.34 (1.22, 1.48)	2	1.5	0.94 (0.76, 1.17)	11
0.75	0.45	1.1	1.33 (1.21, 1.47)	3	1.5	0.89 (0.72, 1.10)	18
0.65	0.55	1.15	1.34 (1.22, 1.48)	1	2	0.99 (0.80, 1.23)	6
0.70	0.50	1.15	1.33 (1.21, 1.47)	3	2	0.93 (0.75, 1.15)	13
0.75	0.45	1.15	1.31 (1.19, 1.44)	4	2	0.87 (0.93, 1.15)	21
0.65	0.55	1.2	1.34 (1.22, 1.48)	2	2.5	0.97 (0.78, 1.20)	8
0.70	0.50	1.2	1.32 (1.20, 1.45)	4	2.5	0.90 (0.73, 1.12)	17
0.75	0.45	1.2	1.29 (1.17, 1.42)	6	2.5	0.83 (0.67, 1.02)	27

[1] Based on paternal smoking data in a sample of CLIC studies

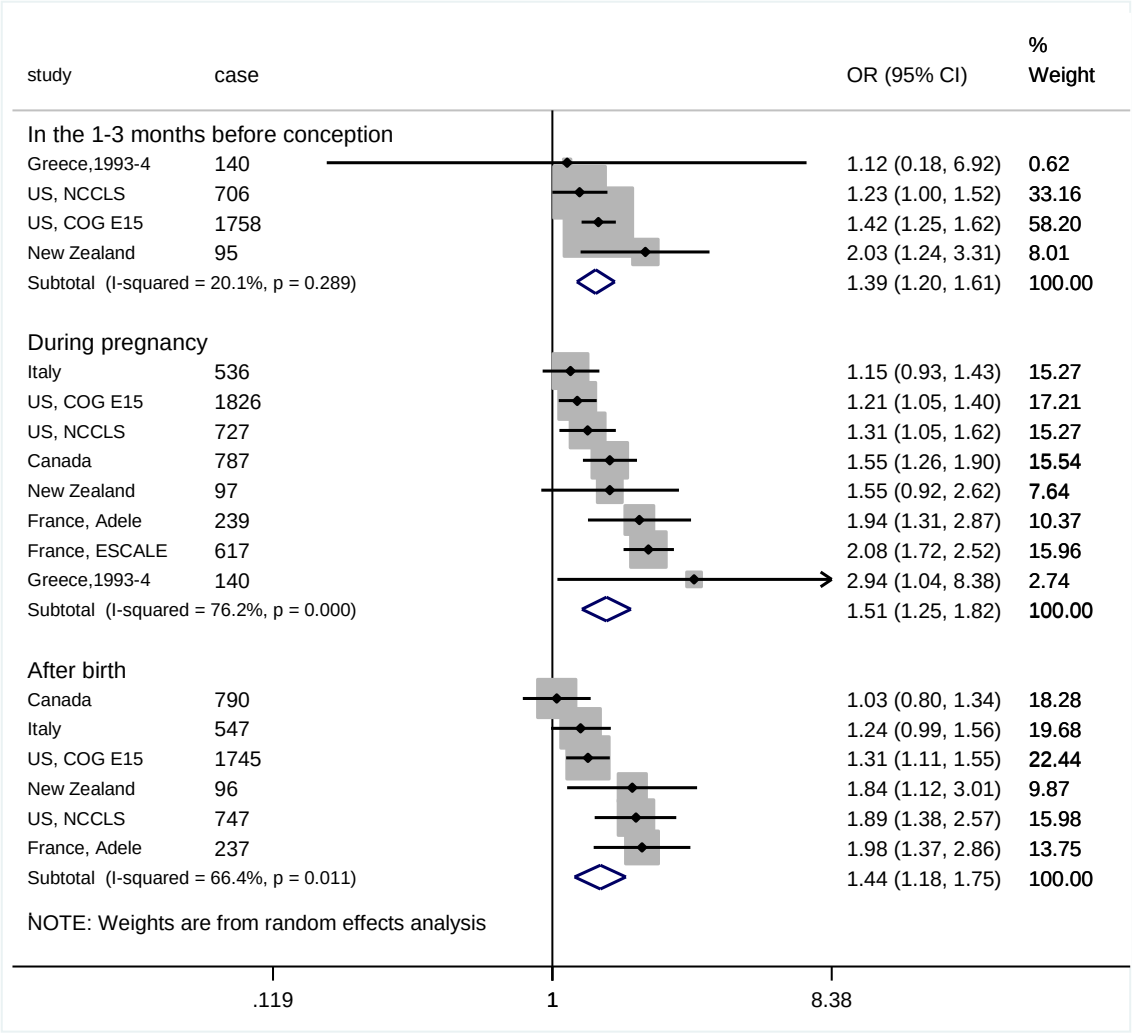
[2] Based on published estimates

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

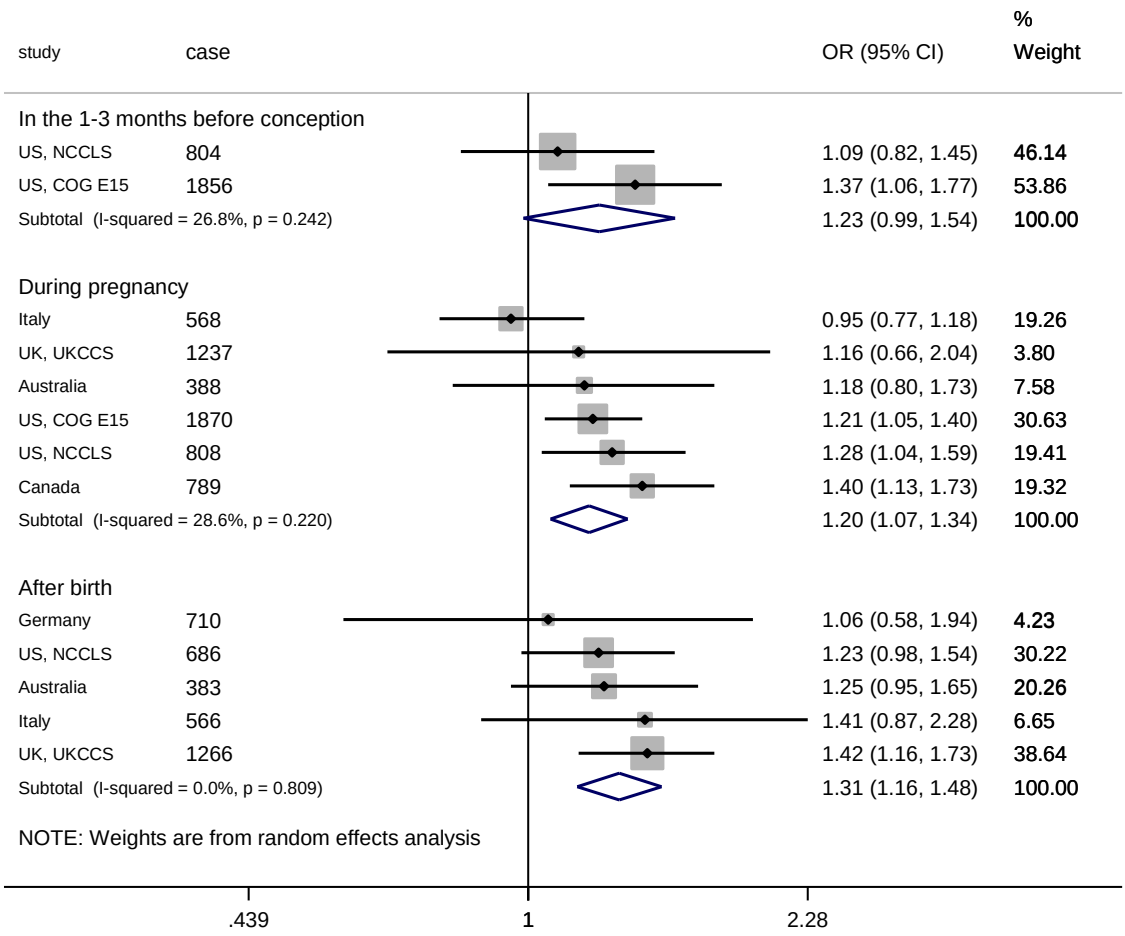
[4] Adjusted for age, sex, birth year group, study, ethnicity, birth order and highest level of education of either parent.

[5] OR Calculated using the Episensi procedure in Stata command (Orsini N, Bellocco R, Bottai M, et al 2008)

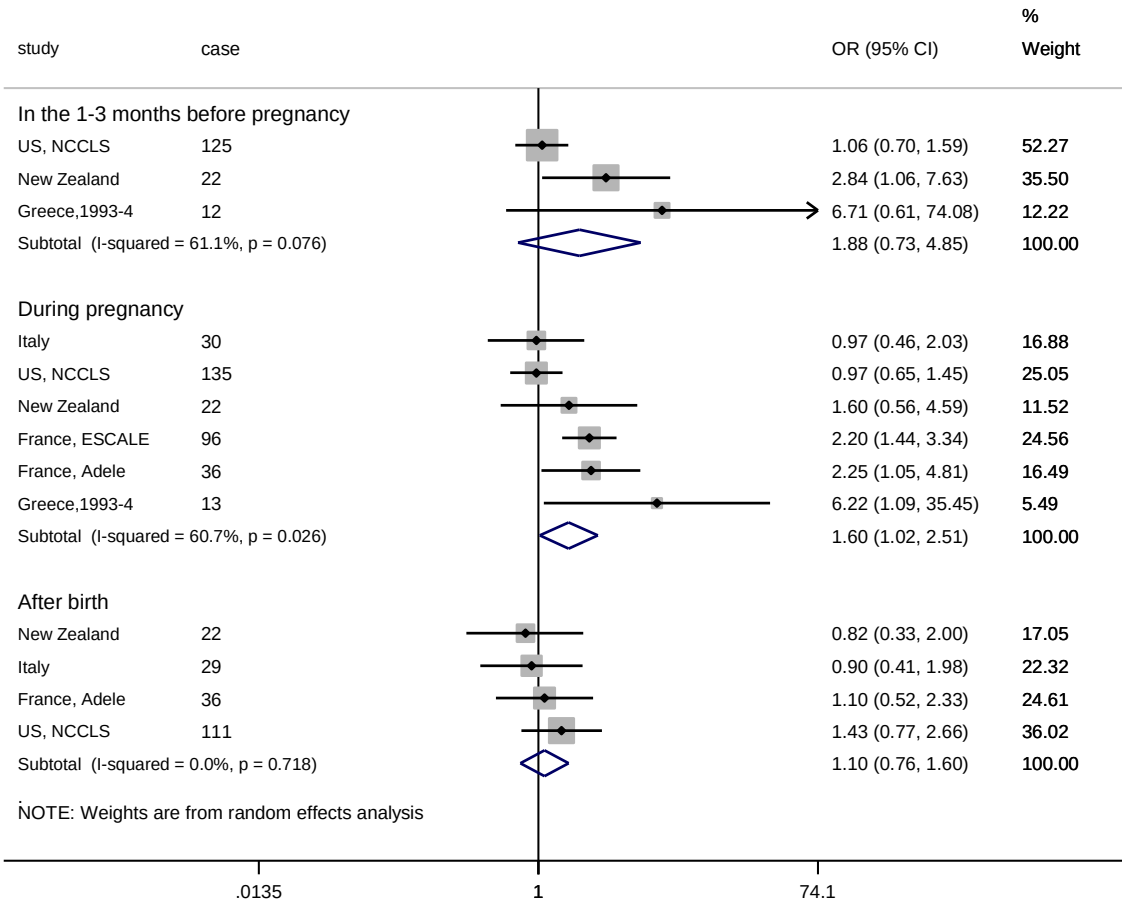
[6] 95% CI calculated using the following formula: 1.96* Standard error of crude ln(OR).



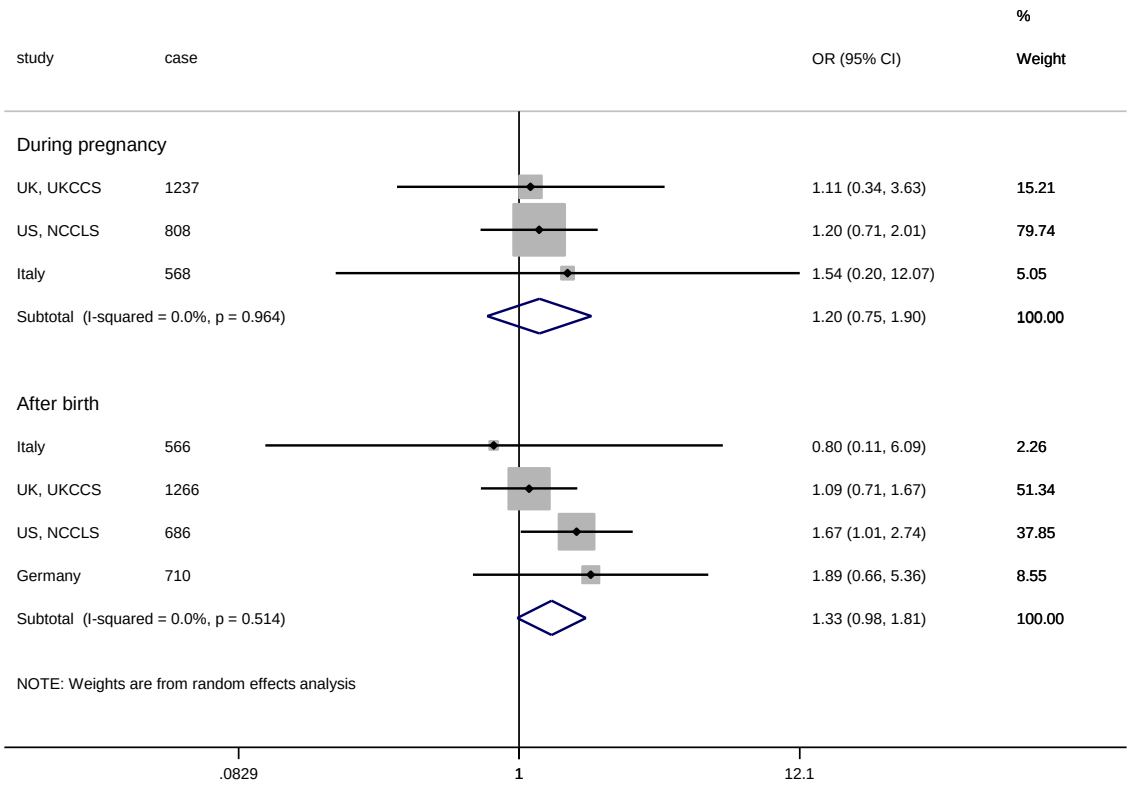
Supplementary Figure 1: Forest plot showing individual and summary odds ratios for home pesticide exposures and the risk of childhood ALL, using random effects models.



Supplementary Figure 2: Forest plot showing individual and summary odds ratios for home professional pest control treatments and the risk of childhood ALL, using random effects models.



Supplementary Figure 3: Forest plot showing individual and summary odds ratios for home pesticide exposures and the risk of childhood AML, using random effects models.



Supplementary Figure 4: Forest plot showing individual and summary odds ratios for home professional pest control treatments and the risk of childhood AML, using random effects models.