International Journal of Hygiene and Environmental Health 222 (2019) 49–67

Contents lists available at ScienceDirect

International Journal of Hygiene and Environmental Health

journal homepage: www.elsevier.com/locate/ijheh

Household exposure to pesticides and risk of leukemia in children and adolescents: Updated systematic review and meta-analysis

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ARTICLE INFO

Keywords:
Child
Leukemia
Household
Pesticides
Systematic review
Meta-analysis

ABSTRACT

Background: The role that pesticides in the domestic environment might play in the etiology of childhood leukemia remains a subject of controversy. Recent studies often reached inconsistent conclusions.
Objective: To update our earlier systematic review on the association between residential/household/domestic exposure to pesticides and childhood leukemia, and to explore potential sources of heterogeneity not previously assessed.
Methods: A systematic search of studies published in English between January 2009 and June 2018 was conducted in MEDLINE, and a "snowball searching" was performed from the reference list of identified publications and from Web of Science citations. Risk estimates were extracted from 15 case-control studies published between 1987 and 2018. The quality of the publications was assessed by using a modified version of the Downs and Black (1998) checklist. A random-effect meta-analysis model was used to calculate summary odds ratios (SOR) and separate analyses were conducted for acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), unspecified AL/leukemia and any leukemia types. Stratification by critical exposure period, exposure location, pesticide biocide category, child age at diagnosis, study quality, specific exposures, type of pest treated, and geographic location were performed.
Results: A statistically significant association between residential pesticide exposure and childhood leukemia was observed by combining all studies (SOR: 1.57; 95% CI: 1.27–1.95) without evidence of publication bias. Statistically significant increased risks were observed for all types of leukemia, and specifically for exposure during pregnancy, indoor exposure, prenatal exposure to insecticides and whatever the age at diagnosis. Statistical significance was also reached for high quality studies, pet treatments, professional pest control treatment and use of insect repellants, mosquito treatment and for studies from USA/Canada or International. The highest increased risks were observed for AML among children aged 2 years or less, as well as for unspecified leukemia type observed after prenatal indoor exposure.
Conclusions: A positive association between domestic pesticide exposure and childhood leukemia is confirmed. Although the literature provides moderate to low-quality of evidence, these new results further justify the need of limiting the use of household pesticides during pregnancy and childhood.

1. Introduction

Leukemia is the most common pediatric cancer, accounting for approximately one third of cancers diagnosed in children under 15 years of age in high income countries. Pediatric leukemia is a phenotypically- and genetically-heterogeneous disease of immature hematopoietic stem and progenitor cells (reviewed in Hernández and Menéndez, 2016 and Wiemels, 2012). Acute leukemia (AL) accounts for more than 95% of all childhood leukemias, including acute lymphoid/lymphoblastic leukemias (ALL), by far the most frequent type (> 75%), and acute myeloblastic leukemias (AML) (16%) (Hunger and Mullighan, 2015; Puumala et al., 2013). The age-specific patterns for lymphoid and myeloid leukemias differ from each other but are generally consistent across worldwide populations. Lymphoid leukemia rates are the highest in the youngest age group (0–4 years) and myeloid leukemia age-specific rates appear generally V-shaped, with the highest rates in the youngest (0–4) and oldest (15–19) age groups and the lowest rates at ages 5–9 (Linet et al., 2016). Even if improved treatments allow to increase survival up to 80–90%, survivors face long-term side effects including the risk of secondary cancer (Oeffinger et al., 2006).

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https://doi.org/10.1016/j.ijheh.2018.08.004
Received 3 May 2018; Received in revised form 16 July 2018; Accepted 6 August 2018

Abbreviations

AL	acute leukemia
ALL	acute lymphoblastic leukemia
AML	acute myeloid leukemia
ANLL	acute non-lymphoblastic leukemia
95% CI	95% confidence interval
CLIC	Childhood Leukemia International Consortium
ICCC	international classification of children cancer
ICD	international classification of diseases
MA	meta-analysis
OP	organophosphate
OR	odds ratio
PYR	pyrethroids
SE	standard error
SOR	summary-odd ratio estimate
95% UI	95% uncertainty interval

Childhood leukemia arises from two or more genetic insults in stem-like cells that block differentiation and drives uncontrolled proliferation and survival of the differentiation-blocked clone (Hernández and Menéndez, 2016; Inaba et al., 2013; Wiemels, 2012). A currently well accepted hypothesis is that leukemia results from precursor mutations initially occurring *in utero* as well as from mutations acquired after exposures to leukemogenic agents during infancy. The etiology of childhood leukemia is consequently multifactorial and probably arises from interactions between exogenous and endogenous exposures and genetic (inherited) susceptibility factors. Despite the growing body of literature implicating several environmental, infectious, and dietary risk factors, the exact etiological factors of childhood leukemia remain largely unknown but probably involve both constitutional and environmental factors (Inaba et al., 2013; Pui et al., 2008). During the last decade potentially new risk factors including birth weight (Milne et al., 2013; O'Neill et al., 2015; Jiménez-Hernández et al., 2018), gene polymorphisms and genetic susceptibility (Ross et al., 2013; Gutierrez-Camino et al., 2017; Wiemels et al., 2018) have emerged. Risk factors with conclusive evidence for ALL include congenital genetic disorders such as Down syndrome, neurofibromatosis, Fanconi anemia and Bloom syndrome. Ionizing radiation (from sources such as diagnostic imaging or atomic bomb) is the only confirmed and generally accepted environmental risk factor, but it explains only a small fraction of childhood leukemia cases (Little, 2008). Suspected environmental factors include prenatal and/or childhood exposure to tobacco and alcohol, household chemicals (such as paint exposure), traffic gases and fumes, benzene, solvents, and pesticides (reviewed in Schüz and Erdmann, 2016). Exposure to pesticides is one of the most frequently scrutinized risk factor for childhood leukemia, and there is a growing concern that chronic low-level pesticide exposure during pregnancy or childhood might increase the risk of childhood leukemia. Due to the relative rarity of childhood leukemia (about 4/100.000 per year) and low levels of many environmental exposures, most previously published epidemiological studies on pesticide exposure and childhood leukemia used a case-control design, rarely reaching sufficient statistical power to detect an effect, particularly for subtypes of leukemias. To overcome this problem, meta- and pooled analyses were performed (Bailey et al., 2015; Chen et al., 2015; Turner et al., 2010; Van Maele-Fabry et al., 2011; Vinson et al., 2011). Of these, the two most recent meta-analyses focused on childhood exposure only (Chen et al., 2015) and a pooled analysis included 12 case-control studies in the Childhood Leukemia International Consortium [CLIC] (Bailey et al., 2015).

The purpose of the present study is to update our systematic review (Van Maele-Fabry et al., 2011) and to meta-analyze the available epidemiological data on the relationship between residential/household/domestic pesticide exposure and childhood leukemia. The aim is to improve our knowledge on the potential involvement of residential exposure to pesticides in the etiology of childhood leukemia (ALL, AML, unspecified AL/leukemia type) by exploring potential sources of heterogeneity in results: exposure time windows, exposure location, specific exposures, specific pesticide/biocide category type of pest treated, child age at diagnosis as well as study quality, specific exposures, type of pest treated, and geographic location.

2. Materials and methods

This study is an updated systematic review and meta-analysis conducted according to the available guidelines, including PRISMA (Liberati et al., 2009) and PRISMA-P (Moher et al., 2015) statements for reporting systematic review and MA, and taking into account the modification and extension of these items for child-centric systematic reviews proposed by Farid-Kapadia et al. (2017).

2.1. Study identification and selection

2.1.1. Study identification

The update combines data from two previous comprehensive meta-analyses (Turner et al., 2010; Van Maele-Fabry et al., 2011) with data from the subsequent literature. We proceeded in three steps: (i) checking studies included in the previous MA, (ii) searching for subsequent studies and (iii) identifying redundancies among full text articles in (i) and (ii). In the first step, studies included in the two previous MA were checked and duplicates were removed. In the second step, we searched all English-language observational studies on childhood leukemia and residential pesticide exposure published in peer-reviewed journals. As the previous comprehensive meta-analyses included studies up to 2010, we conducted an electronic search on MEDLINE (National Library of Medicine, Bethesda, MD) starting one year before. The search was thus performed for the period 2009 (first January) to end of June 2018 (30th June) using the keywords "(pesticides OR herbicides OR insecticides OR fungicides) AND ((children OR childhood) AND leukemia) AND (residential OR domestic OR household)". This was supplemented by various combinations of the following terms: pesticides, biocides, herbicides, insecticides, fungicides, pest control, environmental exposure, environmental pollutants, child, children, childhood, infant, infantile, newborn, preschool child, adolescent, cancer, neoplasm, leukemia, myeloid, myeloblastic, myelogenous, lymphoid, lymphoblastic, lymphocytic, chronic, acute, granulocytic, hematologic, residential, household, domestic, indoor, outdoor, review, meta-analysis. We also performed "snowball searching," which included hand-searching the reference list of the relevant publications and review papers, and using Web of Science for detecting articles that cited included studies. In the third step, possible redundancies were identified among full-text articles assessed for eligibility from steps (i) and (ii), and redundant studies were excluded.

2.1.2. Study selection

Eligible studies were those with a cohort or case-control design, referring to children or adolescents up to 18 years exposed to pesticides from residential use (indoor or outdoor), with (subtypes of) leukemia as the outcome. Studies not published in English, published in the grey literature, studies not reporting original results (reviews, MA, case-reports, comments, letters, editorials, and abstracts), focusing only on genetic data, clearly examining a specific cancer type other than

leukemia, as well as those dealing with non residential exposure, e.g. exposure resulting from agricultural drift or those reporting data for farm-related exposures, were excluded. Were also excluded from the MA: redundant studies (with subjects already included in another more complete or more recent study examining a greater number of subjects or with longer follow-up duration), studies combining adults and children with no separate reporting of children data, studies focusing on a specific pediatric population (e.g. children with Down syndrome), and studies providing insufficient data to determine an estimator of relative risk and its confidence interval for childhood leukemia.

2.2. Data extraction

A structured abstract was derived from each eligible study identified. Abstracted information was: the first author last name, publication year, geographic location, study name, period of diagnosis (years of case accruals), child age at diagnosis (upper age limit), exposure category and source of exposure data, exposed persons, period of exposure (exposure window), leukemia type and source of leukemia definition, number of exposed cases and controls, risk estimates and the corresponding 95% confidence intervals as well as variables adjusted for in the analysis. Two authors (GVM-F and LG-P) read the reports and independently extracted and tabulated the most relevant risk estimators with their 95% CI. The results were compared between both authors and consensus was obtained before the MA.

2.3. Quality rating and assessment of the evidence

2.3.1. Assessing the study's quality for each individual study included

Two authors (GVM-F and LG-P) assessed the quality of all included studies by using a modified version of the Downs and Black (1998) checklist including 15 questions to evaluate external as well as internal validity (bias, exposure, confounding) items, as described in Van Maele-Fabry et al. (2017). The modified checklist is reported in the Supplemental Material-Table 1. Before conducting the quality assessment, both authors discussed the individual items of the checklist to clarify their interpretation, and differences in quality assessment were resolved by consensus. Quality scores were attributed for each item and risk of bias was considered as high, moderate or low according to the score assigned to the item (Supplemental Material-Table 2).

2.3.2. Representative summary of risk of bias across studies

The summary of the risk of bias for each item of the checklist across all studies included is displayed as a bar chart (Supplemental Material-Table 3).

2.4. Statistical analysis

Data of individual case-control studies were combined using the random effect model of Der Simonian and Laird (1986) to obtain a summary risk estimate. As data are from studies gathered from the published literature (performed by researchers operating independently) and as the goal of our MA is to extrapolate to other populations, the random effect model is more justified than the fixed model (Borenstein et al., 2009). An overall MA including data from all case-control studies was performed and is illustrated by a forest plot. Separate analyses conducted on studies reporting data for ALL and AML are shown in two others forest plots.

The between-study heterogeneity was assessed using chi-square-based Q-test and the I^2 statistic. A low P value from the chi-squared test indicates statistically significant heterogeneity, and the I^2 statistic value indicates increasing heterogeneity from 0 (no observed heterogeneity) to 100% (Deeks et al., 2011; Higgins et al., 2003).

Potential sources of heterogeneity were evaluated by subset analyses. The analyses were performed primarily for ALL, AML and unspecified leukemia types and included stratification defined by exposure windows (before pregnancy, during pregnancy, childhood), exposure location (indoor, outdoor), biocide category (insecticides, herbicides) and age at diagnosis ($\leq$2 years, $\leq$ 5 years, $\leq$ 15 years, $\leq$ 18 years). Others stratifications, regardless of the leukemia types, were also carried out and included study quality (high quality, low quality), specific exposure (professional pest exterminator, pet treatments, insect repellant), type of pest treated (mosquito, moth, cockroach) and geographic location (USA/Canada, Europe, others).

The potential for publication bias was explored by the funnel plot graphical method and the linear regression asymmetry test suggested by Egger and collaborators (1997). An asymmetric plot suggests a possible publication bias, and a P value for Egger test less than 0.05 was considered to be representative of statistically significant publication bias. The statistical analyses were performed using Excel software and the forest plot using "R".

To determine the robustness of the findings as well as to evaluate impact of individual studies on the summary risk estimator (SOR), sensitivity analyses were conducted by:

- using both fixed and random effect methods to combine risk estimators of all studies,
- removing studies with partial redundancy (Ding et al., 2012; Zhang et al., 2015)
- excluding studies reporting extreme risk estimator values (Lowengart et al., 1987 and Maryam et al., 2015)
- omitting the especially large study of Bailey et al. (2015) with the highest weight (80%),
- excluding the studies published before 2009 already included in our previous MA (Van Maele-Fabry et al., 2011)
- excluding the studies published before 2009 as well as the study of Bailey et al. (2015).
- re-running the MA while dropping one study out at a time to assess the impact of each study on the combined effect.

A cumulative analysis was also performed by adding studies one at a time according to increasing study quality score.

3. Results

3.1. Study selection and characteristics

A total of 15 studies were identified for inclusion in the MA after the selection process as reported in the flow-diagram of Fig. 1.

In the first step of the selection procedure (checking studies included in the previous comprehensive MA), a total of 30 records were identified (17 in the MA of Turner et al., 2010 and 13 in the MA of Van Maele-Fabry et al., 2011). Ten duplicates were removed as well as seven records from the MA of Turner as they did not respect our inclusion criteria (they were not published in English, were PhD dissertations, included insufficient data and focused on children with Down Syndrome), leaving a total of 13 studies to be assessed for eligibility.

The second step of the study selection procedure (searching for recent studies) identified more than 160 records. After removing duplicates, 54 records were screened and, among them, 39 were excluded as they did not fulfill the including criteria. No cohort study was retrieved but 15 case-control studies evaluating the relationship between residential exposure to pesticides and childhood leukemia between 2009 and 2018 were to be assessed for eligibility. One of them (Bailey et al., 2015) is a pooled analysis including data from 12 case-control studies.

In the third step (identifying redundancies among full text articles to be assessed for eligibility), checking for redundancy of studies issued from step (i) resulted in the exclusion of 7 case-control studies (Infante-Rivard et al., 1999; Ma et al., 2002; Meinert et al., 1996, 2000; Menegaux et al., 2006; Rudant et al., 2007; Urayama et al., 2007) as they were included in the pooled analysis of Bailey et al. (2015). Two additional studies were excluded: the study of Pombo-de-Oliveira and

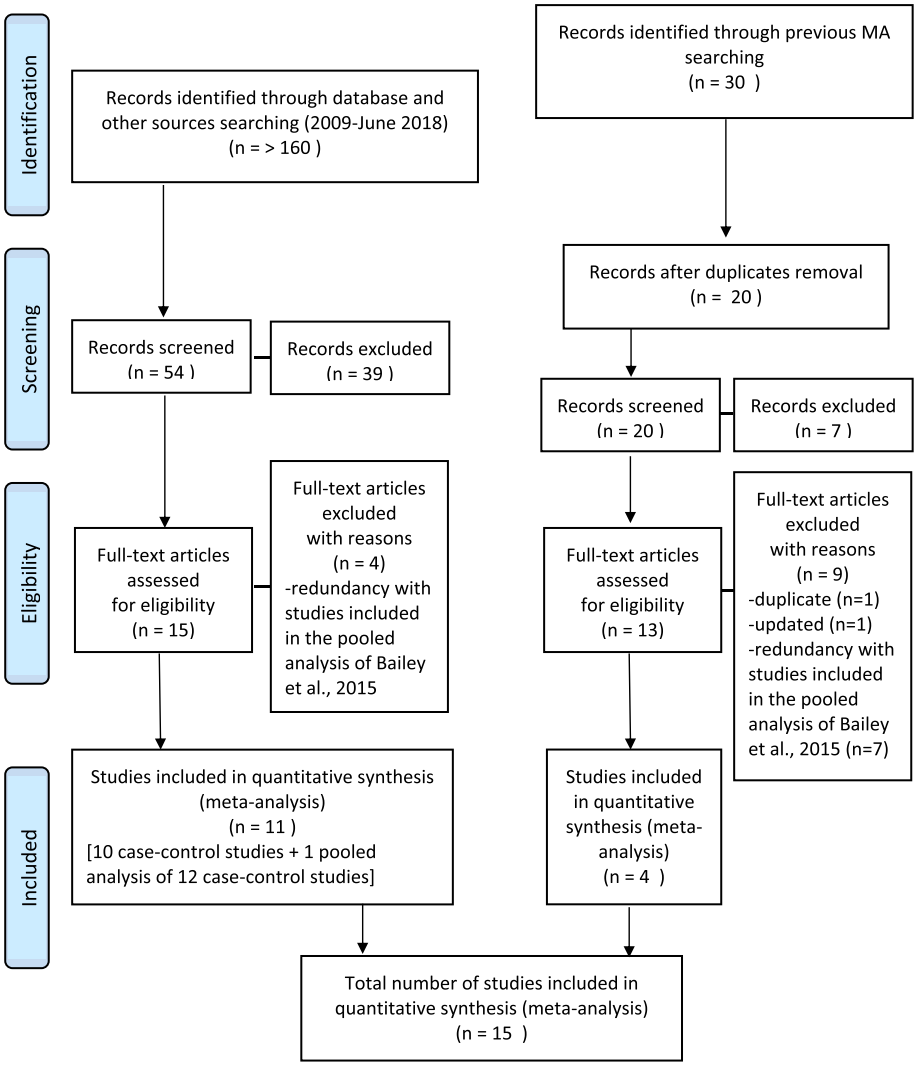

Fig. 1. Prisma Flow diagram (Liberati et al., 2009) summarizing the search strategy for meta-analysis of residential pesticide exposure and childhood leukaemia.

Koifman (2006) as it was updated by Ferreira et al. (2013) and the study of Spix et al. (2009) as it was a duplicate, also identified in step (ii). As a consequence, four studies (Alexander et al., 2001; Buckley et al., 1989; Leiss and Savitz, 1995; Lowengart et al., 1987) originating from the previous MA were included in the present updated MA.

Checking for redundancy among full text articles resulting from step (ii) resulted in the exclusion of four of them (Bailey et al., 2011; Chokkalingam et al., 2012; Metayer et al., 2013; Rudant et al., 2015) as they were included in the pooled analysis of Bailey et al. (2015). Eleven new studies (Bailey et al., 2015; Castro-Jiménez and Orozco-Vargas, 2011; Ding et al., 2012; Ferreira et al., 2013; Ferri et al., 2018; Hyland et al., 2018; Maryam et al., 2015; Slater et al., 2011; Soldin et al., 2009; Spix et al., 2009; Zhang et al., 2015) were thus included in the present updated MA.

As a consequence, a total of 15 case-control studies (4 from previous MA searching and 11 from recent searching) were selected and included in the present updated MA. Characteristics of these studies are summarized in Table 1. Included studies were published between 1987 and 2018. Five were from North America, 3 from South/Central America, 3 from Asia, 2 from Europe and 2 included international data (from different parts of the world). Eight studies reported data for the lymphoblastic subtype of acute leukemia, 5 for the myeloid/non-lymphoblastic subtype and 6 studies related to unspecified AL/leukemia type. The number of variables adjusted/matched for were very different from one study to another (Table 1).

3.2. Quality rating and assessment of the evidence

The individual study quality/risk of bias scores and the summary of the risk of bias for each item across all included studies are presented in Supplemental Table 2 and Supplemental Table 3, respectively. Total scores ranged from 9 to 15 with a median value of 12.5 (maximum score of 20). No tendency towards higher quality scores was observed in most recent studies. Exposure measurement had the worst scores, six studies out of the 15 showing score values lower than half of the maximum score (8) for this item (Supplemental Table 2) and one single study was considered with a low risk of bias (Supplemental Table 3). The summary of the risk of bias judgement revealed also that there were only 4 studies (27%) out of the 15 included in the MA with a low risk of bias for the criteria “external validity” and “bias”.

3.3. Synthesis of results

When the relevant data of all studies (n = 15) were combined, a statistically significant increased risk of childhood leukemia was observed (SOR: 1.57, 95% CI: 1.27–1.95). A forest plot of these studies is presented in Fig. 2(a). One study, being a pooled analysis of individual data from 12 case-control studies, contributed more than 80% of the total weight (Bailey et al., 2015). The overall MA showed strong evidence of heterogeneity ($p = 0.242 \times 10^{-5}$) and inconsistency ($I^2 = 73\%$), arguing against an overall MA of the results. Subset

Table 1
Study summary from relevant publications dealing with residential exposure to pesticides and childhood leukemia.

Reference; Location; [Study name]; Years of case accruals; (Upper age limit)	Source of exposure data Exposure category	Exposed person	Exposure windows	[Leukemia type] (source of case definition) Number of cases/controls	Risk estimator OR (95% CI)	Adjusted (matched) for
Alexander et al., 2001; International (Europe, Middle East, Asia, South America); Population-based pilot case-control study; (< 18 months)	Questionnaire: mothers' interviews			**[AL]**		Matched for gender and dates of birth; Adjusted for sex, region of residence, country
	- Pesticides	Mother	During pregnancy	- 15/10	3.67 (1.54–8.74)	
	- Insectides (mosquitocides)			- 7/3	5.14 (1.27–20.85)	
				[ALL]		
	- Pesticides			- NR	2.53 (0.71–8.97)	
	- Insectides (mosquitocides)			- NR	4.30 (0.66–28.08)	
				[AML]		
	- Pesticides			- NR	5.08 (1.84–14.04)	
	- Insectides (mosquitocides) (exposed *vs* unexposed)			- NR (case ascertainment based on referrals to treating hospitals)	7.82 (1.73–35.39)	
Bailey et al., 2015; International (North America, Europe, Australasia); Pooling of 12 studies in the Childhood Leukemia International Consortium Hospital and population based case control studies; (0-14 years)	Questionnaires: mothers', parents' and guardians' mailed, phone and face-to-face interviews.			**[ALL]**		Adjusted for age, sex, birth year group, study, ethnicity and highest level of education of either parent
	Any pesticide exposure	Parents	1-3 months before conception	- 2785/3635	1.39 (1.25-1.55)	
		Mother	During pregnancy	- 5055/7370	1.43 (1.32-1.54)	
		Child	After birth	- 4162/5179	1.36 (1.23-1.51)	
	Professional pest control treatments	Parents	1-3 months before conception	- 2660/3120	1.24 (1.03-1.50)	
		Mother	During pregnancy	- 5660/8938	1.19 (1.04-1.36)	
		Child	After birth	- 3611/8388	1.28 (1.14-1.45)	
	Household insecticide/ miticide	Parents	1-3 months before conception	- 2529/3027	1.34 (1.19-1.51)	
		Mother	During pregnancy	- 4792/6732	1.28 (1.18-1.38)	
		Child	After birth	- 4032/4832	1.23 (1.12-1.34)	
	Pesticide used on pets	Parents	1-3 months before conception	- 2586/3055	1.17 (1.02-1.34)	
		Mother	During pregnancy	- 3841/5763	1.15 (1.03-1.29)	
		Child	After birth	- 3050/3768	1.15 (1.03-1.29)	
	Insecticide or fungicide used on plants or trees	Parents	1-3 months before conception	- 2699/3166	1.49 (1.14-1.95)	
		Mother	During pregnancy	- 4938/6879	1.26 (1.11-1.44)	
		Child	After birth	- 4006/4786	1.41 (1.26-1.59)	
	Herbicide	Parents	1-3 months before conception	- 2659/3135	1.23 (1.04-1.45)	
		Mother	During pregnancy	- 4938/6879	1.34 (1.19-1.50)	
		Child	After birth	- 4066/4878	1.34 (1.21-1.48)	
	Rodenticide	Parents	1-3 months before conception	- 2686/3150	1.39 (1.10-1.76)	
		Mother	During pregnancy	- 3492/3963	1.42 (1.17-1.73)	
		Child	After birth	- 3251/3547	1.32 (1.12-1.56)	
	Molluscicide	Parents	1-3 months before conception	- 2715/3178	1.06 (0.79-1.43)	
		Mother	During pregnancy	- 3511/3968	1.01 (0.79-1.28)	
		Child	After birth	- 3256/3567	1.06 (0.87-1.30)	
	Personal insect repellant	Parents	1-3 months before conception	- ND	ND	
		Mother	During pregnancy	- 1603/1980	1.42 (1.15-1.77)	
		Child	After birth	- 1431/1739	1.02 (0.86-1.20)	
				[AML]		
	Any pesticide exposure	Parents	1-3 months before conception	- 173/1789	1.49 (1.02-2.16)	
		Mother	During pregnancy	- 345/4666	1.55 (1.21-1.99)	
		Child	After birth	- 198/2655	1.08 (0.76-1.53)	
	Professional pest control treatments	Parents	1-3 months before conception	- ND	ND	
		Mother	During pregnancy	- 388/5322	1.26 (0.79-2.00)	
		Child	After birth	- 468/7531	1.26 (0.94-1.69)	

(*continued on next page*)

Table 1 (*continued*)

Reference; Location; [Study name]; Years of case accruals; (Upper age limit)	Source of exposure data Exposure category	Exposed person	Exposure windows	[Leukemia type] (source of case definition) Number of cases/controls	Risk estimator OR (95% CI)	Adjusted (matched) for
	Household insecticide/ miticide	Parents	1-3 months before conception	- ND	ND	
		Mother	During pregnancy	- 294/4022	1.55 (1.21-2.00)	
		Child	After birth	- 167/2318	1.31 (0.93-1.84)	
	Pesticide used on pets	Parents	1-3 months before conception	- ND	ND	
		Mother	During pregnancy	- 266/3802	1.51 (1.07-2.12)	
		Child	After birth	- 126/1994	1.25 (0.79-1.96)	
	Insecticide or fungicide used on plants or trees	Parents	1-3 months before conception	- ND	ND	
		Mother	During pregnancy	- 302/4118	0.94 (0.53-1.69)	
		Child	After birth	- 157/2241	1.16 (0.70-1.92)	
	Herbicide	Parents	1-3 months before conception	- ND	ND	
		Mother	During pregnancy	- 304/4136	0.84 (0.56-1.26)	
		Child	After birth	- 172/2344	0.78 (0.52-1.19)	
				[ALL] + [AML]		
	Any pesticide exposure	Parents	1-3 months before conception	- 2958/5424	1.37 (1.25-1.50)[a]	
		Mother	During pregnancy	- 5400/12036	1.64 (1.53-1.75)[a]	
		Child	After birth	- 4360/7834	1.44 (1.32-1.58)[a]	
	Professional pest control treatments	Parents	1-3 months before conception	- 2660/3120	1.17 (0.97-1.40)[a]	
		Mother	During pregnancy	- 6048/14260	1.56 (1.38-1.75)[a]	
		Child	After birth	- 4079/15919	1.57 (1.42-1.73)[a]	
	Household insecticide/ miticide	Parents	1-3 months before conception	- 2529/3027	1.31 (1.17-1.48)[a]	
		Mother	During pregnancy	- 5086/10754	1.36 (1.27-1.46)[a]	
		Child	After birth	- 4199/7150	1.18 (1.09-1.27)[a]	
	Pesticide used on pets	Parents	1-3 months before conception	- 2586/3055	1.14 (1.00-1.30)[a]	
		Mother	During pregnancy	- 4107/9565	1.44 (1.31-1.58)[a]	
		Child	After birth	- 3176/5762	1.39 (1.26-1.53)[a]	
	Insecticide or fungicide used on plants or trees	Parents	1-3 months before conception	- 2699/3166	1.41 (1.08-1.84)[a]	
		Mother	During pregnancy	- 5240/10997	1.43 (1.27-1.61)[a]	
		Child	After birth	- 4163/7027	1.47 (1.32-1.62)[a]	
	Herbicide	Parents	1-3 months before conception	- 2659/3135	1.05 (0.90-1.23)[a]	
		Mother	During pregnancy	- 5242/11015	1.51 (1.37-1.66)[a]	
		Child	After birth	- 4238/7222	1.31 (1.21-1.43)[a]	
	Rodenticide	Parents	1-3 months before conception	- 2686/3150	1.43 (1.13-1.80)[a]	
		Mother	During pregnancy	- 3492/3963	1.45 (1.20-1.76)[a]	
		Child	After birth	- 3251/3547	1.26 (1.07-1.49)[a]	
	Molluscicide	Parents	1-3 months before conception	- 2715/3178	0.81 (0.60-1.07)[a]	
		Mother	During pregnancy	- 3511/3968	0.83 (0.65-1.05)[a]	
		Child	After birth	- 3256/3567	0.81 (0.67-0.98)[a]	
	Personal insect repellant (exposure *vs* no pesticide exposure)	Parents	1-3 months before conception	- ND	ND	
		Mother	During pregnancy	- 1603/1980	1.44 (1.17-1.78)[a]	
		Child	After birth	- 1431/1739 (cancer registries, networks of hospitals or physicians)	1.09 (0.94-1.28)[a]	
Buckley et al., 1989; (USA, Canada; North America); Population-based case-control study; [Childrens Cancer Study Group study]; 1980–1984; (< 18 years)	Questionnaire: parents' phone interviews.			**[ANLL]**		Matched by date of birth, race, area code and first five digits of telephone number
	- Household exposure to pesticides: (use in the home) (any exposure *vs* none)	Mother	During pregnancy	- 70/55[a]	1.85 (1.16–2.99)[a]	
		Child	At least 1 yr after birth	- 67/45[a] (French-American-British classification; karyotypes reviewed by 2 cancer cytogeneticists)	2.51 (1.53–4.11)[a]	

(*continued on next page*)

Table 1 (*continued*)

Reference; Location; [Study name]; Years of case accruals; (Upper age limit)	Source of exposure data Exposure category	Exposed person	Exposure windows	[Leukemia type] (source of case definition) Number of cases/controls	Risk estimator OR (95% CI)	Adjusted (matched) for
Castro-Jiménez and Orozco-Vargas, 2011; 6 hospitals in Bogota and Bucaramanga (Colombia; South America); 2000-2005 Neighborhood-based case-control study; (< 15 years)	Questionnaire: face-to-face parents' interview			**[ALL]**		Matched by sex and age at diagnosis and living in the same neighborhood
	- exposure to one or more types of pesticides (environmental exposure in 1 or more houses) (exposed *vs* non-exposed)	Mother	Preconception (24 months)	- NR	1.33 (0.56–3.16)	
		Father	Preconception (24 months)	- NR	1.40 (0.44–4.41)	
		Mother	During pregnancy	- NR (Review of institutional registries; histological and clinical verification)	2.80 (1.01–7.77)	
Ding et al., 2012; Shanghai (China; Asia); Hospital-based case-control study (four hospitals [H.]: Shangai Children's H., Xinhua H., Shangai Children Medical Center, Children's H. of Fudan University); 2010–2011; (≤14 years)	Questionnaire: mothers' interviews. Household pesticide use:			**[ALL]**		Age, sex, household income, parent education level, place of residence, breast-feeding duration
	Mosquito repellent	Family	From birth to diagnosis	- 122/104	1.63 (1.04–2.55)	
	Cockroach killer			- 100/93	1.33 (0.86–2.04)	
	Mothproofing agent			- 50/61	0.89 (0.56–1.42)	
	Rodenticide			- 20/29	0.59 (0.31–1.12)	
	Termite control agent			- 10/13	0.93 (0.39–2.24)	
	Herbicides (use *vs* no-use)			- 9/5 (French-American-British classification)	1.98 (0.63–6.25)	
Ferreira et al., 2013; 13 states in all geographic areas in the country but the Amazon, (Brazil; South America); Hospital-based case-control study; [Multi-institutional Study of Infant Leukemia]; 1999–2007; (0–2 years)	Questionnaire: mothers' interviews. Household (use *vs* no-use)			**[ALL]**		Oral contraceptives during pregnancy, maternal age and education, child's birth weight, skin colour
		Mother	From 3 mo before pregnancy to 3 mo after birth	- 62/89	1.88 (1.20–2.95)	
				[AML]		
				- 25/89	3.12 (1.61–6.05)	
				[ALL + AML]		
				- 87/89 (Cases confirmed by morphology, immunophenotype, standard cytogenetic-molecular methods)	–2.24 (1.57–3.20)[a]	
Ferri et al., 2018; Apulia, Bari (southern Italy); Hospital-based case-control study (hospital Azienda Ospedaliera Universitaria Policlinico); 2010-2015; < 15 years	Questionnaires interviews of parents Maternal use of			**[AL]**		Adjusted by sex, age at diagnosis, birth order, maternal age at birth, maternal cigarette smoking, maternal and paternal education, and polymorphism of CYP2D6*4; also matched on residential area
	Pesticides	Mother	Pregnancy	- 43/49	1.65 (0.92-2.96)	
	Insecticides/rodenticides			- 45/48	1.87 (1.04-3.33)	
	Garden pesticides			- 3/1	4.66 (0.44-48.99)	
	Pesticides	Child	After birth	- 44/72	0.76 (0.45-1.28)	
	Insecticides/rodenticides			- 44/70	0.88 (0.48-1.34)	
	Garden pesticides			- 5/10 (French-American-British classification; cytogenetic and molecular analyses)	0.71 (0.22-2.25)	
Hyland et al., 2018; Costa Rica; population-based case-control study; [Costa Rican Childhood Leukemia Study (CRCLS)]; 1995-2000; (0-14 years)	Questionnaires: face-to-face parents' interviews			**[ALL]**		Adjusted for sex, year of birth and socioeconomic status. In sensitivity analyses, adjustment for parental education and for additional potential confounders or strong predictors of ALL
	Insecticides	Mother	Year before pregnancy	- 160/338	1.28 (0.94-1.75)	
			Pregnancy	- 160/335	1.31 (0.96-1.80)	
			Breastfeeding	- 166/341	1.36 (0.99-1.86)	
		Child	After birth	- 203/481	0.84 (0.57-1.24)	
		Either	Any time period	- 206/486	0.84 (0.57-1.26)	
	Herbicides	Mother	Year before pregnancy	- 44/73	1.44 (0.95-2.17)	
			Pregnancy	- 42/72	1.39 (0.91-2.12)	
			Breastfeeding	- 41/75	1.28 (0.84-1.96)	
		Child	After birth	- 61/145	0.97 (0.68-1.38)	
		Either	Any time period	- 68/147	1.09 (0.78-1.54)	
	Spraying on farm/company near the home	Mother	Year before pregnancy	- 60/18	1.29 (0.90-1.85)	
			Pregnancy	- 62/113	1.43 (1.00-2.05)	

(*continued on next page*)

Table 1 (*continued*)

Reference; Location; [Study name]; Years of case accruals; (Upper age limit)	Source of exposure data Exposure category	Exposed person	Exposure windows	[Leukemia type] (source of case definition) Number of cases/controls	Risk estimator OR (95% CI)	Adjusted (matched) for
			Breastfeeding	- 61/113	1.41 (0.98-2.03)	
		Child	After birth	- 79/160	1.32 (0.95-1.84)	
		Either	Any time period	- 98/174	1.52 (1.11-2.09)	
	High frequency of insecticide use (> 36 times/year)	Mother	Year before pregnancy	- 62/105	1.56 (1.07-2.27)	
			Pregnancy	- 61/101	1.58 (1.08-2.31)	
			Breastfeeding	- 61/103	1.56 (1.07-2.29)	
		Child	After birth	- 77/171	1.06 (0.74-1.52)	
			Any time period	- 78/174 (Costa Rican Cancer Registry, National Children's Hospital)	1.08 (0.75-1.55)	
Leiss and Savitz, 1995; Denver, Colorado (USA; North America); Population-based case-control study; 1976–1983; (< 15 years)	Questionnaire: parents' interviews. Home pest extermination (insects or pests)			**[Leukemia]**		Matched by, sex and geographic location Adjusted for age at diagnosis, father's education, per capita income, residential stability, mother's age, maternal race, sex, maternal smoking, wire code and/or year of diagnosis when these factors proved to be confounders. OR were not adjusted when fewer than 5 exposed cases
		Mother	3rd trim. pregnancy	- 4/27	0.4 (0.1–1.2)	
		Child	From birth to 2 years before diagnosis	- 6/45	0.3 (0.1–0.8)	
			From 2 years before diagnosis to diagnosis	- 7/22	0.9 (0.5–1.4)	
			From birth to diagnosis	- 13/67[a]	0.13 (0.07–0.24)[a]	
	Yard treatment (with insecticides or herbicides)	Mother	3rd trim. pregnancy	- 27/79	1.1 (0.6–1.9)	
			From birth to 2 years before diagnosis	- 36/118	0.9 (0.5–1.8)	
		Child	From 2 years before diagnosis to diagnosis	- 33/98	1.1 (0.8–1.5)	
			From birth to diagnosis	- 69/216[a]	0.01 (0.004–0.03)[a]	
	Pest strips (insecticides) (any use *vs* no use or ever used *vs* never used)	Mother	3rd trim. pregnancy	- 21/26	3.0 (1.6–5.7)	
			From birth to 2 years before diagnosis	- 21/47	1.7 (1.2–2.4)	
		Child	From 2 years before diagnosis to diagnosis	- 18/37	2.6 (1.7–3.9)	
			From birth to diagnosis	- 39/84[a]	0.30 (0.20–0.47)[a]	
Lowengart et al., 1987; Los-Angeles County, California (USA; North America); Population-based case-control study; [Los Angeles County Cancer Surveillance Program]; 1980–1984; (< 11 years)	Questionnaire: parents' phone interviews. Household pesticides [≥1/wk]			**[Leukemia]**		When available, friend control matched on age, sex, race, Hispanic origin for whites.
		Mother	During pregnancy/nursing	- 13/4[b]	3.2 (1.04–9.78)[a]	
		Father	During pregnancy	- 12/3[b]	4.0 (1.13–14.21)[a]	
		Either		- 19/5[b]	3.8 (1.37–13.02)	
	Garden sprays ("herbicides and pesticides") [≥1/mo]	Mother	During pregnancy/nursing	- 9/1[b]	9.0 (1.14–71.23)[a]	
		Father	During pregnancy	- 5/1[b]	5.0 (0.59–42.79)[a]	
		Either		- 13/2[b] (Los Angeles County Cancer Surveillance Program [cancer registry])	6.5 (1.47–59.33)	
Maryam et al., 2015; Fars province (south of Iran; Asia); Hospital-based case-control study; 2011-2012; (< 15 years)	Questionnaire: face-to-face parents' interviews. Form of pesticides:			**[Leukemia]**		Matched by age, sex, state of residence at the time of interview
	Spray	Family (home)		- 39/38	0.80 (0.42–1.52)[a]	
	Home powder			- 58/58	0.55 (0.25–1.20)[a]	
	Spray and home			- 29/10	3.47 (1.54–7.79)[a]	
	Farm/garden			- 30/15	2.24 (1.08–4.64)[a]	
	Home and farm			- 9/2	4.01 (0.84–19.23)[a]	
	Spray and home and farm (exposed *vs* non-exposed)				9.76 (1.18–81.10)[a]	

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Table 1 (*continued*)

Reference; Location; [Study name]; Years of case accruals; (Upper age limit)	Source of exposure data Exposure category	Exposed person	Exposure windows	[Leukemia type] (source of case definition) Number of cases/controls	Risk estimator OR (95% CI)	Adjusted (matched) for
				- 7/1 (New diagnosed cases in the Hematology-Oncology Ward of Nemazee Hospital)		
Slater et al., 2011; (USA/ Canada ; North America); [Children's Oncology Group] 1996-2006; (< 1 year)	Questionnaire: mothers' telephone interviews	Mother	Any (1 month before pregnancy and/ or during pregnancy)	**[ALL]**		Birth year, maternal age, race/ ethnicity
	Insecticides			- 94/117	1.01 (0.71 – 1.45)	
	Moth control			- 15 /15	1.39 (0.64 – 3.01)	
	Rodenticides			- 13/11	1.43 (0.61 – 3.40)	
	Flea or tick control			- 55/60	1.24 (0.80 – 1.91)	
	Herbicides			- 49/70	1.00 (0.65 – 1.53)	
	Insect repellants			- 99/127	0.88 (0.62 – 1.26)	
	Professional pest extermination			- 46/42	1.22 (0.75 – 1.97)	
	Insecticides		Before pregnancy (1 month)	- 78/100	0.95 (0.65 – 1.38)	
	Moth control			- 6/10	0.85 (0.29 – 2.49)	
	Rodenticides			- 8/9	1.17 (0.42 – 3.26)	
	Flea or tick control			- 46/49	1.25 (0.79 – 1.99)	
	Herbicides			- 27/45	0.75 (0.44 – 1.28)	
	Insect repellants			- 62/75	0.96 (0.64 – 1.44)	
	Professional pest extermination			- 28/30	0.94 (0.53 – 1.67)	
	Insecticides		During pregnancy	- 77/91	1.08 (0.74 – 1.58)	
	Moth control			- 15 /11	1.89 (0.82 – 4.47)	
	Rodenticides			- 10/9	1.19 (0.46 – 3.08)	
	Flea or tick control			- 47/47	1.40 (0.87 – 2.24)	
	Herbicides			- 42/55	1.14 (0.72 – 1.81)	
	Insect repellants			- 87/108	0.95 (0.66 – 1.37)	
	Professional pest extermination			- 41/36	1.35 (0.81 – 2.24)	
				[AML]		
	Insecticides		Any (1 month before pregnancy and/ or during pregnancy)	- 69/117	1.30 (0.86 – 1.94)	
	Moth control			- 9/15	1.38 (0.57 – 3.35)	
	Rodenticides			- 5/11	0.74 (0.24 – 2.27)	
	Flea or tick control			- 36/60	1.30 (0.79 – 2.14)	
	Herbicides			- 36/70	1.15 (0.70 – 1.88)	
	Insect repellants			- 66/127	0.97 (0.64 – 1.45)	
	Professional pest extermination			- 30/42	1.22 (0.71 – 2.11)	
	Insecticides		Before pregnancy (1 month)	- 40/100	0.72 (0.46 – 1.12)	
	Moth control			- 4 /10	0.89 (0.26 – 2.99)	
	Rodenticides			- 5/9	1.04 (0.33 – 3.32)	
	Flea or tick control			- 31/49	1.29 (0.76 – 2.19)	
	Herbicides			- 17/45	0.76 (0.41 – 1.42)	
	Insect repellants			- 37/75	0.90 (0.56 – 1.45)	
	Professional pest extermination			- 17/30	0.88 (0.45 – 1.72)	
	Insecticides		During pregnancy	- 58/91	1.35 (0.88 – 2.07)	
	Moth control			- 8 /11	1.70 (0.64 – 4.48)	
	Rodenticides			- 4/9	0.65 (0.19 – 2.26)	
	Flea or tick control			- 28/47	1.28 (0.74 – 2.21)	
	Herbicides			- 33/55	1.45 (0.87 – 2.44)	
	Insect repellants			- 57/108	0.97 (0.64 – 1.49)	
				- 26/36	1.27 (0.71 – 2.26)	

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Table 1 (*continued*)

Reference; Location; [Study name]; Years of case accruals; (Upper age limit)	Source of exposure data Exposure category	Exposed person	Exposure windows	[Leukemia type] (source of case definition) Number of cases/controls	Risk estimator OR (95% CI)	Adjusted (matched) for
	Professional pest extermination					
				[ALL + AML]		
	Insecticides		Any (1 month before pregnancy and/or during pregnancy)	- 163/117[a]	1.06 (0.78 – 1.42)[a]	
	Moth control			- 24 /15[a]	1.20 (0.62 – 2.33)[a]	
	Rodenticides			- 18/11[a]	1.23 (0.57 – 2.63)[a]	
	Flea or tick control			- 91/60[a]	1.16 (0.81 – 1.64)[a]	
	Herbicides			- 85/70[a]	0.88 (0.62 – 1.25)[a]	
	Insect repellants			- 165/127[a]	0.94 (0.70 – 1.27)[a]	
	Professional pest extermination			- 76/42[a]	1.42 (0.94 – 2.13)[a]	
	Insecticides		Before pregnancy (1 month)	- 118/100[a]	0.83 (0.61 – 1.14)[a]	
	Moth control			- 10 /10[a]	0.74 (0.30 – 1.79)[a]	
	Rodenticides			- 13/9[a]	1.08 (0.45 – 2.55)[a]	
	Flea or tick control			- 77/49[a]	1.20 (0.81 – 1.78)[a]	
	Herbicides			- 44/45[a]	0.70 (0.45 – 1.08)[a]	
	Insect repellants			- 97/75[a]	0.95 (0.67 – 1.34)[a]	
	Professional pest extermination			- 45/30[a]	1.13 (0.69 – 1.83)[a]	
	Insecticides		During pregnancy	- 135/91[a]	1.15 (0.84 – 1.58)[a]	
	Moth control			- 23 /11[a]	1.59 (0.76 – 3.30)[a]	
	Rodenticides			- 14/9[a]	1.16 (0.50 – 2.72)[a]	
	Flea or tick control			- 75/47[a]	1.22 (0.82 – 1.82)[a]	
	Herbicides			- 75/55[a]	1.02 (0.69 – 1.49)[a]	
	Insect repellants			- 144/108[a]	0.99 (0.73 – 1.34)[a]	
	Professional pest extermination (any exposure *vs* no exposure)			- 67/36[a] (identified at Children's Oncology Group)	1.45 (0.94 – 2.24)[a]	
Soldin et al., 2009; Washington District of Columbia, California, (USA; North America); Hospital-based case-control study; 2005–2008; (< 18 years)	Questionnaire: mothers' interviews.			**[ALL]**		Matched for age, sex, county of residence
	Use of insecticides as pest control in pets	Mother	Prenatal period (6 mo preconception and during pregnancy)	- 12/10	2.77 (1.08–7.14)[a]	
		Father		- 6/9 (Newly diagnosed in Georgetown University Medical Center and Children's National Medical Center in Washington)	1.30 (0.43–3.93)[a]	
Spix et al., 2009; Germany (Europe); Population-based case-control study; [German Childhood Cancer Registry]; 1993–2003; (< 5 years)	Questionnaire: mothers' phone interviews.			**[Leukemia]**		
	Fungicides (yes *vs* no)	Family	Since conception	- 29/95 (German Childhood Cancer Registry)	0.69 (0.42–1.12)	Matched by sex, age and year of diagnosis
Zhang et al., 2015; Shangai (China; Asia); Hospital-based case-control study (four hospitals [H.]: Shangai Children's H., Xinhua H., Shangai Children Medical Center, Children's H. of Fudan University); 2009–2010; (< 15 years)	Questionnaire: mothers' face to face interviews.			**[AL]**		Matched by gender and age; adjusted for annual household income, paternal age at delivery, maternal and paternal education levels, childhood and maternal passive smoking history
	Household use of pesticides	Family (home use)	???	- 170/61	1.8 (1.1-2.8)	
	Mothproofing agent			- 54/35	0.6 (0.4-1.0)	
	Cockroach killer			- 38/22	0.7 (0.4-1.3)	
	Termite control agent			- 1/0	ND	
	Mosquito repellent			- 135/42	1.9 (1.2-3.1)	
	Rodenticide			- 7/0	ND	
	Herbicide			- 10/1	3.7 (0.5-30.6)	
	Sanitizer			- 13/15	0.3 (0.2-0.8)	

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Table 1 (*continued*)

Reference; Location; [Study name]; Years of case accruals; (Upper age limit)	Source of exposure data Exposure category	Exposed person	Exposure windows	[Leukemia type] (source of case definition) Number of cases/controls	Risk estimator OR (95% CI)	Adjusted (matched) for
	Antiseptic germicide			- 5/8	0.3 (0.1-1.0)	
	Other pesticides (ever exposed *vs* never exposed)			- 3/1 (According to the French-American-British classification)	0.9 (0.1-8.9)	
	Levels of urinary dialkyl phosphate (DAP) metabolites of organophosphates (highest quartile *vs* lowest quartile)	Child	Urine samples collected at the time of the interview			
	Dimethyl metabolites			- 115/28	9.1 (4.1-20.5)	
	Diethyl metabolites			- 71/28	5.5 (2.5-12.5)	
	DAPs			- 83/28	4.8 (2.2-10.4)	

Abbreviations: AL, acute leukemia; ALL, acute lymphoblastic leukemia; ANLL, acute non-lymphocytic leukemia; AML, acute myeloid leukemia; ND, not defined (could not be calculated); NR, information not reported; OR, odds ratio; 95% CI, 95% confidence interval; trim., trimester. [a]Number of cases and/or crude OR and/or 95% CI calculated on the basis of data in paper. [b]Discordant pairs (cases exposed-controls unexposed/cases unexposed-controls exposed).

analyses were, therefore, carried out to identify sources of heterogeneity by combining studies within strata hypothesized a priori to influence the results. Studies included in each subgroup analysis are listed in Supplemental Materials – Appendix 1.

Analyses primarily performed according to the leukemia subtypes (ALL, AML, unspecified leukemia) are reported in Table 2. They included stratification defined by exposure windows (before pregnancy, during pregnancy, childhood), exposure location (indoor, outdoor), biocide category (insecticides, herbicides) and age at diagnosis (≤ 2 years, $\leq$ 5 years, $\leq$ 15 years, $\leq$ 18 years). Statistically significant increased risks were observed for AML after combining the 5 studies reporting this leukemia type and to a lesser extent for ALL subtype (8 studies). Combining the 6 studies not reporting on a specific leukemia type showed also a significant increased risk. Forest plots of ALL and AML studies were reported in Fig. 2(b) and (c), respectively. Heterogeneity and inconsistency were only drastically reduced in a limited number of subgroups. Inconsistency disappeared ($I^2 = 0$) when combining studies reporting prenatal outdoor exposure and prenatal exposure to herbicides, for ALL and AML as well as for prenatal indoor exposure or unspecified leukemia type. Strongly reduced inconsistency ($I^2 \leq 50$) was observed for the stratification by exposure time windows during pregnancy (for ALL, AML and unspecified leukemia types), for preconception exposure (ALL), for prenatal indoor exposure (ALL, AML), for prenatal exposure to insecticides (ALL, unspecified) and childhood exposure to herbicides (ALL). With the exception of exposure to herbicides (AML), and of childhood exposures resulting in unspecified leukemia, all summary risks (SOR) were higher than one. For the three groups (ALL, AML, unspecified leukemia), statistically significant increased risks were observed for exposure during pregnancy, prenatal indoor exposure and prenatal exposure to insecticides and whatever the age at diagnosis. The risk of ALL was also significantly increased for preconception exposure and prenatal exposure to herbicides. The highest statistically significant increased risk was observed for AML diagnosed among children ≤ 2 years and a trend of decreased AML/ANLL summary risks appeared with increasing ages. At corresponding ages, SORs were higher for AML/ANLL as compared to SORs for ALL.

Others subgroup analyses were carried out regardless of the leukemia types, and included study quality (high quality, low quality), specific exposure (professional pest exterminator, pet treatments, insect repellant), type of pest treated (mosquito, moth, cockroach) and geographic location (USA/Canada, Europe, others) (Table 3). Statistically significant increased risks were observed for the high quality studies, for pet treatment, after interventions by professional pest exterminators, for using insect repellant, for treatment against mosquitos and for combined data from North-America and from international studies, the highest statistically significant increased risks being observed when combining international studies.

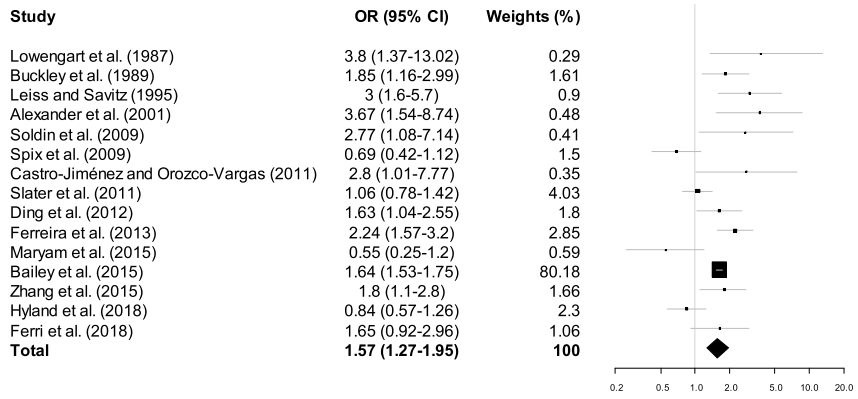
3.4. Publication bias

A funnel plot including all studies on residential exposure to pesticides and childhood leukemia was constructed (Fig. 3). It did not demonstrate any obvious publication bias: the visual inspection of this figure does not clearly detect asymmetry arising from a lack of small studies with low risk estimators. The statistical analysis provided by the linear regression method of Egger et al. (1997) did not yield evidence of asymmetry (intercept: 0.8767; 95% CI: −1.313 to 3.067) ($p > 0.20$).

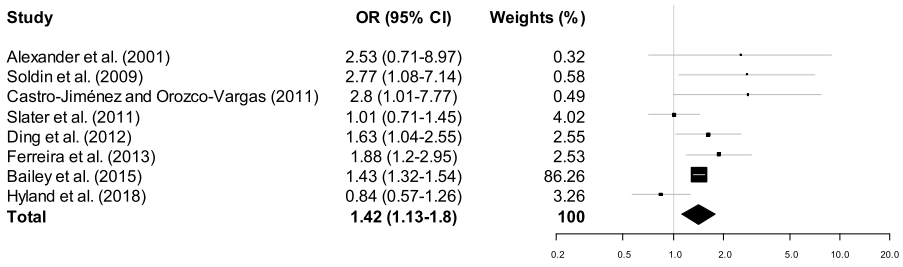
3.5. Sensitivity analyses

None of the performed sensitivity analyses substantially affected the results of the MA (Table 4). Summary odds ratios obtained by applying fixed or random effects models were very similar. Exclusion of studies with partial redundancy, reporting extreme risk estimator values as well as excluding the especially large study of Bailey et al. (2015) did

(a) Forest plot of studies related to residential pesticide exposure and all types of childhood leukemia



(b) Forest plot of studies related to residential pesticide exposure and childhood ALL



(c) Forest plot of studies related to residential pesticide exposure and childhood AML

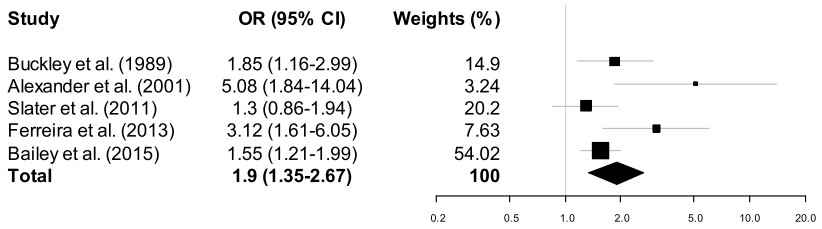


Fig. 2. Forest plot of case-control studies related to (a) all types of leukemia, (b) ALL, (c) AML/ANLL following residential exposure to pesticides.
Note. Odds ratio (OR) and 95% confidence intervals (CIs) of the case-control studies included in the meta-analyses are reported. Each estimator was assigned a weight (w_i) equal to the inverse square of its standard error (SE): $w_i = 1/(SE)^2$. The combined OR estimate (SOR) is presented by a black diamond. Included ORs in forest plot (a): where several ORs were reported in a same case-control study, the most global values for all leukemia types, any exposure time periods and domestic exposure categories were included in the SOR. Where results for all leukemia types were not presented, they were calculated on the basis of data for specific leukaemia types in papers. Where results were not reported for any exposure time periods, the values for exposure during pregnancy (Bailey et al., 2015; Buckley et al., 1989; Castro-Jiménez and Orozco-Vargas, 2011; Ferri et al., 2018; Leiss and Savitz, 1995; Lowengart et al., 1987; Soldin et al., 2009) or before child birth (prenatal) was used (Slater et al., 2011). Where results were reported for several domestic exposure categories, the broader house treatments were selected (pesticides, Alexander et al., 2001, Ferri et al., 2018; any pesticide exposure, Bailey et al., 2015; household use of pesticides, Zhang et al., 2015). Where results were reported by class of pesticides and by indoor and outdoor application, the value for insecticides and indoor were used (pest strips [insecticides], Leiss and Savitz, 1995; household pesticides, Lowengart et al., 1987; insecticides, Slater et al., 2011, Hyland et al., 2018). Where results were reported by types of pest treated or form of pesticides, the value for the higher number of exposed cases was used (mosquito repellent, Ding et al., 2012; home powder, Maryam et al., 2015).

not substantially modify the results. No single study dominated the association between residential exposure to pesticides and childhood leukemia. When combining studies published after 2009 (with and without including the study of Bailey et al., 2015), the SORs were slightly reduced (1.49 and 1.47, respectively) but the risk remained statistically significantly increased. From the cumulative analysis (Table 5) it appeared that the increased risk became statistically significant when including studies with quality scores of 12.5 and more, with a slight tendency towards increasing risks with increasing quality scores.

4. Discussion

4.1. Summary of results

This updated MA includes results from 15 case-control studies. One of them being a pooled analysis of 12 studies; thus reflecting the results from 26 case-control studies. This comprehensive updated MA provides additional support for the association between exposure to household/residential pesticides and the risk of childhood leukemia. A statistically significant increased risk of childhood leukemia was observed when all studies were combined as well as after grouping studies according to the types of leukemia (ALL, AML, unspecified). Within these three groups, significantly increased risks were observed for exposure during pregnancy, prenatal indoor exposure, prenatal exposure to insecticides and whatever the age at diagnosis, with the higher SOR observed for AML among children of ≤2 years. Evidence of between study heterogeneity and inconsistency was observed when combining all studies or in several subgroup analyses. This is not surprising as these studies were performed by different teams in different places on different populations with different study design characteristics such as different adjustments for confounding.

4.2. Comparison with others MA

The association between domestic/residential/household exposure to pesticides and childhood leukemia has already been investigated and documented in others MAs (Bailey et al., 2015; Chen et al., 2015; Turner et al., 2010; Van Maele-Fabry et al., 2011; Vinson et al., 2011). The three oldest MAs included case-control studies published up to 2007. Chen et al. (2015) combined studies published up to 2012 and focused on exposure during childhood (not during pregnancy). Bailey et al. (2015) took two distinct approaches to analyze the data from case-control studies in the CLIC, meta-analysis and individual data pooling,

Table 2
Meta-analyses after stratification of the case-control studies according to the type of leukemia, using random effects model.

Stratification	ALL					AML/ANLL					Unspecified AL/leukemia type				
	N	SOR (95% CI)	Homogeneity			N	SOR (95% CI)	Homogeneity			N	SOR (95% CI)	Homogeneity		
			Q	P-value	I^2 (95% UI) %			Q	P-value	I^2 (95% UI) %			Q	P-value	I^2 (95% UI) %
All studies	8	**1.42** (1.13–1.80)	16.523	0.0208	58 (7–81)	5	**1.90** (1.35–2.67)	10.004	0.404	60 (0–85)	6	**1.93** (1.14–3.28)	21.017	0.804×10^{-3}	70 (12–89)
Exposure time windows															
Preconception	4	**1.30** (1.12–1.51)	3.735	0.292	20 (0–88)	2	1.05 (0.51–2.13)	5.999	0.0143	83 (31–96)	0	/	/	/	/
Pregnancy	5	**1.39** (1.21–1.60)	4.778	0.311	16 (0–83)	4	**1.72** (1.25–2.37)	5.982	0.1125	50 (0–83)	3	**2.39** (1.48–3.87)	2.673	0.263	25 (0–92)
Childhood	3	1.24 (0.90–1.70)	6.343	0.0419	69 (0–91)	2	1.38 (0.82–2.33)	3.211	0.0731	69 (0–93)	2	0.47 (0.19–1.17)	7.284	0.696×10^{-2}	86 (45–97)
Exposure location															
Indoor exposure															
Prenatal	5	**1.27** (1.07–1.51)	5.572	0.234	28 (0–72)	4	**1.64** (1.20–2.25)	5.646	0.130	47 (0–82)	3	**2.45** (1.69–3.55)	1.801	0.406	0 (0–88)
Childhood	3	1.19 (0.90–1.57)	5.178	0.0751	61 (0–89)	2	1.77 (0.94–3.34)	4.506	0.0338	78 (3–95)	2	0.51 (0.18–1.46)	9.975	0.159×10^{-2}	90 (63–97)
Outdoor exposure															
Prenatal	3	1.29 (ND)	1.299	0.522	0 (0–84)	2	1.10 (0.94–1.29)	0.269	0.604	0 (ND)	3	2.35 (0.65–8.47)	4.318	0.115	54 (0–87)
Childhood	3	1.27 (0.93–1.72)	4.282	0.118	53 (0–87)	1	/	/	/	/	2	0.08 (0.00–5.44)	29.497	0.560×10^{-7}	97 (91–99)
Pesticide biocide category															
Insecticides															
Prenatal	5	**1.28** (1.07–1.53)	5.880	0.208	32 (0–74)	3	**1.64** (1.04–2.56)	5.115	0.0775	61 (0–89)	2	**2.33** (1.47–3.69)	1.157	0.282	14 (ND)
Childhood	3	1.19 (0.90–1.57)	5.178	0.0751	61 (0–89)	1	/	/	/	/	1	/	/	/	/
Herbicides															
Prenatal	3	**1.34** (1.32–1.36)	1.738	0.419	0 (0–88)	2	0.95 (0.70–1.28)	0.928	0.335	0 (ND)	0	/	/	/	/
Childhood	3	1.24 (0.96–1.60)	3.461	0.177	42 (0–83)	1	/	/	/	/	0	/	/	/	/
Age at diagnosis															
≤2 years	4	**1.59** (1.09–2.30)	9.049	0.0286	67 (3–89)	3	**2.50** (1.11–5.65)	9.082	0.0107	67 (4–89)	0	/	/	/	
≤5 years	4	**1.47** (1.12–1.93)	6.669	0.0832	55 (0–85)	4	**2.24** (1.39–3.62)	9.282	0.0258	68 (6–69)	1	/	/	/	/
≤15 years	7	**1.37** (1.08–1.73)	14.559	0.024	59 (5–82)	4	**1.99** (1.27–3.12)	9.825	0.0201	70 (12–89)	6	**1.93** (1.14–3.28)	21.017	0.804×10^{-3}	70 (12–89)
≤18 years	8	**1.42** (1.13–1.80)	16.523	0.0208	58 (7–81)	5	**1.90** (1.35–2.67)	10.004	0.0404	60 (0–85)	6	**1.93** (1.14–3.28)	21.017	0.804×10^{-3}	70 (12–89)

Abbreviations: AL, acute leukemia; ALL, acute lymphoblastic leukemia; ANLL, acute non-lymphocytic leukemia; AML, acute myeloid leukemia; N, number of studies; ND, not defined (could not be calculated); /, information not reported for 2 studies or more; *S*OR, summary-odd ratio estimate; 95% CI, 95% confidence interval; SOR are in bold when the 95% CI do not include 1; 95% UI, 95% uncertainty interval; Q, chi-square based Q-test.

Table 3
Meta-analyses after stratification of the case-control studies regardless type of leukemia, using random effects model.

Stratification	N.	SOR	95% CI	Homogeneity			
				Cochran's Q (χ^2 Woolf)	P-value	I^2	95% UI
Residential pesticide exposure							
Study quality							
high quality (≥median)	8	**1.65**	1.32–2.05	15.967	0.0254	56	3–80
low quality (< median)	7	1.53	0.92–2.54	32.813	0.11-$4 \times 1\text{-}0^{-4}$	82	63–91
Specific exposure							
Pet treatments	3	**1.41**	1.11–1.78	3.256	0.196	39	0–81
Professional pest exterminator	4	**1.47**	1.20–1.80	4.711	0.1942	36	0–78
Insect repellant	4	**1.38**	1.04–1.84	8.706	0.0335	66	0–88
Type of pest treated							
Mosquito	3	**1.88**	1.31–2.70	2.367	0.306	16	0–91
Moth	3	0.82	0.56–1.19	3.157	0.206	37	0–80
Cockroach	2	1.00	0.53–1.86	2.965	0.0851	66	0–92
Pesticide biocide category							
Rodenticides							
All studies	3	1.07	0.61–1.88	6.967	0.0307	71	3–91.6
Geographic location							
North America (USA/Canada)	5	**2.04**	1.22–3.40	14.720	0.00532	73	32–89
Asia	3	1.28	0.71–2.30	6.953	0.03.9	71	2–92
Central/South- America	3	1.64	0.75–3.59	14.520	0.70-$3 \times 1\text{-}0^{-3}$	86	60–95
International	2	**2.17**	1.02–4.62	3.288	0.0698	70	0–93
Europe	2	1.05	0.45–2.47	5.018	0.0251	80	14–95

Abbreviations: N., number of studies; SOR, summary-odd ratio estimate; 95% CIs, 95% confidence interval; SOR are in bold when the 95% CI do not include 1; 95% UI, 95% uncertainty interval; Q, chi-square based Q-test.

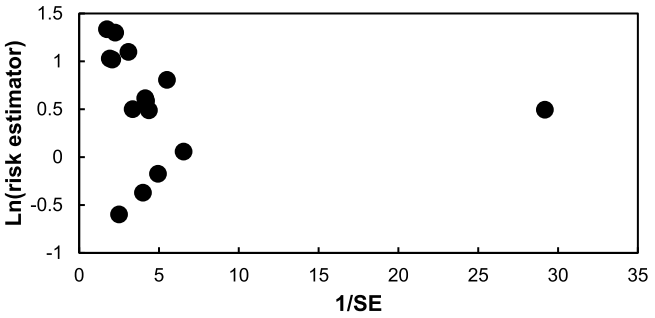


Fig. 3. Case-control studies of residential pesticide exposure and childhood leukaemia: funnel plot of natural logarithms of risk estimates (OR) vs the inverse of their standard errors (1/SE) (lnOR of the 15 case-control studies combined = 0.454).

with years of cases accruals between 1980 and 2008. The results of our updated MA, including studies published up to 2018, corroborates previous MA. Although there is a substantial overlap in the studies included in the different MA, the inclusion of recent studies confirms the statistically significant association between residential exposure to pesticides and childhood leukemia previously reported. The methodological differences between the MAs (inclusion and exclusion criteria, study selection period, combined data, as examples) prevents a systematic comparison of the results for the subgroup analyses. In spite of these differences, our results are in fair agreement with the main observations in previous MA: statistically significant increased risks of childhood leukemia was associated with exposure during pregnancy/prenatal to unspecified residential pesticides (Bailey et al., 2015; Turner et al., 2010; Van Maele-Fabry et al., 2011; Vinson et al., 2011) and more specifically to insecticides and for indoor use (Turner et al., 2010; Van Maele-Fabry et al., 2011). The risk for both types of acute leukemia (ALL and AML/ANLL) was significantly increased after prenatal exposure to insecticides (Bailey et al., 2015; Turner et al., 2010; Van Maele-Fabry et al., 2011). During childhood, indoor exposure is significantly associated with leukemia (all types) in the MA of Chen et al. (2015), Turner et al. (2010) and Van Maele-Fabry et al. (2011) as in the present updated-MA (SOR, 1.42; 95% CI, 1.06–1.90, data not shown). Outdoor exposure resulted in significantly increased risks in the MA of Turner et al. (2010) but non-significant increased risks were reported by Chen et al. (2015), Van Maele-Fabry et al. (2011) and in our updated-MA (SOR, 1.22; 95% CI, 0.89–1.67). Subgroup analyses by type of leukemia showed significant associations between exposure to insecticides after birth and risk of ALL in the MA of Bailey et al. (2015) and of Van Maele-Fabry et al. (2011) but not of Turner et al. (2010) nor in our updated-MA. Two MA reported a significant association between herbicide exposure and risk of ALL (Bailey et al., 2015, our updated-MA for prenatal exposure). No data and/or non-significant increased risks were observed between herbicide exposure and AML/ANLL (Bailey et al., 2015; Turner et al., 2010; Van Maele-Fabry et al., 2011; our updated-MA).

4.3. Strengths of the study

The present updated MA allowed to include relevant data provided by 10 recently published studies (one of them pooling data from 12 case-control studies). The substantially increased number of cases from these recent studies is of particular interest for the subgroup analyses, increasing the statistical power and reducing the degree of uncertainty as compared to the previous MA. This allowed a detailed analysis and re-analysis of a wide range of variables taking into account the type of leukemia (exposure time windows, exposure location, specific pesticide biocide category, and child age at diagnosis) as well as regardless of the leukemia type (quality of the studies, specific exposures, type of pest treated and geographic location).

The association observed in the present meta-analysis does not appear to be significantly influenced by publication bias. The possible impact of non-inclusion of unpublished small studies or of non-English language studies has already been analysed in MA on pesticide

Table 4
Sensitivity analyses –residential exposure to pesticides and childhood leukemia.

Rerunning MA	N.	SOR	95% CI	Homogeneity			
				Cochran's Q (χ^2 Woolf)	P-value	I^2	95% UI
Statistical pooling using							
Random effect model	15[a]	**1.57**	1.27–1.95	52.387	0.242×10^{-5}	73	55–84
Fixed model	15	**1.60**	1.51–1.70				
Excluding study(ies) -with partial redundancy[b]							
Ding et al., 2012	14	**1.58**	1.25–1.99	52.381	0.116×10^{-5}	75	58–85
Zhang et al., 2015	14	**1.56**	1.24–1.97	52.140	0.128×10^{-5}	75	58–85
-reporting extreme risk estimators values[c]							
Maryam et al., 2015 and Lowengart et al., 1987	13	**1.61**	1.30–1.99	42.980	0.228×10^{-4}	72	51–84
-higher precision value							
Bailey et al., 2015,[d]	14	**1.61**	1.21–2.14	49.825	0.320×10^{-5}	74	56–85
-studies published before 2009							
Five excluded studies[e]	10	**1.47**	1.17–1.85	31.181	0.276×10^{-3}	71	45–85
-studies published before 2009 and Bailey et al., 2015							
Six excluded studies	9	**1.45**	1.06–1.98	27.458	0.589×10^{-3}	71	42–85
-one study at a time							
Lowengart et al., 1987	14	**1.53**	1.23–1.91	50.114	0.285×10^{-5}	74	56–85
Buckley et al., 1989	14	**1.56**	1.24–1.97	52.021	0.134×10^{-5}	75	58–85
Leiss and Savitz, 1995	14	**1.51**	1.21–1.88	48.594	0.519×10^{-5}	73	55–84
Alexander et al., 2001	14	**1.52**	1.22–1.89	48.859	0.467×10^{-5}	73	55–84
Soldin et al., 2009	14	**1.54**	1.24–1.92	51.086	0.194×10^{-5}	75	57–85
Spix et al., 2009	14	**1.67**	1.35–2.05	40.908	0.986×10^{-4}	68	45–82
Castro-Jiménez and Orozco-Vargas, 2011	14	**1.54**	1.24–1.93	51.228	0.183×10^{-5}	75	57–85
Slater et al., 2011	14	**1.64**	1.31–2.07	44.815	0.225×10^{-4}	71	50–83
Ding et al., 2012	14	**1.58**	1.25–1.99	52.381	0.116×10^{-5}	75	58–85
Ferreira et al., 2013	14	**1.52**	1.21–1.92	48.861	0.467×10^{-5}	73	55–84
Maryam et al., 2015	14	**1.65**	1.33–2.03	45.220	0.192×10^{-4}	71	51–83
Bailey et al., 2015	14	**1.61**	1.21–2.14	49.825	0.320×10^{-5}	74	56–85
Zhang et al., 2015	14	**1.56**	1.24–1.97	52.140	0.128×10^{-5}	75	58–85
Ferri et al., 2018	14	**1.57**	1.25–1.98	52.376	0.116×10^{-5}	75	58–85
Hyland et al., 2018	14	**1.66**	1.34–2.06	42.000	0.655×10^{-4}	69	46–82

Abbreviations: N., number of studies; SOR, summary-odd ratio estimate; 95% CIs, 95% confidence interval; SOR are in bold when the 95% CI do not include 1; 95% UI, 95% uncertainty interval; Q, chi-square based Q-test.
Notes.
[a] The 15 included studies are as in Fig 2(a).
[b] Partial redundancy may exist between the study of Ding et al. (2012) and that of Zhang et al. (2015) as a part of the diagnostic period (January 2010–December 2010) is similar between the two studies. Despite the fact that the two studies aimed to detect exposure to different classes of pesticides (organophosphate by Zhang and pyrethroids by Ding) it cannot be excluded that individuals included in one study were also exposed to the class of pesticides analysed in the other study and be also included in this last study.
[c] Extreme risk estimator values were: OR: 0.55, 95% CI: 0.25–1.2 (Maryam et al., 2015) and OR: 3.8, 95% CI: 1.37–13.02 (Lowengart et al., 1987).
[d] The higher precision value was 80.18% for the study of Bailey et al. (2015) reporting pooled data from 12 case-control studies.
[e] The excluded studies (Lowengart et al., 1987; Buckley et al., 1989; Leiss and Savitz, 1995; Alexander et al., 2001 and Spix et al., 2009) were those already included in our previous MA (Van Maele-Fabry et al., 2011). The study of Soldin et al. (2009) was not excluded as it was not introduced in our previous MA.

exposure and childhood leukemia (Turner et al., 2010; Van Maele-Fabry et al., 2011) and revealed that including these studies did not substantially modify the results of the MAs (Van Maele-Fabry et al., 2011).

The statistically significant increased risk of childhood leukemia recorded when combining the 8 high quality studies as compared to the non-significant increased risk observed when combining the 7 low quality studies reinforces the strength of the evidence.

The robustness of the results was confirmed by sensitivity analyses and no single study dominated the association.

4.4. Limitations of the study

The interpretation of a MA is constrained by the limitations of the original studies, particularly regarding exposure assessment and potential source of bias.

In the available studies on residential pesticide exposure and childhood leukemia, exposure was assessed retrospectively, after diagnosis, leaving a long time between the first windows of susceptibility to leukemogenic agents (prenatal period) and the time period when investigators started measuring exposure to those agents. To circumvent the need of collecting biological or environmental samples by the time the child is under study, a variety of strategies have been used and/or proposed by the investigators. These strategies were reviewed by Whitehead et al. (2016) and included parent interviews to assess children exposures, measuring chemicals in settled dust, estimating ambient environmental exposures using geographic information systems and measuring chemicals in archived pre-diagnostic biospecimens. In the case-control studies included in the updated MA, exposure histories were most frequently self-reported by the mothers via a questionnaire. However, residential exposure is clearly a complex environmental exposure that is difficult to measure accurately and precisely through the use of a questionnaire (Teitelbaum, 2002). A case-control study using a questionnaire is prone to recall bias if parents of case and control children report exposure in different ways, and is potentially limited by the lack of information on specific chemicals. To facilitate accurate recall, Slater et al. (2011) mailed interview guides describing categories of household chemicals with examples of products used to all study participants before the interview. The reliability of maternal-reported household pesticide use among case and control has been investigated and similar results were reported, suggesting that differential recall may not be substantial (Slusky et al., 2012). In our updated MA, the nature of the information on specific chemicals differs from one study to the other: one study refered to pesticides most likely to be used for

Table 5
Cumulative analysis –residential exposure to pesticides and childhood leukemia.

Rerunning MA	N.	SOR	95% CI	Homogeneity			
				Cochran's Q (χ^2 Woolf)	P-value	I^2	95% UI
Adding one study at a time[a]							
Ferreira et al., 2013	1	/	/	/	/	/	/
+Castro-Jiménez and Orozco-Vargas, 2011	2	1.47	ND	0.164	0.686	0	ND
+Alexander et al., 2001	3	1.88	ND	1.141	0.565	0	0–82
+ Maryam et al., 2015	4	1.86	0.88–3.94	13.092	0.444×10^{-2}	77	38–92
+Spix et al., 2009	5	1.49	0.73–3.07	26.309	0.274×10^{-4}	85	66–93
+Lowengart et al., 1987	6	1.69	0.87–3.29	28.774	0.257×10^{-4}	83	63–92
+ Slater et al., 2011	7	1.53	0.92–2.54	32.813	0.114×10^{-4}	82	63–91
+ Bailey et al., 2015	8	**1.49**	1.06–2.10	36.559	0.568×10^{-5}	81	63–90
+Leiss and Savitz, 1995	9	**1.61**	1.17–2.22	40.254	0.287×10^{-5}	80	63–89
+Zhang et al., 2015	10	**1.62**	1.22–2.16	40.460	0.627×10^{-5}	78	59–88
+Buckley et al., 1989	11	**1.64**	1.26–2.11	40.765	0.124×10^{-4}	76	56–86
+Ferri et al., 2018	12	**1.63**	1.28–2.08	40.769	0.264×10^{-4}	73	52–85
+Ding et al., 2012	13	**1.63**	1.31–2.03	40.769	0.536×10^{-4}	71	48–83
+Soldin et al., 2009	14	**1.66**	1.34–2.06	42.000	0.655×10^{-4}	69	46–82
+Hyland et al., 2018	15	**1.57**	1.27–1.95	52.387	0.242×10^{-5}	73	56–84

Abbreviations: N., number of studies; SOR, summary-odd ratio estimate; 95% CIs, 95% confidence interval; SOR are in bold when the 95% CI do not include 1; 95% UI, 95% uncertainty interval; Q, chi-square based Q-test; ND, not defined (could not be calculated); /, information not reported for 2 studies or more.
Notes.
[a] The 15 included studies are as in Fig. 2(a). Studies were added one at a time according to increasing study quality score.

home extermination, yard treatment and pest strips without giving results for these specific pesticides (Leiss and Savitz, 1995), others reported risk estimates for specific chemical classes of pesticides including carbamates [Baygon] (Alexander et al., 2001), pyrethroids (PYR) and organophosphates (OP) (Ferreira et al., 2013) and in three studies residential exposures were determined by questionnaire as well as by urinalysis of OP (Soldin et al., 2009; Zhang et al., 2015) and PYR (Ding et al., 2012) metabolites. PYR urinary metabolite levels (Ding et al., 2012) and maternal use of PYR (Ferreira et al., 2013) were associated with an increased risk of childhood ALL. In their analyses, Soldin et al. (2009) and Zhang et al. (2015) focused on 6 and 5 metabolites of OP, respectively. For 2 metabolites (diethylthiophosphate [DETP] and diethyldithiophosphate [DEDTP]), Soldin and collaborators reported statistically significant higher urinary levels in ALL cases than in controls. Zhang et al. (2015) showed significantly elevated median urinary levels for 5 OP metabolites (dimethylphosphate [DMP], dimethylthiophosphate [DMTP], diethylphosphate [DEP], DETP and DEDTP) in acute leukemia cases compared with those of the controls. When categorized by quartiles, the summed dialkyl phosphate, dimethyl and diethyl metabolites in the three higher quartiles were all significantly associated with an elevated risk of childhood AL when compared with those of the lowest quartiles, with positive trends. These results suggested a possible dose-response relationship between exposure and childhood AL (Zhang et al., 2015). Similar observations were reported for total and individual PYR metabolites (Ding et al., 2012). However, it has to be stressed that in two of the three urinalysis studies, self-reported use of household pesticides did not correlate with the metabolite levels measured in urine samples. Possible explanations included sources of exposure others than household (agricultural applications, contaminated food, as examples), lack of details regarding the frequency of use, the chemicals used and the conditions of use, the metabolism and possible misclassifications due to retrospective reporting by maternal interviews (Ding et al., 2012; Soldin et al., 2009). In addition, with a half-life of less than 24–48 h, PYR and OP are rapidly metabolized and eliminated primarily in urine. Urinary metabolite concentrations thus reflect recent exposure (Glorennec et al., 2017). In most studies, metabolite measurements were performed at a single time point (right after diagnosis or a referent time [at the time of the interview]) (Ding et al., 2012; Zhang et al., 2015). It is unclear to what extent these measurements reflect exposure over critical windows before conception and during pregnancy (Zhang et al., 2015).

Another limitation is due to the lack of exclusivity of exposure in case-control studies reporting data for several subgroups as it makes it difficult to highlight differences in risks and may partially explain the lack of variability in risk between subgroups. As examples, those people who use pesticides before conception also likely use them during pregnancy or postnatally, those who used pesticides indoor also possibly use them outdoor.

4.5. Biological plausibility

Several studies suggest that home dust is an important carrier of pesticide indoor exposure for children (Becker et al. 2006), due to household use of insecticides such as PYR (Deziel et al., 2017; Glorennec et al., 2017) or OP compounds (Lu et al., 2008), to the agricultural activity of the neighborhood or the take-home pesticide exposure among agricultural workers and their children (Coronado et al., 2006; Curl et al., 2002). In order to understand the positive correlation between residential pesticide exposure and the increased risk of developing leukemia in children, we analysed the literature for the possible mechanisms that could account for a role of OP compounds and PYR in the etiology of childhood leukemia.

Experimental exposure of animals to OP has been shown to disrupt hematopoietic cells differentiation (parathion: 4 mg/kg p.o.) (Gallicchio et al., 1987a; INSERM, 2013) and to induce weak clastogenic effects in bone marrow cells (malathion LD50; 1/2, 1/5 and 1/10 LD50) (Dzwonkowska and Hübner, 1986; INSERM, 2013). *In vitro* exposure of human bone marrow cells or $CD34^+$ human hematopoietic stem cells to OP led respectively to a decreased capacity of progenitors to differentiate (Gallicchio et al., 1987a; b; Nakadai et al., 2006) and to DNA double strand breaks and MLL gene rearrangements (Lu et al., 2015). *In vitro* treatment of human leukemic cell lines with OP led to DNA damage (isofenphos), hypermethylation of genes involved in the cell cycle or tumour suppressor genes (diazinon) or chromosomal damage (fenithrothion) (reviewed in Hernández and Menéndez, 2016). PYR may also exert effects consistent with a leukemogenic potential. Cytotoxic, genotoxic impact as well as inhibitory effects on differentiation have been reported *in vitro* in human lymphocytes (Assayed et al., 2010; Kocaman and Topaktas, 2009; Verma et al., 2016) and in hematopoietic stem cells from human cord blood respectively (Mandarapu and Prakhya, 2015). In addition, some PYR (permethrin, cypermethrin) have been shown to induce apoptosis *in vivo* in

hematopoietic cells (Prater et al., 2002) or to increase chromosomal aberrations in bone marrow cells (INSERM, 2013). The endocrine disruptor potential of PYR may also have consequences on hematopoiesis that is dependent on the surrounding estrogenic activities (Brander et al., 2016; Sun et al., 2007, 2014; Zhang et al., 2008). Moreover it is noteworthy that the impact of OP and PYR on the immune system may also contribute to their leukemogenic potential (Corsini et al., 2013; Huang et al., 2016; Li, 2007; Zhang et al., 2010).

Although there is few data on environmental gene interactions for OPs and PYRs, it may be suggested that exposure to contaminants targeting topoisomerases in individuals with reduced detoxification capabilities due to the presence of some genetic polymorphic variants can contribute to the development of leukemia in children (Hernández and Menéndez, 2016; Hernández et al., 2013a,b,c; Infante-Rivard et al., 1999; Sherborne et al., 2011).

In conclusion, the pathological consequences of the observed effects of OP and PYR *in vitro* or *in vivo* are not clearly established and need to be investigated in particular with doses close to that found in dust and during a chronic and long term cutaneous exposure. The combination of epidemiological approaches, genome-wide association studies (GWAS), a better knowledge of the exposure levels and experimental approaches would provide a better understanding of the genetic and biological mechanisms by which pesticides may increase the risk of leukemia in children.

4.6. Evaluation of the body of evidence

There is no consensus yet on the details of how the confidence in a body of evidence should be determined in the environmental (and occupational) health context. Several systems for rating confidence in the body of evidence have been proposed, including the Grading of Recommendations Assessment, Development and Evaluation (GRADE, Rooney et al., 2014), the approaches developed and/or used by the National Toxicology Program (2015) and the Navigation Guide (Woodruff and Sutton, 2014), as examples. However, the experience with these approaches in environmental (and occupational health) is just emerging and there are features of the different sources of evidence used in environmental health that will require further consideration using GRADE (Morgan et al., 2016). The approaches used in these systems are similar and will guide us without following strictly one of them. The GRADE approach starts by setting an initial level of confidence depending on study types, randomized controlled trials starting high and observational studies starting low. In the present analysis, the association between domestic exposure to pesticides and childhood leukemia can only be addressed by observational studies and it is not realistic to consider all the available studies as of low confidence. The level of evidence brought by the observational studies is different depending of the study design (prospective cohort studies > case-control studies > cross-sectional studies > case series > case reports). No cohort study was retrieved and only case-control studies were available. As a consequence we estimate the initial level of confidence as moderate. In the GRADE approach, this level can be decreased for five reasons (risk of bias, inconsistency, indirectness, imprecision, publication bias) or increased for three reasons (large effect, dose-response [evidence of a gradient], all plausible residual confounding [would reduce a demonstrated effet; would suggest a spurious effect if no effect was observed]) (Balshem et al., 2011). In our MA, the main limiting factors that would justify to downgrade the level of evidence are the exposure assessment (mostly "self-reported" and unspecific) and potential source of bias, as detailed in section 4.4 (limitations of the study). Immunophenotypes and cytogenetic classifications of leukemia were not included in our MA due to the too scarce and/or lack of data in the individual studies. With regards to inconsistency, although there was evidence of statistical heterogeneity between study results, the direction of the effect is consistent across studies (12 out of the 15 included in the MA showed statistically significant increased risks) and it did not allow to make a downgrading of evidence. Justification for an upgrading of evidence is the statistically significant increased risk of childhood leukemia recorded when combining the 8 high quality studies and the robustness of the results. Existing biological knowledge with regards to OP and PYR is consistent with an association with an increased risk of leukemia among children. However, the existing data are too scarce to imply causality. Based on the available data, the overall quality of evidence must be considered as moderate to low.

5. Conclusion

Inclusion of new studies in the present systematic review and MA confirms the significant association between residential/household/domestic exposure to pesticides and childhood leukemia, already observed in earlier MAs. Although efforts were made to improve exposure assessment (e.g. by measuring urinary metabolite levels of specific pesticides) or disease classification (ALL immunophenotype and cytogenetic classification), these parameters remain major weaknesses in most original studies, and prevent causality establishment. The overall quality of existing evidence appears moderate to low. This level could be upgraded by the inclusion of large epidemiologic studies, using a better exposure assessment and disease description and ideally incorporating genetic and molecular exploration to allow assessment of gene-environment interactions. In view of the low incidence of childhood leukemia, this will require a very large international effort to reach sufficient statistical power. Pending such studies and in spite of the remaining uncertainties and limitations, reducing household exposure to pesticides is desirable whenever possible. In addition to childhood exposure, prenatal maternal exposure should certainly receive more attention than it has had so far.

Acknowledgements

This study was funded by "The French National Research Program for Environmental and Occupational Health of Anses with the support of the Cancer TMOI of the French National Alliance for Life and Health Sciences (AVIESAN) (2014/1/026)". The funding source had no involvement in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ijheh.2018.08.004.

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