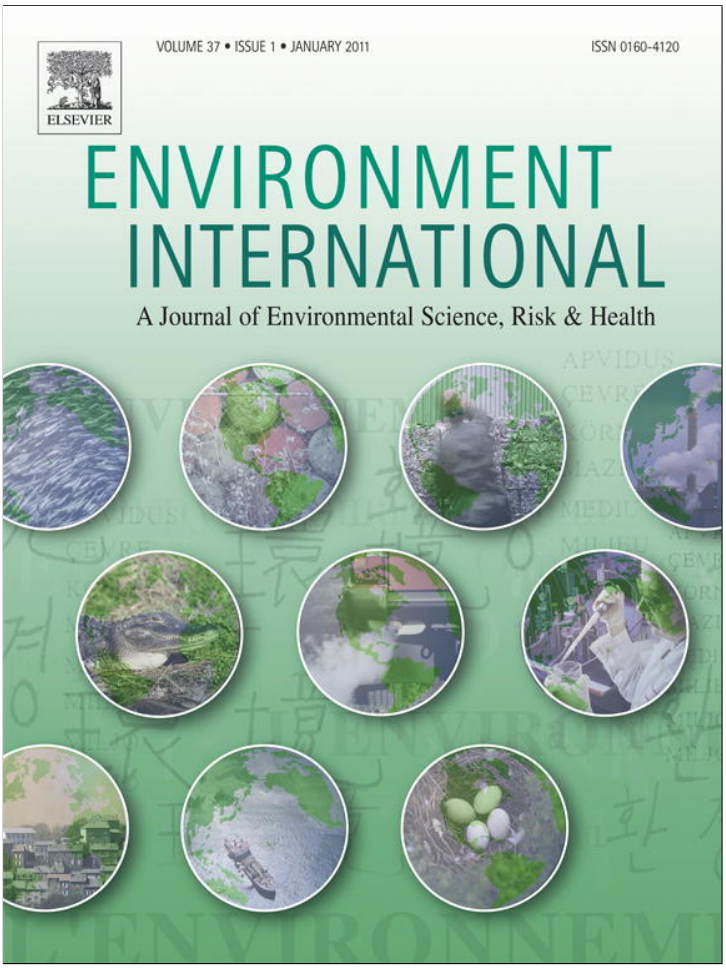

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Review

Residential exposure to pesticides and childhood leukaemia: A systematic review and meta-analysis

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ABSTRACT

Objective: To conduct a systematic review of published studies on the association between residential/household/domestic exposure to pesticides and childhood leukaemia, and to provide a quantitative estimate of the risk.

Methods: Publications in English were searched in MEDLINE (1966–31 December 2009) and from the reference list of identified publications. Extraction of relative risk (RR) estimates was performed independently by 2 authors using predefined inclusion criteria. Meta-rate ratio estimates (mRR) were calculated according to fixed and random-effect models. Separate analyses were conducted after stratification for exposure time windows, residential exposure location, biocide category and type of leukaemia.

Results: RR estimates were extracted from 13 case-control studies published between 1987 and 2009. Statistically significant associations with childhood leukaemia were observed when combining all studies (mRR: 1.74, 95% CI: 1.37–2.21). Exposure during and after pregnancy was positively associated with childhood leukaemia, with the strongest risk for exposure during pregnancy (mRR: 2.19, 95% CI: 1.92–2.50). Other stratifications showed the greatest risk estimates for indoor exposure (mRR: 1.74, 95% CI: 1.45–2.09), for exposure to insecticides (mRR: 1.73, 95% CI: 1.33–2.26) as well as for acute non-lymphocytic leukaemia (ANLL) (mRR: 2.30, 95% CI: 1.53–3.45). Outdoor exposure and exposure of children to herbicides (after pregnancy) were not significantly associated with childhood leukaemia (mRR: 1.21, 95% CI: 0.97–1.52; mRR: 1.16, 95% CI: 0.76–1.76, respectively).

Conclusions: Our findings support the assumption that residential pesticide exposure may be a contributing risk factor for childhood leukaemia but available data were too scarce for causality ascertainment. It may be opportune to consider preventive actions, including educational measures, to decrease the use of pesticides for residential purposes and particularly the use of indoor insecticides during pregnancy.

Contents

Abbreviations: AL, acute leukaemia; ALL, acute lymphocytic leukaemia; AML, acute myelogenous leukaemia; ANLL, acute non-lymphocytic leukaemia; CI, confidence interval; CLL, chronic lymphocytic leukaemia; CML, chronic myeloid leukaemia; MA, meta-analysis; mRR, meta-rate ratio estimate; OR, odds ratio; RR, relative risk; UI, uncertainty interval.

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1. Introduction

For years, pesticides have been widely used against insects, fungi, rodents, noxious weeds, etc. that can damage crops, property and human health. As with any biologically active agents, pesticides may, however, have unwanted side-effects, including cancer.

Children can be exposed to pesticides from various sources at different levels than adults under the same exposure scenario.

The first possible source of exposure to pesticides in childhood is indirect contamination from parental occupational exposure. Children can also be directly exposed to pesticides from indoor uses (in homes, schools, and other buildings), from outdoor uses (garden, playing areas/public lands, agricultural application drift, overspray or off-gassing), through contaminated food and drinking water, by handling treated or contaminated pets or others (e.g. through the use of insecticidal shampoos for lice infestation) (Zahm and Ward, 1998).

Children may be especially vulnerable to adverse health effects of pesticides due to both developmental (physiological) and behavioural factors that can increase the dose and toxicity as compared with adults who live in the same environment (Bearer, 1995; Bruckner and Weil, 1999; Karr et al., 2007; Moya et al., 2004). Air concentrations of pesticides have been found to be higher closer to the floor (Fenske et al., 2000). As children are low to the ground, they may have greater exposure to volatile pesticide vapours. Their metabolism is also significantly different from that in adults, resulting in different levels of toxic metabolites in foetus and young children compared with adults (Garry, 2004; Weiss et al., 2004). Their immune system is also less mature.

It has long been recognised that childhood leukaemia is not a homogeneous disease. Acute leukaemia deriving from the lymphocytic or from the myeloid lineage are by far the most frequently observed among children. The most common type is acute lymphocytic (or lymphoblastic or lymphoïd) leukaemia (ALL) which accounts for 75–80% of all cases of childhood leukaemia. Acute myeloïd (myelocytic, myelogenous or non lymphoblastic) leukaemia (AML), also termed acute non lymphoblastic leukaemia (ANLL), is less frequent (about 20%). The chronic forms, chronic myeloïd leukaemia (CML) and chronic lymphocytic leukaemia (CLL), are rarely seen during childhood (Belson et al., 2007; Onciu and Pui, 2006). This major morphological division is supplemented by the identification of a range of subsets based on gene expression, antigens that delineate cell type or differentiation status, and chromosomal and molecular abnormalities. Leukaemia is a clonal disease (originating in a single cell) evolving by the accrual of mutations within a clone. There is now compelling evidence that the first or initiating event in leukaemia is a chromosome translocation occurring during foetal development but one or more additional postnatal genetic alterations are needed for leukaemia development (Greaves, 2002).

The aetiology of childhood leukaemia remains largely unknown. The difficulty arises from the fact that paediatric leukaemias, like most cancers, have multifactorial aetiologies involving the interaction between various aspects originating from the environment as well as human genetics. In addition, the investigation of childhood leukaemia requires cognizance of the timing of exposure, regardless of its environmental and molecular origins (Buffler et al., 2005). Epidemiological studies on acute leukaemia in children have examined possible risk factors including genetic, infectious and environmental factors (e.g., ionizing radiation, non-ionizing radiation, electromagnetic fields, cigarette smoking, alcohol consumption, hydrocarbons, and pesticides). So far ionizing radiation has been the most significantly linked with either ALL or AML. The strongest evidence of an association with AML has been found for benzene and cytotoxics (alkylators and topoisomerase II inhibitors). Most other factors have been weakly or inconsistently associated with either forms of childhood leukaemia (Belson et al., 2007; Eden, 2010; Linet et al., 2003). Among environmental chemicals, pesticides have been specifically scrutinized. There is growing evidence in support of an association between pesticides exposure and childhood leukaemia. Most of the studies evaluating exposure to household pesticides suggest that an increased risk is associated with *in utero* and postnatal pesticide exposures, although the subtype of leukaemia, definition of exposure, and exposure period at risk differ among these studies (Buffler et al., 2005).

Several literature reviews on pesticides exposure and childhood cancers have been published recently (Infante-Rivard and Weichenthal, 2007; Metayer and Buffler, 2008; Nasterlack, 2006, 2007). These authors considered that investigating in the acquisition and critical review of exposure information was a crucial step for establishing causal association. Suggestions for future work on chemical risk factors and childhood leukaemia included the need of pooling data and analyses as well as carrying out in-depth reviews of studies with the goal of understanding the reasons for discrepant results (Infante-Rivard, 2008). In the last months, systematic reviews and meta-analyses have been conducted with regard to childhood leukaemia and parental occupational exposure to pesticides (Van Maele-Fabry et al., 2010; Wigle et al., 2009). Both meta-analyses concluded that the strongest evidence of an increased risk of childhood leukaemia comes from maternal occupational exposure to pesticides, the associations with paternal exposure being weaker and less consistent.

The purpose of the present study is to perform a systematic review and meta-analysis of published studies that have examined the association between residential exposure to pesticides and leukaemia among children with the aim to enhance our understanding of the potential involvement of such exposure in the aetiology of childhood leukaemia. To this end, our review focuses on several exposure issues

distinguishing the sources of pesticide exposure (indoor and outdoor use of pesticides) as well as the critical exposure windows including prenatal and postnatal exposures. A biocide category-specific approach is also followed in an attempt to identify whether specific category(ies) is(are) predominantly involved. Finally, as a common cause for all types and subtypes of childhood leukaemia is highly unlikely (Rossig and Juergens, 2008), an attempt is made to assess the results according to the type of leukaemia.

2. Materials and methods

2.1. Study identification and selection

2.1.1. Study identification

An electronic search on PubMed (National Library of Medicine, Bethesda, MD) was conducted for the period 1966 to 31 December 2009. Various combinations of the following key words were used: pesticide, biocide, insecticide, fungicide, herbicide, rodenticide, pets insecticides, (professional) pest control, environmental exposure, environmental pollutants, child, children, childhood, infant, newborn, preschool child, adolescent, youth, teenager, leukaemia, myeloid, myeloblastic, myelogenous, lymphoid, lymphoblastic, lymphocytic, chronic, acute, granulocytic, hematologic neoplasm, residential, indoor, outdoor, household, domestic with no restriction of publication type or publication date. This was supplemented by the scanning of recent articles in relevant journals to identify other potential articles. Finally, the reference lists of the relevant publications identified were checked for additional studies.

2.1.2. Inclusion and exclusion criteria

A study was considered eligible for further review if (1) it referred to children exposure to pesticides from residential (or household or domestic) use (indoor or outdoor), (2) if the outcome included (subtypes of) leukaemia (myeloid, lymphoid) and (3) if the study used a cohort or a case-control design. Excluded studies were those published in a non-English language, those that were not published in the open literature in peer-reviewed journals, those that did not report original results (reviews, meta-analyses, case-reports, comments, letters, editorials, and abstracts), experimental studies and ecological studies. Studies focusing only on genetic data as well as studies that clearly examined a specific cancer type other than leukaemia or that combined leukaemia data with other specific cancer types were not included. Studies dealing with non domestic exposure, e.g. exposure resulting from agricultural application drift, were not considered.

2.1.3. Study selection

As selection or rejection of articles does not require a difficult judgement, study selection was performed by a single reviewer (GVMF). The process for selecting studies (screening, determining eligibility, including in the systematic review and in the meta-analysis) was based on the PRISMA statement for reporting systematic reviews and meta-analyses proposed by Liberati et al. (2009). The screening step was performed by evaluating the titles and abstracts of the studies identified by the electronic searches. The full text of potentially relevant studies was then examined and the eligibility criteria were applied to select the included studies. Were excluded 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, those studies with adults or combining adults and children with no separate reporting of children's data, studies that combined leukaemia data with other specific cancer types, studies reporting data for exposure resulting from proximity to agricultural pesticide applications as well as studies focusing on a specific paediatric population (e.g. children with Down's syndrome). Among the studies included in the qualitative synthesis, those providing insufficient data to determine an estimator of relative risk for childhood leukaemia and its confidence interval as well as studies providing no data on exposure to pesticides (or pesticide groups) but to chemical family or brand name were excluded from the meta-analysis.

2.2. Data extraction

A structured abstract was derived from each eligible study identified. Two authors (GVMF and ACL) read the reports and independently extracted and tabulated the most relevant RR estimators, with their 95% CIs. The results of this exercise were compared between the authors and consensus was obtained before the meta-analysis.

The most relevant results were combined including the widest exposure time window, the broadest and highest pesticide exposure category and all types of leukaemia data. Where such overall results were not available, indoor rather than outdoor values and before birth exposure (before conception and during pregnancy) rather than after pregnancy data were used. The data were also included in stratified meta-analyses by:

1) Exposure time windows
   - During pregnancy
   - After pregnancy (childhood)
   - Others
2) Exposure location and exposure windows
   - Indoor exposure
     - All studies
     - Pregnancy
     - Childhood
   - Outdoor exposure
     - All studies
     - Pregnancy
     - Childhood
   - Indoor and outdoor exposure
     - All studies
     - Pregnancy
     - Childhood
3) Specific exposures
   - Pets insecticides
   - Professional pest control
4) Biocide category and exposure windows
   - Insecticides
     - All studies
     - Pregnancy
     - Childhood
   - Herbicides
     - All studies
     - Pregnancy
     - Childhood
   - Fungicides
     - All studies
5) Leukaemia type and biocide category and exposure windows:
   - ANLL
     - All studies
     - Insecticides
       Pregnancy
   - ALL
     - All studies
     - Insecticides
       All studies
       Pregnancy
       Childhood
     - Herbicides
       All studies
       Pregnancy
       Childhood

2.3. Data analysis

2.3.1. Evaluation of heterogeneity

As the conventional statistical approach (chi-squared test, the Cochran's Q) to evaluate heterogeneity has low power when there are few studies (Hardy and Thompson, 1998) and as meta-analyses often include small numbers of studies, the I^2 statistic proposed by Higgins and Thompson (2002), Higgins et al. (2003) is preferable. This statistic was described in details in our companion study (Van Maele-Fabry et al., 2010). The advantages of this measure of inconsistency are that it does not inherently depend on the number of studies and that it is accompanied by an uncertainty interval.

2.3.2. Statistical pooling

When there was little variation between studies ($I^2 \leq 25\%$), meta-analyses were performed by computing RR estimators and CIs using a fixed model which assumes that results across studies differ only by sampling error (using the inverse variance statistical method); for more details, see our companion study (Van Maele-Fabry et al., 2010).

When data were heterogeneous ($I^2 > 25\%$) or if there was reason to believe that publication bias existed, the random effects model was more appropriate. Under this model, the point estimate of the pooled effect measure and its CI incorporate the additional variability due to between-study variance (τ^2). Random effects models were applied using the method described by DerSimonian and Laird (1986). Potential sources of heterogeneity were evaluated by subset analysis.

The meta-analyses including all studies for maternal, parental and childhood exposure to indoor pesticides as well as to outdoor pesticides were illustrated by forest plots as detailed in Van Maele-Fabry et al. (2010).

2.3.3. Publication bias

Potential publication bias due to study size was explored by plotting the natural logarithm of the estimate of RR (ln RR) versus the inverse of standard error (1/SE). Funnel plot asymmetry, which can result from the non publication of small studies with negative results, was tested using the linear regression method suggested by Egger et al. (1997). Other factors such as differences in study quality or study heterogeneity could also produce asymmetry in funnel plots.

2.3.4. Sensitivity analyses

To determine whether some of the decisions made had a major effect on the results of the review and to determine how robust the findings are, we conducted sensitivity analyses in the MA of all studies including (a) deletion of studies reporting extreme RR estimators values (Lowengart et al., 1987; Spix et al., 2009), (b) deletion of studies reporting extreme precision values: % weight>25 (Rudant et al., 2007) and % weight<2 (Alexander et al., 2001; Infante-Rivard et al., 1999; Lowengart et al., 1987), (c) deletion of the study reporting data from occupational and non-occupational exposure to pesticides combined (Alexander et al., 2001) and (d) performing the MA using fixed and random effects methods.

3. Results

3.1. Literature selection and study characteristics

More than 1500 articles were retrieved from MEDLINE and hand searching in the reference lists of the relevant publications. We reduced these to a list of 261 potentially relevant studies. The majority of these studies (N=240) were excluded because they were not in English (N=16), were of a design other than case-control or cohort (N=114), concerned occupational exposure (N=27), dealt with risk assessment, exposure assessment or methodology (N=30), dealt with data for teenagers mixed with data for adults (N=14) or with genetic data (N=8), or did not report data with regard to pesticides or leukaemia (N=31). After this screening process based essentially on titles and abstracts, we retained 21 eligible studies for further evaluation. Among these studies, 8 were excluded: three studies were excluded because they provided insufficient data to determine an estimator of relative risk (RR) for childhood leukaemia and its confidence interval (Buckley et al., 1994, 2000; Schwartzbaum et al., 1991); one study reported leukaemia data combined with other specific cancer types (such as lymphoma) and concerned a population combining children and adults (Mulder et al., 1994); one study focused on a specific paediatric population (Down's syndrome cases only) (Alderton et al., 2006); one study reported data on individual (specific) pesticides only (Ward et al., 2009) and one on environmental (e.g. pesticides use for railways and parks maintenance) and not residential exposure (Deschamps and Band, 1993) and finally, a methodological study (analysing the best control group for a case-control study for a severe disease) used data previously reported (Infante-Rivard, 2003). The 13 remaining case-control studies were included in the present analyses. No relevant cohort study was located.

Table 1 provides summary data from the 13 case-control studies used in this analysis, including reference and location of the studies, upper age limit of the children, source of exposure data and exposure category, the exposed person, the period of exposure considered, the leukaemia type, the number of cases and controls and the estimator of relative risk. The data reported by each author varied greatly. As an example, the periods of exposure considered covered 4 defined windows of exposure: before pregnancy (n=1), during pregnancy (n=8), after pregnancy (n=6), and others (n=6). The "before pregnancy" window included parental exposure 3 months before pregnancy (Ma et al., 2002); the majority of studies included in the "during pregnancy" window concerned maternal exposure during the total duration of pregnancy, except Leiss and Savitz (1995) who only took into account the last three months of pregnancy, Lowengart et al. (1987) who reported data on paternal exposure during pregnancy and Ma et al. (2002) taking into account parental exposure. Three studies of the "after pregnancy" window reported data on exposure from birth to diagnosis (Infante-Rivard et al., 1999; Meinert et al., 2000; Menegaux et al., 2006), two on exposure during year 1 after birth (Buckley et al., 1989; Ma et al., 2002) and Leiss and Savitz (1995) considered exposure from birth to 2 years prior to diagnosis and from 2 years prior to diagnosis through diagnosis. The last window of exposure includes less clearly defined exposure windows (Lowengart et al., 1987: exposure during pregnancy or nursing; Spix et al., 2009: since conception) or longer durations of exposure: from 1 month before pregnancy to the end of pregnancy (Infante-Rivard et al., 1999), from 3 months before pregnancy to 3 years old (Ma et al., 2002), from 2 years before birth up to diagnosis (Meinert et al., 1996) and at any time from 1 year before birth through the first 3 years of life (Urayama et al., 2007).

3.2. Data synthesis

3.2.1. Meta-analyses

Table 2 summarises the results of the different meta-analyses as well as the assessment of inconsistency (heterogeneity). When the main data of all studies were combined, a statistically significant association with childhood leukaemia was observed (mRR: 1.74, 95% CI: 1.37–2.21). A forest plot of the 13 studies is shown in Fig. 1. One study contributed more than 25% of the total weight (Rudant et al., 2007, weight=34.9%). When combining the main data of all studies, strong evidence of heterogeneity (I^2 of 73%) was observed, arguing against an overall meta-analysis of the data. Further analyses were therefore carried out to identify sources of heterogeneity combining studies according to different stratification variables.

Meta-rate ratios were calculated after stratification of the studies according to the critical exposure window (during, after pregnancy, and others), residential exposure location (indoor, outdoor, indoor + outdoor), specific exposure (pets' insecticides, professional pest control), as well as biocide category (insecticides, herbicides, and fungicides) and type of leukaemia (ALL and ANLL). The studies included in these meta-analyses are reported at the bottom of Table 2.

Stratification by windows of exposure strongly reduced heterogeneity and inconsistency among the results for all windows except "others". Statistically significant increased meta-rate ratios were observed for the windows of exposure "during pregnancy" (mRR: 2.19; 95% CI: 1.92–2.50) and "after pregnancy (childhood)" (mRR: 1.65; 95% CI: 1.33–2.05).

The stratification of studies according to the residential exposure location showed statistically significant increased risks of childhood leukaemia for all studies reporting indoor, outdoor or indoor+outdoor exposures but did not strongly reduce heterogeneity among studies. Additional substratification by exposure time window yielded the highest statistically significant increased meta-RR for each exposure location during pregnancy (1.96, 1.51 and 2.18 for indoor, outdoor and indoor+outdoor exposures, respectively) without evidence of heterogeneity between studies (I^2 of 0%). Results were less consistent for childhood exposure: statistically significant increased risks were observed after indoor and indoor+outdoor exposures but not after outdoor exposure (mRR: 1.21; 95% CI: 0.97–1.52; I^2 of 45%). No statistically significant increased risk of childhood leukaemia was associated for exposure to pets' insecticides or for professional pest control.

Stratification by biocide category showed statistically significant increased risks for all groups of studies reporting exposure to insecticides. No significantly increased risk was observed after combining studies reporting data following fungicide exposure but inconsistency in the study results was observed (I^2 of 66%). Data on exposure to herbicides were less consistent: statistically significant increased risks were observed after combining all studies and after combining those reporting exposure during pregnancy but non statistically significant increased risks were observed when studies reporting data on exposure during childhood were combined.

Stratification by type of leukaemia showed increased meta-rate ratios with a statistical significance for each group (ANLL: mRR=2.30, 95% CI: 1.53–3.45 and ALL:

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

Reference Location (Upper age limit)	Source of exposure data Exposure category	Exposure	Period of exposure considered	[Leukaemia type] Number of cases/controls	Estimator of relative risk: OR (95% CI)
Alexander et al., 2001; International (Europe, Middle East, Asia, South America) (<18 months)	Questionnaire: mothers' interviews			[AL]	
	–Pesticides	–Maternal	–During pregnancy	–15ca/10co	–3.67 (1.54–8.74)
	–Insectides (mosquitocides)			–7ca/3co	–5.14 (1.27–20.85)
				[ALL]	
	–Pesticides			–NR	–2.53 (0.71–8.97)
	–Insectides (mosquitocides)			–NR	
				[AML]	–4.30 (0.66–28.08)
	–Pesticides			–NR	–5.08 (1.84–14.04)
	–Insectides (mosquitocides) ("exposed" *vs* "unexposed")			–NR	–7.82 (1.73–35.39)
Buckley et al., 1989; USA, Canada (<18 yrs)	Questionnaire: parents' phone interviews			[ANLL]	
	–Household exposure to pesticides: (including garden or agricultural sprays, professional pest treatment) (*data on subcategories according to frequency of use [<1/wk, 1–2/wk, most days] available*)	–Maternal	–During pregnancy	–70ca/55co*	–1.85 (1.16–2.99)*
		–Child	–At least 1 yr after birth	–67ca/45co	–2.51 (1.53–4.11)*
Infante-Rivard et al., 1999; Québec, Canada (0–9 yrs)	Questionnaire: parents' phone interviews.			[ALL]	
	–Herbicides (used in garden, yard and interior plants)	–Maternal	–From 1 mo before pregnancy to birth	–118ca/71co	–1.84 (1.32–2.57)
		–Child	–From birth to diagnosis	–178ca/144co	–1.41 (1.06–1.86)
	–Insecticides used in the home	–Maternal	–From 1 mo before pregnancy to birth	–96ca/67co	–1.59 (1.11–2.26)
		–Child	–From birth to diagnosis	–137ca/87co	–2.99 (1.42–2.82)
	–Professional pest control (>5 times)	–Maternal + Child	–From 1 yr before pregnancy to diagnosis	–15ca/7co	–2.35 (0.89–6.17)
	–Insecticides and rodenticides indoor (including pet treatment, professional pest treatment; ≥4 agents used)	–Maternal	–From 1 mo before pregnancy to birth	–NR	–2.17 (0.66–7.09)
		–Child	–From birth to diagnosis	–NR	–2.08 (0.78–5.52)
	–Pesticides (used in garden, yard and interior plants; ≥4 agents used) (*data on subcategories according to frequency of use [0, 1–5 times, >5 times] and number of agents used [≥1, ≥2, ≥3, ≥4] available*)	–Maternal	–From 1 mo before pregnancy to birth	–NR	–1.98 (0.59–6.62)
		–Child	–From birth to diagnosis	–NR	–2.27 (0.93–5.55)
Leiss and Savitz, 1995; Denver, Colorado, USA (<15 yrs)	Questionnaire: parents' interviews			[Leukaemia]	
	–Home pest extermination	–Maternal	–3rd trimester of pregnancy	–4ca/27co	–0.4 (0.1–1.2)
		–Child	–From birth to 2 yrs before diagnosis	–6ca/45co	–0.3 (0.1–0.8)
			–From 2 yrs before diagnosis to diagnosis	–7ca/22co	–0.9 (0.5–1.4)
	–Yard treatment (with insecticides or herbicides)	–Maternal	–3rd trimester of pregnancy	–27ca/79co	–1.1 (0.6–1.9)
		–Child	–From birth to 2 yrs before diagnosis	–36ca/118co	–0.9 (0.5–1.8)
			–From 2 yrs before diagnosis to diagnosis	–33ca/98co	–1.1 (0.8–1.5)
	–Pest strips (insecticides) (*"any use" vs "no use" or "ever used" vs "never used"*)	–Maternal	–3rd trimester of pregnancy	–21ca/26co	–3.0 (1.6–5.7)
		–Child	–From birth to 2 yrs before diagnosis	–21ca/47co	–1.7 (1.2–2.4)
			–From 2 yrs before diagnosis to diagnosis	–18ca/37co	–2.6 (1.7–3.9)
Lowengart et al., 1987; Los Angeles County, California, USA (<11 yrs)	Questionnaire: parents' phone interviews			[Leukaemia]	
	–Household pesticides [≥1/wk]	–Maternal	–During pregnancy/nursing	–13/4#	–3.2 (1.04–9.78)*
		–Paternal	–During pregnancy	–12/3#	–4.0 (1.13–14.21)*
		–Either		–19/5#	–3.8 (1.37–13.02)
	–Garden sprays ("herbicides and pesticides") [≥1/mo]	–Maternal	–During pregnancy/nursing	–9/1#	–9.0 (1.14–71.23)*
		–Paternal	–During pregnancy	–5/1#	–5.0 (0.59–42.79)*
		–Either		–13/2#	–6.5 (1.47–59.33)
Ma et al., 2002; Northern California, USA (0–14 years)	Questionnaire: primary care givers (usually mothers), face to face interviews			[Leukaemia]	
	–Professional pest control	–Parents	–3 mo before pregnancy	–16ca/12co	–1.7 (0.7–3.9)
			–During pregnancy	–22ca/14co	–2.2 (1.0–4.8)
		–Child	–Year 1	–25ca/16co	–2.3 (1.1–4.9)
		–P + C	–From 3 mo before pregnancy to 3 yrs	–39ca/25co	–2.8 (1.4–5.7)

	–Insecticides (including insect repellents and various products to control ants, flies, cockroaches, spiders, termites, plant/tree insects but excluding flea control products)	–Parents	–3 mo before pregnancy	–63ca/49co	–1.8 (1.1–3.1)
			–During pregnancy	–79ca/56co	–2.1 (1.3–3.5)
		–Child	–Year 1	–90ca/76co	–1.7 (1.0–2.9)
		–P + C	–From 3 mo before pregnancy to 3 yrs	–93ca/80co	–2.1 (1.1–4.3)
	–Flea control products (indoor foggers, flea collars, flea soaps or shampoos, sprays, dusts, or powders for fleas);	–Parents	–3 mo before pregnancy	–26ca/32co	–0.9 (0.5–1.7)
			–During pregnancy	–27ca/34co	–0.8 (0.4–1.4)
		–Child	–Year 1	–34ca/42co	–0.8 (0.5–1.4)
		–P + C	–From 3 mo before pregnancy to 3 yrs	–40ca/45co	–0.9 (0.5–1.6)
	–Herbicides (professional lawn service and use of weed control products)	–Parents	–3 mo before pregnancy	–31ca/23co	–1.8 (0.9–3.5)
			–During pregnancy	–34ca/29co	–1.6 (0.9–3.0)
		–Child	–Year 1	–35ca/50co	–0.7 (0.4–1.2)
		–P + C	–From 3 mo before pregnancy to 3 yrs	–38ca/41co	–1.0 (0.6–1.8)
	–Indoor pesticides	–Parents	–During pregnancy	–NR	–2.2 (1.3–3.6)
		–Child	–Year 1	–90ca/78co	–1.6 (1.0–2.7)
		–P + C	–From 3 mo before pregnancy to 3 yrs	–NR	–1.8 (1.0–3.4)
	–Outdoor pesticides	–Child	–Year 1	–37ca/37co [ALL]	–1.2 (0.7–2.2)
	–Professional pest control	–Parents	–3 mo before pregnancy	–15ca/10co	–1.9 (0.7–4.7)
			–During pregnancy	–20ca/12co	–2.3 (0.9–5.4)
		–Child	–Year 1	–22ca/15co	–2.1 (1.0–4.7)
		–P + C	–From 3 mo before pregnancy to 3 yrs	–36ca/24co	–2.6 (1.2–5.4)
	–Insecticides	–Parents	–3 mo before pregnancy	–53ca/42co	–1.7 (1.0–3.1)
			–During pregnancy	–68ca/46co	–2.3 (1.3–4.0)
		–Child	–Year 1	–75ca/63co	–1.7 (1.0–2.9)
		–P + C	–From 3 mo before pregnancy to 3 yrs	–80ca/68co	–2.2 (1.0–4.6)
	–Flea control products	–Parents	–3 mo before pregnancy	–22ca/29co	–0.8 (0.4–1.6)
			–During pregnancy	–22ca/30co	–0.7 (0.4–1.4)
		–Child	–Year 1	–31ca/38co	–0.9 (0.5–1.6)
		–P + C	–From 3 mo before pregnancy to 3 yrs	–36ca/39co	–1.0 (0.5–1.8)
	–Herbicides	–Parents	–3 mo before pregnancy	–24ca/18co	–1.6 (0.8–3.3)
			–During pregnancy	–30ca/23co	–1.8 (0.9–3.5)
		–Child	–Year 1	–32ca/43co	–0.8 (0.4–1.4)
		–P + C	–From 3 mo before pregnancy to 3 yrs	–35ca/37co	–1.0 (0.6–1.8)
	Outdoor pesticides (*score assigned according to frequency of use: 0, 1–4 times, ≥5 times*)	–Parents	–During pregnancy	–NR	–0.95 (0.5–1.8)*
Meinert et al., 1996; Northern Germany (<15 yrs)	Questionnaire: parents' mailed and phone interviews			[Leukaemia]	
	–Pesticide in gardens	–Family	–From 2 yrs before birth to diagnosis	–20ca/10co	–2.52 (1.03–6.14)
	–Indoor pest extermination by parents			–37ca/54co	–0.87 (0.54–1.41)*
	–Professional indoor pest extermination ("yes" *vs* "no")			–3ca/4co	–1.00 (0.22–4.54)*
Meinert et al., 2000; West Germany (<15 yrs)	Questionnaire: parents' mailed and phone interviews			[Leukaemia]	
	–Pesticide in gardens ("yes" *vs* "no")	–Child	–From birth to diagnosis	–164ca/371co	–1.0 (0.8–1.2)
	–Household insecticides by parents (>1/yr)			–90ca/162co	–1.2 (0.9–1.6)
	–Professional indoor pest extermination ("yes" *vs* "no") (*Household insecticides: other categories of frequency of use available [1/yr, 2–5/yr, 6–10/yr, >10/yr]*)			–25ca/42co	–1.3 (0.8–2.3)
Menegaux et al., 2006; Lille, Lyon, Nancy, Paris; France (<15 yrs)	Questionnaire: parents' face to face interviews			[AL]	
	–Home insecticides	–Maternal	–During pregnancy	–92ca/60co	–1.8 (1.2–2.8)
		–Child	–From birth to diagnosis	–111ca/84co	–1.7 (1.1–2.4)
	–Garden pesticides (insecticides, herbicides and fungicides) used by the mother	–Maternal	–During pregnancy	–14ca/7co	–2.5 (0.8–7.2)
		–Child	–From birth to diagnosis	–70ca/45co	–1.7 (1.1–2.7)
	–Insecticides	–Maternal	–During pregnancy	–9ca/4co	–1.9 (0.6–6.5)
		–Child	–From birth to diagnosis	–47ca/20co	–2.4 (1.3–4.3)
	–Herbicides	–Maternal	–During pregnancy	–6ca/3co	–5.9 (0.7–52)
		–Child	–From birth to diagnosis	–40ca/31co	–1.4 (0.8–2.4)
	–Fungicides	–Maternal	–During pregnancy	–3ca/0co	–NR
		–Child	–From birth to diagnosis	–17ca/8co	–2.5 (1.0–6.2)
	–Pediculosis treatment ("ever" *vs* "never" use)	–Child	–From birth to diagnosis	–70ca/60co	–1.9 (1.1–3.2)

(continued on next page)

Table 1 (*continued*)

Reference Location (Upper age limit)	Source of exposure data Exposure category	Exposure	Period of exposure considered	[Leukaemia type] Number of cases/controls	Estimator of relative risk: OR (95% CI)
Pombo-de-Oliveira et al., 2006; Brazil (10 states) (≤21 months)	Questionnaire: mothers' face to face interviews –Pesticide use at home (*no indication concerning exposure criteria*)	–Maternal	–During pregnancy	[AL] –91ca/119co	–2.18 (1.53–2.95)°
Rudant et al., 2007; France (<15 yrs)	Questionnaire: mothers' phone interviews –Household pesticide use	–Maternal	–During pregnancy	[AL] –401ca/620co	–2.2 (1.8–2.6)
		–Paternal	–During pregnancy or childhood	–473ca/942co	–1.5 (1.2–1.8)
	–Insecticides	–Maternal	–During pregnancy	–383ca/590co	–2.1 (1.7–2.5)
		–Paternal	–During pregnancy or childhood	–389 ca/732co	–1.4 (1.2–1.7)
	–Home	–Maternal	–During pregnancy	–324ca/521co	–1.9 (1.6–2.3)
		–Paternal	–During pregnancy or childhood	–304ca/530co	–1.5 (1.3–1.8)
	–Pets	–Maternal	–During pregnancy	–156ca/204co	–2.0 (1.5–2.5)
		–Paternal	–During pregnancy or childhood	–175ca/323co	–1.3 (1.0–1.6)
	–Garden crops	–Maternal	–During pregnancy	–29ca/48co	–1.5 (1.0–2.5)
		–Paternal	–During pregnancy or childhood	–103ca/245co	–1.0 (0.7–1.3)
	–Herbicides	–Maternal	–During pregnancy	–53ca/92co	–1.5 (1.0–2.2)
		–Paternal	–During pregnancy or childhood	–318ca/685co	–1.2 (1.0–1.4)
	–Fungicides	–Maternal	–During pregnancy	–17ca/41co	–0.9 (0.5–1.7)
		–Paternal	–During pregnancy or childhood	–126ca/271co	–1.1 (0.9–1.4)
				[ALL]	
	–Any pesticide	–Maternal	–During pregnancy	–NR	–2.3 (1.9–2.8)
		–Paternal	–During pregnancy or childhood	–NR	–1.5 (1.2–1.9)
	–Insecticides	–Maternal	–During pregnancy	–NR	–2.2 (1.8–2.6)
		–Paternal	–During pregnancy or childhood	–NR	–1.5 (1.2–1.9)
	–Herbicides	–Maternal	–During pregnancy	–NR	–1.7 (1.2–2.5)
		–Paternal	–During pregnancy or childhood	–NR	–1.2 (1.0–1.5)
	–Fungicides	–Maternal	–During pregnancy	–NR	–1.1 (0.6–2.0)
		–Paternal	–During pregnancy or childhood	–NR	–1.1 (0.9–1.5)
				[AML]	
	–Any pesticide	–Maternal	–During pregnancy	–NR	–2.2 (1.4–3.3)
		–Paternal	–During pregnancy or childhood	–NR	–1.5 (0.9–2.4)
	–Insecticides	–Maternal	–During pregnancy	–NR	–2.1 (1.4–3.3)
		–Paternal	–During pregnancy or childhood	–NR	–1.3 (0.8–2.0)
	–Herbicides	–Maternal	–During pregnancy	–NR	–1.2 (0.5–2.8)
		–Paternal	–During pregnancy or childhood	–NR	–1.0 (0.7–1.7)
	–Fungicide ("ever" *vs* "never")	–Maternal	–During pregnancy	–NR	–NR
		–Paternal	–During pregnancy or childhood	–NR	–1.1 (0.6–2.0)
Spix et al., 2009; Germany (<5 yrs)	Questionnaire: mothers' phone interviews –Fungicides ("yes" vs" no")	–Family (?)	–Since conception	[Leukaemia] –29ca/95co	–0.69 (0.42–1.12)
Urayama et al., 2007; Northern and Central California, USA (<15 yrs)	Questionnaire: primary care givers' face to face interviews –Indoor insecticides (including professional pest control, insect repellents, indoor flea floggers and a variety of insect control products commonly used indoors) ("yes" *vs* "no")	–Parents + Child	–From 1 yr before birth to 3 yrs of life	[ALL] –240ca/277co	–1.65 (1.10–2.47)

Note: only available summary data with regard to leukaemia are reported in the table.
OR, odds ratio; 95% CI, 95% confidence interval; P, parents; C, child.
AL, acute leukaemia; ALL, acute lymphocytic leukaemia; ANLL, acute non-lymphocytic leukaemia; AML, acute myeloid leukaemia).
NR: information not reported; wk, week; mo, month; yr, year.
* Number of cases and/or crude OR and/or 95% CI calculated on the basis of data in paper.
# Discordant pairs (cases exposed-controls unexposed/cases unexposed-controls exposed).
° The exact upper 95% CI value (2.95 in place of 2.13 as indicated in the original paper) was obtained by corresponding with the author (Maria Pombo-de-Oliveira).

mRR = 2.17, 95% CI: 1.83–2.56) with low levels of inconsistency (I^2 of 36% and 0%, respectively). Additional substratification by biocide category and by window of exposure showed statistically significant increased risks for exposure to insecticides but not herbicides. Only exposure to herbicides during pregnancy yielded a statistically significant increased risk without evidence of heterogeneity.

3.2.2. Sensitivity analyses

Sensitivity analyses did not substantially alter the results of the MA. Exclusion of the studies with the lowest or highest estimator of RR, exclusion of the studies with the highest and lowest percentage weight and deletion of the study reporting combined data for occupational and non-occupational exposure to pesticides did not substantially modify the results (data not shown). Results of meta-analyses performed with fixed or random effects models were all similar (data not shown).

3.2.3. Funnel plot and asymmetry

Funnel plot of ln(RR) versus 1/SE for the meta-analysis including all studies for residential exposure to pesticides was constructed (Fig. 2). The visual inspection of this figure did not clearly allow us to detect asymmetry arising from a lack of small studies with low RR estimators. The statistical analysis provided by the linear regression method of Egger et al. (1997) did not yield evidence of asymmetry (intercept 0.6664; 95% CI: −3.645 to 4.978) ($p>0.2$).

4. Discussion

4.1. Summary of evidence

This systematic review and meta-analysis examined the relevant epidemiological studies reporting an association between residential exposure to pesticides and childhood leukaemia. Overall, residential use of pesticides was associated with childhood leukaemia. The increased risk was statistically significant and did not vary substantially when omitting extreme value studies (estimators of relative risk or study weight). This conclusion is consistent with the results of narrative reviews (Daniels et al., 1997; Infante-Rivard and Weichenthal, 2007; Zahm and Ward, 1998) and of an independent meta-analysis (Turner et al., 2010) published during the writing of this paper but using a slightly different approach (as will be discussed in the later part). These results support the suggestion that residential exposure to pesticides may be a potential causal factor for childhood leukaemia. However, the strong evidence of heterogeneity (I^2 of 73%) argues against an overall meta-analysis of the data. Further analyses were therefore carried out to identify sources of heterogeneity and to improve the analysis of the data available.

4.1.1. Critical windows of exposure

Stratification by exposure time windows (during and after pregnancy) strongly reduced heterogeneity. The association was stronger for exposure during pregnancy. This is in agreement with the current evidence suggesting that leukaemia results from molecular damage that may be incurred during pregnancy and may develop during infancy and childhood (for review, see Buffler et al., 2005). Many chromosomal rearrangements are associated with childhood acute leukaemias but a few predominate, including MLL-various partner genes, TEL-AML1 and AML1-ETO. The same gene rearrangements have been identified in neonatal blood spots collected at birth, providing strong evidence that many childhood leukaemias are initiated *in utero* (Wiemels et al., 1999, 2002). However, additional mutations must occur before leukaemia develops in most children. A study investigated the relationship between prenatal pesticide exposures and the AML1-ETO translocation in umbilical cord blood samples (Lafiura et al., 2007). Different pesticides (propoxur and cypermethrin) were quantitatively detected in meconium, which can provide a cumulative picture of exposure throughout the pregnancy. The AML1-ETO transcript levels in cord blood were positively correlated with propoxur concentrations in the meconium in exposed infants.

4.1.2. Exposure location and biocide category

The risk was the highest when "indoor + outdoor" exposure occurred during pregnancy as well as during childhood. Regarding exposure during pregnancy, the strongest associations were observed for indoor exposure as compared to outdoor exposure and for insecticide exposure as compared to herbicide or fungicide exposures. Data with regard to childhood exposures were less consistent and no significant increase was observed for outdoor exposure or herbicide exposure. There is probably redundancy between insecticide and indoor pesticide exposure as well as between herbicides and outdoor exposure. Results regarding indoor exposure were similar to that for insecticides and those regarding outdoor exposure were similar to what was seen for herbicides. Our results with regard to insecticide exposure during and after pregnancy (childhood) as well as with regard to herbicide exposure during and after pregnancy are in agreement with those of Turner et al. (2010).

4.1.3. Specific exposure

Available data on childhood leukaemia and use of professional pest control services as well as on the use of pet insecticides are scarce, leading to conflicting and heterogeneous results. The number of families who engaged a professional pest controller to exterminate insects was low in some studies and statistical power to detect an association is limited. As a consequence, the data of the MA focusing on specific exposure should be taken with caution.

4.1.4. Type of leukaemia

Only a limited number of studies reported data for a specified type of leukaemia, especially ANLL. In children, ANLL is substantially less common than ALL, accounting for less than 20% of leukaemia. In the present paper, the highest increased risks were observed for ANLL. These results are in contrast with those of Turner et al. (2010), reporting lower and non statistically significant meta-RR for AML following exposure during pregnancy to unspecific pesticides. The discrepancy is probably due to the non-inclusion by Turner et al. (2010) of the data by Alexander et al. (2001) and to the inclusion of the unpublished data of Steinbuch (1994). The heterogeneity between studies reported by Turner et al. (2010) for AML was high ($I^2 = 80\%$); that in our meta-analysis for ANLL is 36%. However, only three studies were available in each meta-analysis, most providing data for all leukaemia types and not for a specific type of leukaemia. As a consequence, findings should be interpreted cautiously. Substratifications of ALL data taking into account the biocide category leads to results in agreement with data reported for all types of leukaemia. As ALL is the most common form of childhood leukaemia, studies that group all types of leukaemias generally reflect ALL (Daniels et al., 1997).

4.2. Limitations

Original studies may be subject to limitations related to exposure assessment and potential sources of bias. Interpretation of the MA is constrained by the same limitations.

The major weakness of the original studies on residential pesticide exposure and childhood cancer is the crudeness of the exposure measures. Reported results are limited to broad types of pesticides. Specific pesticides were not identified in most studies, which relied primarily on parental reports about pesticide use. Only a few number of authors specified the pesticide likely to have been used for residential extermination (Alexander et al., 2001; Infante-Rivard et al., 1999; Leiss and Savitz, 1995; Ma et al., 2002). They included organophosphorous (chlorpyrifos, diazinon, dichlorvos, malathion, and cygon), carbamates (propoxur and carbaryl), organochlorines (chlordane and heptachlor), pyrethrins and piperonyl butoxide. Menegaux et al. (2006) specified pesticides (pyrethroid, lindane and malathion) that could be included in shampoos to treat pediculosis. However, no specific product could be singled out.

Recently, as recommended by Colt et al. (2004), Ward et al. (2009) used carpet dust as an alternative exposure assessment method that

allows identifying individual compounds without recall bias. They applied this methodology to examine the risk of childhood leukaemia in relation to residential exposure to persistent organochlorine chemicals, including pesticides (DDT [dichlorodiphenyltrichloroethane], DDE [dichlorodiphenyldichloroethylene], chlordane, methoxychlor and pentachlorophenol). Although no significant positive association was observed for these pesticides, this approach seems promising as positive associations were observed with PCBs (polychlorinated biphenyls).

Some authors tried to establish a dose–response-like relationship between residential pesticide exposure and childhood leukaemia using different categorizations of the frequency of pest extermination. They showed that the risk of leukaemia is increased with frequency of use of unspecified pesticides (Buckley et al., 1989; Ma et al., 2002) or of home insecticides (Infante-Rivard et al., 1999; Ma et al., 2002; Meinert et al., 2000) during pregnancy and/or during childhood. These observations provide limited additional support to the suspicion of a positive exposure–response relationship between residential pesticide exposure and childhood leukaemia.

Recall bias is a major concern in case-control studies in which questionnaire data are used to assess past exposure. A validation study conducted by Infante-Rivard and Jacques (2000) on risk factors for ALL in children showed that parental recall can be differential but the authors suggested that non-differential misclassification of exposure may be of greater concern.

The potential for selection bias in case-control studies on household exposure to pesticides and childhood leukaemia was investigated by Rudant et al. (2010). These authors found potential sources of bias in all studies (source populations that gave rise to cases and controls, probabilistic selection of subjects from the source, losses of the subjects actually selected, as examples) but none of them was observed across all studies. They concluded that overall, selection bias does not seem to explain the positive results of the studies and their analysis provides arguments strengthening the conclusions on associations reported in earlier studies.

Among the potential limitations of the present work is also the possibility for publication bias. The association observed in the meta-analysis including all studies for residential exposure to pesticides

Table 2
Meta-analyses after stratification of the case-control studies.

Stratification				Homogeneity			
	N.	mRR	95% CI	χ^2 Woolf	P-value	I^2	95% UI
Residential pesticide exposure[†]							
A. All studies (A.1)	13	**1.74**	1.37–2.21	44.538	0.124×10^{-4}	73.1	53.1–84.5
B. Exposure time windows							
(B.1) During pregnancy	9	**2.19**	1.92–2.50	4.513	0.808	0	0–37.6
(B.2) After pregnancy (childhood)	6	**1.65**	1.33–2.05	7.823	0.166	36.1	0–74.5
(B.3) Others	5	1.28	0.81–2.03	13.626	0.859×10^{-2}	70.6	25.4–88.5
C. Indoor and/or outdoor exposure							
Indoor exposure							
(C.1) All studies	12	**1.74**	1.45–2.09	24.507	0.0108	55.1	14.1–76.6
(C.2) Pregnancy	9	**1.96**	1.73–2.22	6.541	0.587	0	0–57.0
(C.3) Childhood	6	**1.84**	1.37–2.48	18.155	0.276×10^{-2}	72	36.5–88.1
Outdoor exposure							
(C.4) All studies	8	**1.47**	1.07–2.02	19.764	0.61×10^{-2}	64.6	24.4–83.4
(C.5) Pregnancy	6	**1.51**	1.10–2.09	8.155	0.148	0	0–75.6
(C.6) Childhood	5	1.21	0.97–1.52	7.306	0.121	45.3	0–79.9
Indoor + Outdoor exposure							
(C.7) All studies	6	**1.79**	1.15–2.78	21.025	0.801	76.2	46.7–89.4
(C.8) Pregnancy	5	**2.18**	1.86–2.55	1.901	0.754	0	0–56.2
(C.9) Childhood	3	**2.12**	1.52–2.96	1.132	0.568	0	0–81.6
D. Specific exposure							
(D.1) Pets insecticides	3	1.17	0.61–2.23	20.809	0.3×10^{-4}	90.4	74.6–96.4
(D.2) Professional pest Control	5	1.29	0.63–2.63	13.536	0.89×10^{-2}	70.5	24.8–88.4
E. Biocide category							
Insecticides							
(E.1) All studies	9	**1.73**	1.33–2.26	23.719	0.255×10^{-2}	66.3	31.6–83.4
(E.2) Pregnancy	6	**2.13**	1.82–2.49	3.271	0.658	0	0–61.2
(E.3) Childhood	5	**1.50**	1.25–1.79	3.849	0.427	0	0–78.4
Herbicides							
(E.4) All studies	4	**1.53**	1.10–2.13	4.964	0.175	39.6	0–79.5
(E.5) Pregnancy	4	**1.70**	1.35–2.15	1.925	0.588	0	0–761
(E.6) Childhood	3	1.16	0.76–1.76	5.149	0.0762	61.2	0–88.9
Fungicides							
(E.7) All studies	3	1.05	0.55–2.01	5.938	0.0513	66.3	0–90.3
F. Leukaemia type							
ANLL							
(F.1) All studies	3	**2.30**	1.53–3.45	3.120	0.210	35.9	0–79.5
(F.2) Insecticides, pregnancy	2	**3.13**	1.45–6.75	1.911	0.167	16.0	0–55.3
ALL							
(F.3) All studies	5	**2.17**	1.83–2.56	2.187	0.701	0	0–62.0
Insecticides							
(F.4) All studies	5	**2.11**	1.80–2.48	2.186	0.702	0	0–62.0
(F.5) Pregnancy	4	**2.22**	1.87–2.64	0.503	0.918	0	0–8.7
(F.6) Childhood	2	**1.78**	1.12–2.84	0.126	0.723	0	ND
Herbicides							
(F.7) All studies	3	1.47	0.98–2.2	5.485	0.0644	63.5	0–89.6
(F.8) Pregnancy	3	**1.78**	1.41–2.24	0.099	0.952	0	0–0
(F.9) Childhood	2	1.14	0.67–1.95	2.617	0.106	61.8	0–91.2

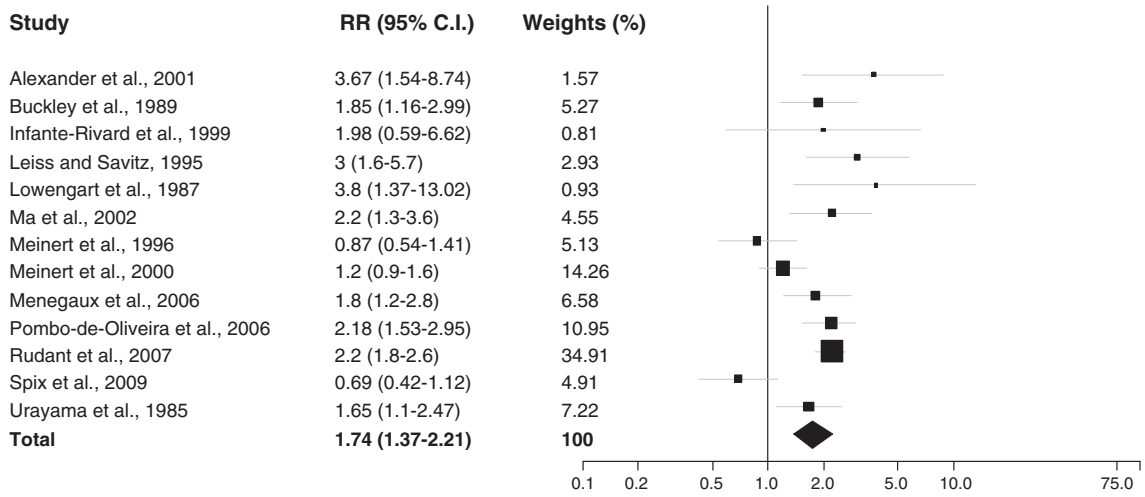

Fig. 1. Forest plot of case-control studies on childhood leukaemia following residential exposure to pesticides. *Note*. Estimators of RR and 95% confidence intervals (CIs) of case-control studies included in the meta-analysis "all studies, parental exposure priority" are presented. Each estimator was assigned a weight (w_i) equal to the inverse square of its standard error (SE): $w_i = 1/(SE)^2$.

does not appear to have been significantly influenced by publication bias. There was no clear evidence for a substantial deficit in small negative studies with effect sizes smaller than those from larger studies. However, publication bias may not be totally excluded as some data were omitted from the present analysis as a result of the study selection procedure. The impact of the exclusion of non-published studies as well as of studies published in other languages than English can be assessed as Turner et al. (2010) identified these studies for inclusion in their MA. Three unpublished studies (Davis, 1991; Dell, 2004; Steinbuch, 1994) and two studies in other languages (Fajardo-Gutierrez et al., 1993; Kishi et al., 1993) were retrieved. Rerunning our meta-analysis after including these studies slightly

Notes to Table 2:
Abbreviations: N., number of studies; mRR, meta-rate ratio; 95% CIs, 95% confidence interval; meta-rate ratios are in bold when the 95% CI do not include 1; 95% UI, 95% uncertainty interval; ND, not defined (could not be calculated).
Studies included in the meta-analyses:
(A.1) Alexander et al. (2001); Buckley et al. (1989); Infante-Rivard et al. (1999); Leiss and Savitz (1995); Lowengart et al. (1987); Ma et al. (2002); Meinert et al. (1996); Meinert et al. (2000); Menegaux et al. (2006); Pombo-de-Oliveira et al. (2006); Rudant et al. (2007); Spix et al. (2009); Urayama et al. (2007).
(B.1) Alexander et al. (2001); Buckley et al. (1989); Leiss and Savitz (1995); Lowengart et al. (1987); Ma et al. (2002); Menegaux et al. (2006); Pombo-de-Oliveira et al. (2006); Rudant et al. (2007).
(B.2) Buckley et al. (1989); Infante-Rivard et al. (1999); Leiss and Savitz (1995); Ma et al. (2002); Meinert et al. (2000); Menegaux et al. (2006).
(B.3) Infante-Rivard et al. (1999); Lowengart et al. (1987); Ma et al. (2002); Meinert et al. (1996); Spix et al. (2009); Urayama et al. (2007).
(C.1) Alexander et al. (2001); Buckley et al. (1989); Infante-Rivard et al. (1999); Leiss and Savitz (1995); Lowengart et al. (1987); Ma et al. (2002); Meinert et al. (1996); Meinert et al. (2000); Menegaux et al. (2006); Pombo-de-Oliveira et al. (2006); Rudant et al. (2007); Urayama et al. (2007).
(C.2) Alexander et al. (2001); Buckley et al. (1989); Infante-Rivard et al. (1999); Leiss and Savitz (1995); Lowengart et al. (1987); Ma et al. (2002); Menegaux et al. (2006); Pombo-de-Oliveira et al. (2006); Rudant et al. (2007).
(C.3) Buckley et al. (1989); Infante-Rivard et al. (1999); Leiss and Savitz (1995); Ma et al. (2002); Meinert et al. (2000); Menegaux et al. (2006).
(C.4) Infante-Rivard et al. (1999); Leiss and Savitz (1995); Lowengart et al. (1987); Ma et al. (2002); Meinert et al. (1996); Meinert et al. (2000); Menegaux et al. (2006); Rudant et al. (2007).
(C.5) Infante-Rivard et al. (1999); Leiss and Savitz (1995); Lowengart et al. (1987); Ma et al. (2002); Menegaux et al. (2006); Rudant et al. (2007).
(C.6) Infante-Rivard et al. (1999); Leiss and Savitz (1995); Ma et al. (2002); Meinert et al. (2000); Menegaux et al. (2006).
(C.7) Alexander et al. (2001); Buckley et al. (1989); Infante-Rivard et al. (1999); Ma et al. (2002); Rudant et al. (2007); Spix et al. (2009).
(C.8) Alexander et al. (2001); Buckley et al. (1989); Infante-Rivard et al. (1999); Ma et al. (2002); Rudant et al. (2007).
(C.9) Buckley et al. (1989); Infante-Rivard et al. (1999); Ma et al. (2002).
(D.1) Infante-Rivard et al. (1999); Ma et al. (2002); Rudant et al. (2007).
(D.2) Infante-Rivard et al. (1999); Leiss and Savitz (1995); Ma et al. (2002); Meinert et al. (1996); Meinert et al. (2000).
(E.1) Alexander et al. (2001); Infante-Rivard et al. (1999); Leiss and Savitz (1995); Ma et al. (2002); Meinert et al. (1996); Meinert et al. (2000); Menegaux et al. (2006); Rudant et al. (2007); Urayama et al. (2007).
(E.2) Alexander et al. (2001); Infante-Rivard et al. (1999); Leiss and Savitz (1995); Ma et al. (2002); Menegaux et al. (2006); Rudant et al. (2007).
(E.3) Infante-Rivard et al. (1999); Leiss and Savitz (1995); Ma et al. (2002); Meinert et al. (2000); Menegaux et al. (2006).
(E.4) Infante-Rivard et al. (1999); Ma et al. (2002); Menegaux et al. (2006); Rudant et al. (2007).
(E.5) Infante-Rivard et al. (1999); Ma et al. (2002); Menegaux et al. (2006); Rudant et al. (2007).
(E.6) Infante-Rivard et al. (1999); Ma et al. (2002); Menegaux et al. (2006).
(E.7) Menegaux et al. (2006); Rudant et al. (2007); Spix et al. (2009).
(F.1) Alexander et al. (2001); Buckley et al. (1989); Rudant et al. (2007).
(F.2) Alexander et al. (2001); Rudant et al. (2007).
(F.3) Alexander et al. (2001); Infante-Rivard et al. (1999); Ma et al. (2002); Rudant et al. (2007); Urayama et al. (2007).
(F.4) Alexander et al. (2001); Infante-Rivard et al. (1999); Ma et al. (2002); Rudant et al. (2007); Urayama et al. (2007).
(F.5) Alexander et al. (2001); Infante-Rivard et al. (1999); Ma et al. (2002); Rudant et al. (2007).
(F.6) Infante-Rivard et al. (1999); Ma et al. (2002).
(F.7) Infante-Rivard et al. (1999); Ma et al. (2002); Rudant et al. (2007).
(F.8) Infante-Rivard et al. (1999); Ma et al. (2002); Rudant et al. (2007).
(F.9) Infante-Rivard et al. (1999); Ma et al. (2002).
† Where there was no overall RR estimate reported but only data for parental and childhood exposure, separately, data following parental exposure were included; maternal exposure from 1 month before pregnancy to birth reported by Infante-Rivard et al. (1999) was assimilated to exposure during pregnancy; pets insecticides = use of pesticides on pets any time, professional pest control = homes professionally treated against pests at any time.

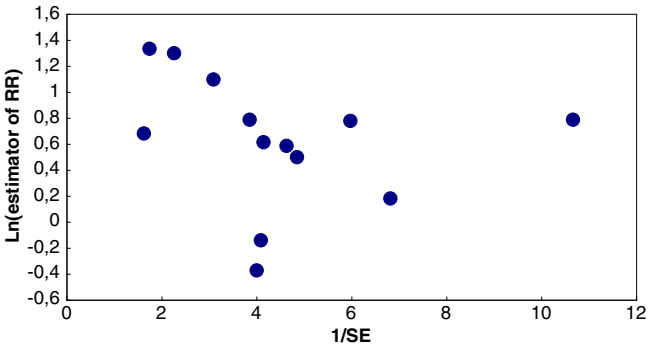

Fig. 2. Case-control studies of residential pesticide exposure and childhood leukaemia: funnel plot of natural logarithms of relative risk (RR) estimates vs the inverse of their standard errors (1/SE) (lnRR of the 13 case-control studies combined = 0.555).

reduced the risks but did not substantially modify the results (mRR 1.65; 95% CI: 1.29–2.10 vs mRR 1.74; 95% CI: 1.37–2.21).

4.3. Comparison with the other systematic review

As another MA was published (Turner et al., 2010) during the writing of this paper dealing with the same topic but using slightly different methods, it was of great interest to compare our results and to point out the origin of the foremost differences.

The major methodological differences concern the literature search, the quality assessment of the included studies and the study stratifications. Turner et al. (2010) conducted a comprehensive literature search by applying their search strategy to several databases with no language restriction and including unpublished studies. We searched in one database (Medline) for published studies in English because published studies are likely to be more reliable than unpublished reports. We retrieved three additional published studies (Alexander et al., 2001; Spix et al., 2009; Urayama et al., 2007), one being probably published during the publication process of the MA of Turner and collaborators. Three unpublished studies as well as one in Spanish and one in Japanese (see references above) were included by Turner et al. (2010).

The second methodological difference between the two independent MA is the quality assessment of the included studies. Turner et al. (2010) applied a modified Downs and Black (1998) tool including external and internal validity factors (bias, exposure measurement, and confounding) and focusing on the quality of exposure assessment and the ability to identify exposure windows. It has to be stressed that these authors reported very similar results when the summary data including studies with high total quality scores were compared to summary values including all studies (e.g. exposure to unspecified pesticides during pregnancy: high total quality score: mRR 1.56; 95% CI:1.08–2.27 and all studies: mRR 1.54; 95% CI: 1.13–2.11). As there is no consensus with regard to available scales or checklists for measuring the quality of observational studies, we decided not to use a quality assessment checklist. This aspect was discussed in our companion publication (Van Maele-Fabry et al., 2010).

Although the authors of the two MA followed similar approaches to refine the analysis of the available data (e.g. taking into account the exposure windows, the biocide category, and the leukaemia type), the differences in the definition of the subgroups make it impossible to systematically compare the results. However, the main conclusions of the two MA were the same: in both MA a positive association was observed between exposure to residential pesticides during pregnancy and childhood and childhood leukaemia, with the strongest associations observed for insecticides, which strongly reinforces the validity of the conclusions. These results are in agreement with the conclusions of previous narrative reviews (Daniels et al., 1997; Infante-Rivard and Weichenthal, 2007; Zahm and Ward, 1998).

Differences were also observed among the results of the two MA. A first difference is the significantly increased risk of leukaemia following outdoor exposure to pesticides during pregnancy and the non significantly increased risk during childhood observed in our MA as opposed to the inverse reported by Turner et al. (2010)) (no statistical significance for outdoor exposure during pregnancy and statistical significance during childhood). For indoor exposure, however, both MA reported statistically significant increased risks during pregnancy or childhood. The significantly increased risk for childhood indoor exposure to pesticides and non significantly increased risk for childhood outdoor exposure observed in our MA is not surprising: indoor sources can be a major contributor to pesticide exposure for children as pesticides persist indoor in carpets, where they are protected from degradation by rain, sunlight, moisture, microorganisms (Lewis et al., 1994; Simcox et al., 1995) and as young children spend most of their time indoors and frequently put their hands in their mouth. In addition, the non significantly increased risk observed in both MA for childhood exposure to herbicides, mostly used outdoor, reinforces our results. In the two recent MA examining the association of parental occupational exposure to pesticides and childhood leukaemia, the strongest evidence of an increased risk comes from maternal exposure (Van Maele-Fabry et al., 2010; Wigle et al., 2009). A significantly increased risk during pregnancy appears therefore coherent. Another difference concerns the types of leukaemia: a non significantly increased risk was observed by Turner et al. (2010) for AML following pesticide exposure during pregnancy and childhood whereas we observed significant risks for ANLL. Significantly increased risks of childhood ANLL or AML were previously observed following maternal occupational exposure to pesticides (Van Maele-Fabry et al., 2010; Wigle et al., 2009). The slight discrepancies between the results of the two MA are not surprising as most of them are based on a limited number of studies and studies included in the subgroups may differ according to the inclusion criteria. Such results, once again, point to the absolute necessity for further work to improve as much as possible the quality of exposure data, leukaemia types, specific (groups of) pesticides used indoor or outdoor and, when possible, genetic susceptibility markers.

5. Conclusions

Overall, the present MA provides quantitative evidence to consider residential exposure to pesticides as a contributing risk factor for childhood leukaemia. The strongest associations were observed for exposure during pregnancy. Risk estimates were the greatest for indoor exposure as well as for insecticides. As the development of childhood leukaemia is probably multifactorial, there is a need for additional studies to assess gene–environment interactions and to correlate improved exposure data with genetic predisposition and well defined subtypes of leukaemia. The consistency of our results and those from previous reviews and MA suggests that it may be opportune to consider preventive actions including educational measures to increase the awareness of the public and particularly of pregnant women about the potential adverse influence of pesticides on children's health.

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Conflict of interest statement

There are none.

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