Cancer Causes Control (2010) 21:787–809
DOI 10.1007/s10552-010-9516-7

REVIEW ARTICLE

Childhood leukaemia and parental occupational exposure to pesticides: a systematic review and meta-analysis

Geneviève Van Maele-Fabry · Anne-Catherine Lantin · Perrine Hoet · Dominique Lison

Received: 20 October 2009 / Accepted: 23 January 2010 / Published online: 21 February 2010

Abstract
Objective To conduct a systematic review and meta-analysis of published studies on the association between parental occupational exposure to pesticides and childhood leukaemia.
Methods Studies were identified from a MEDLINE search through 31 July 2009 and from the reference lists of identified publications. Relative risk (RR) estimates were extracted from 25 studies published between 1985 and 2008. Meta-rate ratio estimates (mRR) were calculated according to fixed and random-effect meta-analysis models. Separate analyses were conducted after stratification for study design, definition of exposure (employment in a farm/agriculture assuming exposure to pesticides versus exposure to pesticides stipulated), exposed parent, window of exposure, type of leukaemia and biocide category.
Results No statistically significant association between childhood leukaemia and parental occupation as farmers/agricultural workers was observed. When exposure to pesticides was stipulated, positive associations were reported for maternal exposure for all studies combined (mRR: 1.62; 95% CI: 1.22–2.16), in all exposure windows considered and for acute non-lymphocytic leukaemia (ANLL). There was no association with paternal exposure when combining all studies (mRR: 1.14; 95% CI: 0.76–1.69). However, significant increased risks were seen for paternal exposure, in some exposure windows as well as for the biocide category.
Conclusions The strongest evidence of an increased risk of childhood leukaemia comes from studies with maternal occupational exposure to pesticides. The associations with paternal exposure were weaker and less consistent. These results add to the evidence leading to recommend minimizing parental occupational exposure to pesticides. Our findings also support the need to rely more on studies that clearly stipulate exposure to pesticides rather than those that assume pesticide exposure because of farm/agriculture employment.

Keywords Child · Leukaemia · Parental occupational exposure · Pesticides · Systematic review · Meta-analysis

Abbreviations

ALL	Acute lymphocytic leukaemia
AML	Acute myelogenous leukaemia
ANLL	Acute non-lymphocytic leukaemia
95% CI	95% Confidence interval
CLL	Chronic lymphocytic leukaemia
CML	Chronic myeloid leukaemia
MA	Meta-analysis
mRR	Meta-rate ratio estimate
OR	Odds ratio
PMR	Proportional mortality ratio
RR	Relative risk
95% UI	95% Uncertainty interval

G. Van Maele-Fabry (✉) · A.-C. Lantin · P. Hoet · D. Lison
Louvain Center for Toxicology and Applied Pharmacology (LTAP), Université catholique de Louvain,
Avenue E. Mounier 53.02, 1200 Brussels, Belgium
e-mail: genevieve.vanmaele@uclouvain.be

Introduction

Childhood leukaemia is a heterogeneous group of diseases and the most common type of cancer in children, accounting for about 30% of all childhood cancer cases diagnosed under 15 years. The vast majority of childhood leukaemias are, by far, acute. The most common type is acute lymphocytic (or lymphoblastic or lymphoïd) leukaemia (ALL) which accounts for 75–80% of all leukaemia, while acute myeloïd (myelocytic, myelogenous or non-lymphoblastic) leukaemia (AML) also termed acute non-lymphoblastic leukaemia (ANLL) represents about 20% of the cases. By contrast, the chronic forms of these leukaemia, chronic myeloïd leukaemia (CML) and chronic lymphocytic leukaemia (CLL), are rarely seen in childhood [1, 2].

The aetiology of those malignancies remains largely unknown. It is hypothesized that the varying forms of leukaemia have different aetiologies. Epidemiological studies of 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, pesticides). Only ionizing radiation has been significantly linked with either ALL or AML. Most other factors have been weakly or inconsistently associated with either forms of childhood leukaemia [2, 3]. Among environmental chemicals, pesticides have been particularly scrutinized.

There are several possible sources of exposure to pesticides in childhood. The first possible source is indirect contamination from parental (occupational) exposure to pesticides. The second possible source is from a direct exposure of the children to pesticides. Parental exposures to occupational hazards may contribute to the risk of leukaemia in offspring through damage to germ cells of either parent prior to pregnancy; intrauterine exposure through transplacental transmission during gestation; or finally exposure of the child through breast feeding, take-home exposure through contaminated person(s) or work-clothes and/or equipment [4, 5]. Children can also be directly and ubiquitously exposed to pesticides from indoor use (in homes, schools, other buildings), from outdoor use (garden, playing areas/public lands, agricultural application drift, overspray or off-gassing), through food and contaminated drinking water, by handling treated or contaminated pets or others (e.g. through the use of insecticidal shampoos for lice infestation) [6]. The present work focuses on the potential association between childhood leukaemia and pesticide exposure via parental occupational exposure to pesticides. A companion study will address childhood leukaemia and domestic exposure to pesticides.

Narrative reviews with regard to childhood cancer and pesticide exposure have been recently conducted. The evidence of a possible association between childhood leukaemia and parental pesticide exposure was suggestive but not conclusive [7–9]. These authors considered that investing in the acquisition and critical review of exposure information was the crucial step for establishing a causal association. To this end, our review focuses on several exposure issues distinguishing: (1) general employment in agriculture/farm versus use of pesticides specifically considered; (2) the exposed parent (paternal, maternal, both); (3) the critical exposure windows including preconception, intrauterine and postnatal exposures; (4) the types of leukaemia (ALL, ANLL); (5) the biocide categories (insecticides, herbicides and fungicides).

The present systematic review and meta-analysis was undertaken with the aim to enhance our understanding of the potential involvement of parental occupational pesticide exposure in the childhood disease aetiology.

Materials and methods

Study identification and selection

Study identification

A search on MEDLINE (National Library of Medicine, Bethesda, MD) was conducted for the period 1966 to 31 July 2009. An electronic search using "(pesticides OR herbicides OR fungicides OR insecticides) AND ((children OR childhood) AND cancer) AND (occupation OR occupational)" was initially undertaken. This was supplemented with various combinations of the following key words: pesticide(s), child, children, childhood, infant, newborn, preschool child, adolescent, leukaemia, myeloid, myeloblastic, myelogenous, lymphoid, lymphoblastic, lymphocytic, chronic, acute, granulocytic, occupation, occupational, farmers, agriculture, horticulture, pesticide applicators, manufacturing workers with no restriction of publication type or publication date. Recent articles in occupational medicine and epidemiology journals were also scanned for relevant publications. Finally, the reference lists of the relevant publications identified were checked for additional studies. The search was limited to studies published in English in the open literature in peer-reviewed journals. The analysis was restricted to published studies as they are likely to be more reliable than unpublished reports. All titles or abstracts were screened to determine the suitability of the publication.

Study selection

A study was considered eligible for further review if (1) it referred to children exposed to pesticides from parental occupational exposure (farmers, pesticide applicators, workers engaged in the manufacture of pesticides and others such as horticulturists, greenhouse workers, gardeners), (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 did not report original results (reviews, meta-analyses, case–reports, comments, letters, editorials, abstracts), experimental studies and proportional mortality ratios (PMR) studies (mainly because of ambiguities in interpreting results) as well as ecological studies. Studies on veterans who served in Vietnam or Cambodia, studies on treatment outcome, with therapy-related leukaemia, studies focusing 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 not dealing with occupational exposure or dealing with combined occupational and domestic exposure with no separate reporting of occupational data were also excluded. Studies dealing only with other occupational groups than those sus-mentioned were not included. Among the eligible studies, were excluded those providing no leukaemia cases or insufficient data to determine an estimator of relative risk (RR) for childhood leukaemia and its confidence interval, those including subjects already included in another more complete or more recent study examining a greater number of subjects or with longer follow-up duration, and those studies with adults or combining adults and children with no separate reporting of children's data.

The systematic review and identification of eligible studies was performed by one reviewer (VMFG).

Data extraction

A structured abstract was derived from each study identified. Two authors (VMFG and LAC) 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.

Cohort studies: if more than one follow-up analysis had been published for the same population, the most recently published report was used. When multiple estimates of RR were given, we retained the overall data for the total cohort. We did not include data resulting from further stratification, e.g. by children age groups.

Case–control studies: no overall meta-analysis was performed for case–control studies because several studies reported multiple odds ratios (ORs), and the available data did not allow us to calculate a combined OR. The data were, however, included in stratified meta-analyses. Stratifications were performed for:

1. the definition of occupational exposure:
   - general employment in agriculture/farms used as surrogate for pesticide exposure
   - exposure to pesticides stipulated
2. the exposed parent:
   - paternal exposure
   - maternal exposure
   - both or either (unspecified)
3. the critical exposure windows:
   - before pregnancy (or before conception)
   - during pregnancy
   - after pregnancy
   - before + during pregnancy + at birth (or up to birth)
   - any time or unspecified or ever
4. the types of leukaemia:
   - ALL
   - ANLL
5. the categories of biocides:
   - insecticides
   - herbicides
   - fungicides.

Data analysis

Evaluation of homogeneity

Homogeneity among data was evaluated. The significance of the between-study variance was evaluated with the ln(RR) or Q statistic test which has a χ^2 distribution with degrees of freedom equal to the number of studies pooled minus 1. The applied formula is $\chi^2 = \Sigma w_i[\ln(RR)_i - \ln(RR)_p]^2$, for $i = 1$ to N, where N is the number of studies combined, RR_p is the overall pooled RR estimate, RR_i is the RR for the ith study, and $w_i = 1/V_i$ where V_i is the variance of the $\ln(RR)_i$. A low p value for this statistic indicates the presence of heterogeneity, which questions the validity of the pooled estimates [10, 11]. Meta-analyses often include small numbers of studies, and the power of the test in such circumstances is low [12]. An alternative approach that quantifies the effect of heterogeneity, providing a measure of the degree of inconsistency in the studies' results, has been developed [13]. The quantity called I^2 describes the percentage of total variation across studies, which is due to heterogeneity rather than chance. I^2 can be calculated as $I^2(\%) = 100(Q - df)/Q$, where Q is Cochran's heterogeneity statistic and df the degrees of freedom. Negative values of I^2 are put equal to zero so that

I^2 lies between 0% and 100%. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity. Confidence limits of I^2 reflecting uncertainty in the extent of heterogeneity were calculated as proposed by Higgins and Thompson [14].

Statistical pooling

When there was little variation between studies ($I^2 \leq 25\%$), we calculated RRs and CIs according to a fixed model which assumes that results across studies differ only by sampling error. The study variance (V_i) was calculated, using the CI given, according to the equation $V_i = [(\ln(CI_{upper}) - \ln(CI_{lower}))/3.92]^2$. As detailed by Stewart and collaborators [15] and Dennis [16], the maximum likelihood estimate of the pooled RR in the fixed effect model is the $\exp(\ln(RR)_p)$. The pooled $\ln(RR)_p$ equals $\Sigma[\ln(RR)_i/V_i]/[\Sigma(1/V_i)]$, where V_i is the variance for an individual study as described above and $\ln(RR)_i$ is the log RR estimate for study i. This is a variance-weighted least square mean. The variance of the pooled $\ln(RR)_p$, $Var(\ln(RR)_p)$ or V_p is given by: $[SE(\ln(RR)_p)]^2 = [\Sigma(1/V_i)]^{-1}$, where SE is the standard error. The pooled variance is used to calculate a 95% CI around the pooled RR estimate.

When data are heterogeneous ($I^2 > 25\%$) or if there is reason to believe that publication bias exists, the random effects model is 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 Der Simonian and Laird [17]. These authors proposed a non-iterative estimator of τ^2 defined as $est(\tau^2) = \max\{0, [Q - (k - 1)]/[\Sigma w_i - (\Sigma(w_i^2))/\Sigma w_i]\}$, where Q is the heterogeneity statistic, k is the total number of studies, and w_i are the inverse variance weights for ln(RR). Potential sources of heterogeneity were evaluated by subset analysis.

The two meta-analyses including all studies for maternal or for paternal occupational exposure to pesticides were illustrated by forest plots where the confidence interval for each study is represented by a horizontal line and the point estimate by a square. The size of the square corresponds to the weight of the study in the meta-analysis. The confidence interval for the total is symbolized by a diamond.

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 was tested using the linear regression method suggested by Egger and collaborators [18].

Sensitivity analyses

To determine whether some of the decisions we made had a major impact on the results of the review, sensitivity analyses were conducted by:

- removing the study of Ali et al. [44] reporting a particularly high result and the most imprecise value (weight of 0.5%),
- re-estimating summary relative risks excluding the data of the studies considering upper age limits higher than 15 years [41, 43–46, 51, 56] to avoid under-rated associations since the incidence of childhood leukaemia varies with age,
- rerunning the meta-analyses after replacing the data of the first trimester of pregnancy by the data of the second and of the third trimesters. In the study of Monge et al. [5], exposure during pregnancy was assessed for the first, the second and the third trimesters. Data of the first trimester were included in the meta rate-ratios of the studies with regard to paternal pesticide exposure during pregnancy and to maternal pesticide exposure during pregnancy.
- re-estimating the summary relative risks including data from different sources of controls (cancer controls or cancer-free controls and area controls or local controls). Pearce et al. [56] matched cases to controls from two independent sources: cancer controls and cancer-free controls. Data for cancer-free controls were included in the meta-rate ratios of the subgroups "paternal exposure to pesticides, all studies" and "paternal pesticide exposure, before + during pregnancy + at birth". In the study of Gardner et al. [46], cases were compared to controls unmatched (area controls) and matched (local controls) for civil parish of residence. Data for local controls were included in the meta-analyses of the subgroups "paternal exposure, farming/agriculture, all studies" and "paternal exposure, farming/agriculture, before + during pregnancy + at birth".
- performing the meta-analyses using both fixed and random effect methods to assess the robustness of the results.

Results

Literature selection and study characteristics

The study selection is summarized in Fig. 1. A large number of articles were retrieved from MEDLINE and hand searching in the reference lists of the relevant publications of which 257 were potentially relevant. Retrieved articles or references were considered potentially relevant

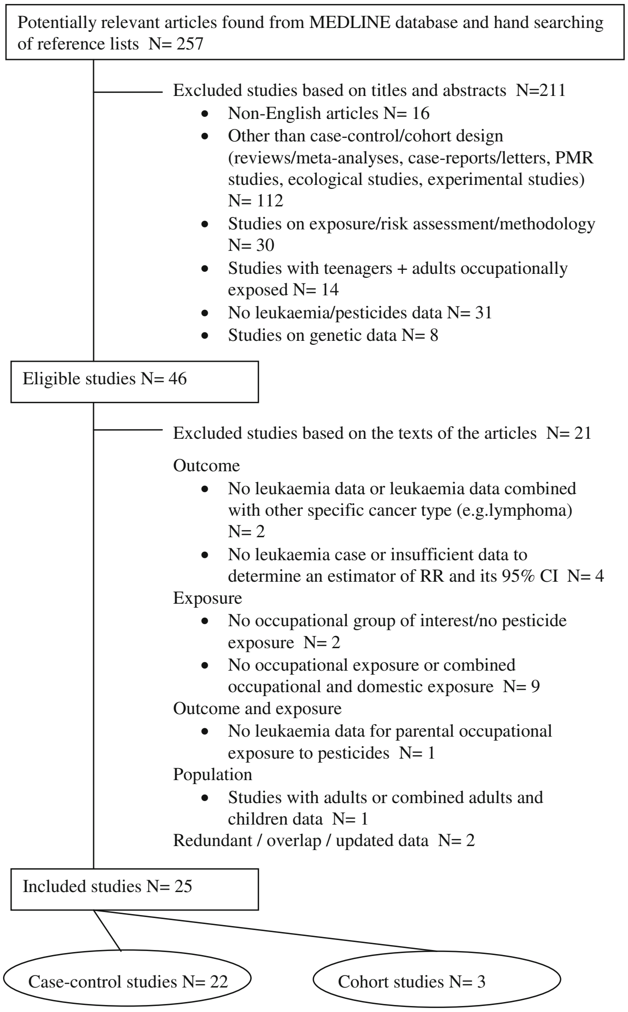


Fig. 1 Study selection. *Note*: N = number of studies

if they focused on the population of concern (children), and/or on the outcome of concern (leukaemia) and/or on the exposure of concern (parental occupational exposure to pesticides). In the next step, selection or rejection of articles was only based on the title or on the abstract of the articles. The reasons of exclusion for the majority of these studies ($N = 211$) are reported in Fig. 1. We retained 46 studies for further evaluation. Among these studies, 21 were excluded after reading of the full paper as they did not fulfil the inclusion criteria with regard to the outcome [19–24], or to the exposure [25–35] or to both [36] or to the population [37]. One cohort [38] and one case–control study [39] were also excluded because the data were redundant/updated/overlapped.

The remaining 25 studies were included in present analyses. Three cohort studies [40–42] and twenty-two case–control studies [4, 5, 43–61] were identified as fulfilling the inclusion criteria. The reference of Heacock et al. [41] was included in the case–control studies as well as in the cohort studies, because these authors reported data for a cohort analysis and for a nested case–control analysis in the same publication.

Table 1 provides selected characteristics of the case–control and cohort studies used in the analysis. The studies were published between 1985 and 2008. Thirteen case–control studies and 1 cohort study were from Europe, 4 case–control and 2 cohort studies from USA/Canada and 5 case–control studies were from other parts of the world. The upper age limits were 5 ($n = 1$) [58], 10 ($n = 1$) [48], 11 ($n = 1$) [50], 15 ($n = 11$) [4, 5, 47, 49, 52–55, 59–61], 16 ($n = 1$) [57], 18 ($n = 1$) [45], 20 ($n = 3$) [40, 41], 25 ($n = 2$) [46, 56], 30 ($n = 1$) [44] and unspecified in 3 studies [43, 51, 52]. Ten of the included case–control studies had data on maternal exposure, 18 of the case–control and 2 of the cohort studies provided data on paternal exposure, and 6 case–control and 1 cohort studies had data on parental exposure. The period of exposure varied greatly among the studies and is detailed in Table 1. Studies were included into 5 defined windows of exposure: before pregnancy ($n = 7$), during pregnancy ($n = 9$), after pregnancy ($n = 6$), before pregnancy up to birth ($n = 5$) and anytime/unspecified/ever exposure ($n = 11$). Case–control studies differed for occupational exposure definition, either restricted to general employment in agriculture/farms ($n = 13$) or use of pesticides by the parents clearly stipulated ($n = 16$). For the great majority of studies, information on parental occupational exposure to pesticides was self-reported (parents or closest relative attending the children). The sources of exposure were parental occupation on birth records in 3 case–control studies [46, 56, 58], on employee records in 1 study [41], on maternal welfare centres records in 1 study [47] and on licensed pesticide applicators registers in 2 cohort studies [40, 42]. Cumulative measures of exposure were reported by Buckley and collaborators [45] as well as by Heacock and coworkers [41].

The case numbers, estimators of the relative risk and confidence intervals for children to develop leukaemia after parental occupational pesticide exposures are also presented in Table 1 taking into account the exposure characteristics, the difference of definition of leukaemia cases and the category of biocide concerned. All included studies were based on leukaemia incidence. There was no mortality study fulfilling the inclusion criteria. Studies differed according to the definition of leukaemia cases: most studies did not specify the type of leukaemia or presented data for all types of leukaemia. Seven studies reported data restricted to ALL [4, 43, 48, 51, 52, 60, 61], three restricted to ANLL [45, 56, 60], 1 restricted to CML [56] and 3 restricted to acute leukaemias [55, 57, 59]. In most studies, exposure to pesticides was reported without specification of the biocide category. Only few studies specified pesticide

Table 1 Study summary from publications dealing with occupational parental exposure to pesticides and childhood leukaemia

Reference; geographic location	Exposure assessment A. source of exposure data B. exposure category	Occupational exposure	Parental exposure	Period of exposure considered	[Leukaemia type] Number of cases (cases/controls)	Estimator of relative risk (95% CI)
Case–control						
Abadi-Korek et al. [43]; Petach-Tikva, Israel	A. Questionnaire: face-to-face or phone interviews				[ALL]	OR
		Pesticides	Both	All times (preconception + gestation + postnatal)	45ca/14co	2.35 (1.10–5.00)
	B. Employment in agricultural occupations: exposed to *pesticides* versus unexposed to pesticides					
Ali et al. [44]; Taiwan	A. Questionnaire: parents and subjects >16 years, face-to-face or phone interviews				[Leukaemia]	OR
		Pesticides	Paternal	All times	5ca/2co	16.03 (1.77–145.49)
	B. Job title classification among which: *wood treaters*			Preconception (job that ended > 1 year prior to birth)	4ca/1co	12.17 (1.36–109.21)
				Perinatal (between 1 year prior to birth and birth)	4ca/1co	13.08 (1.38–125.50)
Buckley et al. [45]; USA, Canada	A. Questionnaire: parents, phone interviews				[ANLL]	OR
	B. Occupations classification: ever versus never exposed; Occupational exposure to agents among which *pesticides*; Duration of exposure: none, short (1–1,000 days), prolonged (> 1,000 days); frequency times, cumulative index	Pesticides	Paternal	All times (before + during + after index of pregnancy)	27ca/20co	1.41 (0.76–2.63)*
			Maternal		11ca/4co	2.85 (0.89–9.10)*
			Both (either)		36ca/22co	1.80 (1.01–3.20)*
Gardner et al. [46]; West Cumbria, UK	A. Questionnaire: mothers (fathers), mailed; Birth certificates: parental occupation; Computer file of past and present workers at Sellafield				[Leukaemia]	RR
		Farmers	Paternal	At birth (and at conception)	5ca/11co	2.63 (0.77–8.95)
	B. Occupations classification among which: *farmers*					
Heacock et al. [41]; British Columbia, Canada	A. Industry records; Questionnaire: experienced workers, managers, engineers & chlorophenate distributors.				[Leukaemia]	OR
		Pesticides (exposure ≥3,560 h)	Paternal	From commencement of exposure until diagnosis (before conception until diagnosis)	5ca/19co	0.80 (0.20–3.60)
	B. Index of cumulative duration of exposure to *chlorophenate* for each worker validated by measurements of urinary metabolites; 2 categories of exposure of sawmill workers based on the index: high (≥3,560 h), low (<3,000 h)					

Table 1 continued

Reference; geographic location	Exposure assessment A. source of exposure data B. exposure category	Occupational exposure	Parental exposure	Period of exposure considered	[Leukaemia type] Number of cases (cases/controls)	Estimator of relative risk (95% CI)
Hemminki et al. [47]; Finland	A. Data on parents' occupations collected from maternal welfare centres				[Leukaemia]	OR
	B. Occupational groups among which: *agriculture*, *gardening*, *forestry*	Agriculture, gardening, forestry	Paternal	During pregnancy	156[a]	1.26 (0.92–1.73)*
Infante-Rivard et al. [4]; Provinces of Castellon, Valencia, Alicante, Murcia, Madrid, Albacete, Spain	A. Questionnaire: mothers, face-to-face interviews				[ALL]	RR
	B. Occupations among which: *agriculture*; Occupational exposure to broad categories of substances (determined with the help of an industrial hygienist) among which: *insecticides*	Agriculture	Maternal	During pregnancy	9/5[a]	
		Pesticides (insecticides)			7/5[a]	1.40 (0.44–4.41)
Infante-Rivard and Sinnett [48]; Québec, Canada	A. NR				[ALL]	OR
	B. Occupational exposure categories determined by expert chemists among which: *pesticides* (fungicides, insecticides, herbicides)	Pesticides	Paternal	2 Years prior to pregnancy (preconception)	66ca/47co	1.56 (1.02–2.40)
		Fungicides			15ca/3co	5.11 (1.46–17.81)
		Insecticides			50ca/38co	1.38 (0.87–2.18)
		Herbicides			19ca/10co	2.05 (0.93–4.56)
Laval and Tuyns [49]; 9 departments around Lyon, France	A. Questionnaire: parents, face-to-face and phone interviews, medical files				[Leukaemia]	OR
	B. Occupations among which: *"exposure to pesticides"*	Pesticides	Either	NR	12ca/3co	4.19 (1.16–15.08)*
Lowengart et al. [50]; Los-Angeles County, California	A. Questionnaire: parents, phone interviews				[Leukaemia]	OR
	B. Occupations classification among which: *agriculture*	Agriculture	Paternal	From 1 year before conception to until 0.5 or 1 year before diagnosis	6/6[a]	1.00 (0.27–3.74)
Magnani et al. [51]; Turin, Italy	A. Questionnaire: parents, face-to-face interviews				[ALL]	OR
	B. Occupations classification among which: *farmer* (exposure = "ever worked as farmer")	Farmer	Paternal	Up to child's birth	4ca/5co	1.80 (0.50–6.50)
				Between birth and diagnosis	5ca/2co	5.60 (1.30–24.30)
				Up to diagnosis	9ca/7co	2.90 (1.05–7.91)*

Table 1 continued

Reference; geographic location	Exposure assessment A. source of exposure data B. exposure category	Occupational exposure	Parental exposure	Period of exposure considered	[Leukaemia type] Number of cases (cases/controls)	Estimator of relative risk (95% CI)
McKinney et al. [52]; UK	A. Questionnaire: parents, face-to-face interviews				[Leukaemia]	OR
	B. Occupational groups (based on job title and industrial monitoring data and determined by an experienced experts group) among which: *agriculture*; Occupational exposure to agents among which: *agrochemicals*; Exposed vs unexposed (possibly exposed were excluded)	Pesticides	Maternal	Periconception (job held 1 year prior to birth)	5ca/27co	0.81 (0.31–2.12)
			Paternal		36ca/185co	0.83 (0.58–1.19)
		Agriculture	Maternal		7ca/22co	1.41 (0.60–3.31)
			Paternal		29ca/140co	0.90 (0.60–1.34)
					[ALL]	
		Pesticides	Maternal		5ca/27co	0.97 (0.37–2.52)
			Paternal		31ca/185co	0.85 (0.58–1.24)
		Agriculture	Maternal		7ca/22co	1.68 (0.72–3.95)
			Paternal		25ca/140co	0.92 (0.59–1.40)
Meinert et al. [53]; Lower Saxony, Northern Germany	A. Questionnaire: parents, mailed and phone interviews				[Leukaemia]	OR
	B. Occupations classification with potential exposure to pesticides among which: *farmer*, *gardener*, *florist* Direct occupational exposure to *pesticides*	Pesticides	Paternal	1 Year before pregnancy	9ca/9co	1.29 (0.50–3.31)*
				During pregnancy	9ca/7co	1.66 (0.61–4.56)*
				After birth up to diagnosis	5ca/6co	1.04 (0.31–3.46)*
				Ever	9ca/9co	1.29 (0.50–3.31)*
			Maternal	1 Year before pregnancy	4ca/2co	2.59 (0.47–14.30)*
				During pregnancy	2ca/0co (1co)**	2.68 (0.24–29.79)*
				After birth up to diagnosis	2ca/0co (1co)**	2.68 (0.24–29.79)*
				Ever	4ca/2co	2.59 (0.47–14.30)*
			Either	1 Year before pregnancy	12ca/10co	1.53 (0.65–3.64)*
				During pregnancy	11ca/7co	2.07 (0.79–5.46)*
				After birth up to diagnosis	7ca/6co	1.54 (0.51–4.66)*
				Ever	12ca/10co	1.53 (0.65–3.64)*
		Farmer	Paternal	2 Years before pregnancy to diagnosis	6ca/7co	1.17 (0.38–3.53)*
			Maternal		4ca/3co	1.73 (0.38–7.82)*
			Either		16ca/21co	1.04 (0.52–2.06)*
		Farmer/ gardener/florist	Paternal		7ca/8co	1.20 (0.43–3.37)*
			Maternal		5ca/5co	1.31 (0.37–4.60)*

Table 1 continued

Reference; geographic location	Exposure assessment A. source of exposure data B. exposure category	Occupational exposure	Parental exposure	Period of exposure considered	[Leukaemia type] Number of cases (cases/controls)	Estimator of relative risk (95% CI)
Meinert et al. [54]; West Germany	A. Questionnaire: parents, mailed and phone interviews				[Leukaemia]	OR
	B. Occupation as *farmer*; Direct occupational exposure to *pesticides* (herbicides, insecticides, fungicides)	Pesticides	Paternal	1 Year before pregnancy	62ca/88co	1.50 (1.10–2.20)
				During pregnancy	57ca/77co	1.60 (1.10–2.30)
				After pregnancy	49ca/78co	1.30 (0.90–1.90)
				Ever	68ca/91co	1.60 (1.10–2.30)
			Maternal	1 Year before pregnancy	19ca/16co	2.10 (1.10–4.20)
				During pregnancy	15ca/8co	3.60 (1.50–8.80)
				After pregnancy	12ca/8co	2.50 (1.00–6.40)
				Ever	24ca/17co	2.50 (1.30–4.70)
		Farmer	Paternal	At the time of diagnosis	NR	1.50 (1.00–2.40) [2.10 (1.10–2.20) when 1:1 matched analysis]
			Maternal	At the time of diagnosis	NR	1.30 (0.60–2.90)
			Parental	From birth to diagnosis	54ca/81co	1.50 (1.00–2.20) [1.90 (1.10–3.30) when 1:1 matched analysis]
Menegaux et al. [55]; Lille, Lyon, Nancy, Paris, France	A. Questionnaire: parents, face-to-face interviews				[Acute leukaemia]	OR
	B. Occupational exposure to *pesticides*	Pesticides	Either	Childhood	5ca/3co	1.73 (0.41–7.32)*
			Maternal	During pregnancy	2ca/1co	2.07 (0.19–22.90)*

Table 1 continued

Reference; geographic location	Exposure assessment A. source of exposure data B. exposure category	Occupational exposure	Parental exposure	Period of exposure considered	[Leukaemia type] Number of cases (cases/controls)	Estimator of relative risk (95% CI)
Monge et al. [5]; Costa Rica	A. Questionnaire: parents, face-to-face interviews (focusing on pesticides exposure) B. Exposure model construction for 25 pesticides in five time periods; Tasks classified according to estimated hazard; Exposures expressed as qualitative (yes/no), semiquantitative (unexposed, low exposure, high exposure) and quantitative metrics for specific pesticides and groups of pesticides (data not reported); Occupational exposure to biocide categories: all *pesticides*, insecticides, herbicides, fungicides	Pesticides	Paternal	1 Year before conception	64ca	1.20 (0.90–1.80)
				1st Trimester of pregnancy	45ca	1.30 (0.90–2.00)
				2nd Trimester of pregnancy	45ca	1.50 (1.00–2.30)
				3rd Trimester of pregnancy	36ca	1.20 (0.80–1.90)
				First year of life	60ca	1.20 (0.80–1.80)
				Anytime	66ca	1.40 (0.90–2.00)
			Maternal	1 Year before conception	11ca	2.40 (1.00–5.90)
				1st Trimester of pregnancy	11ca	22.00 (2.80–171.50)
				2nd Trimester of pregnancy	9ca	4.50 (1.40–14.7)
				3rd Trimester of pregnancy	9ca	2.20 (0.80–5.80)
				First year of life	10ca	2.00 (0.80–4.80)
				Anytime	13ca	2.20 (1.00–4.80)
		Insecticides	Paternal	Anytime	44	1.40 (0.99–2.10)
			Maternal		9	3.00 (1.00–8.40)
		Herbicides	Paternal		60	1.40 (0.90–2.00)
			Maternal		11	1.40 (0.90–2.00)
		Fungicides	Paternal		36	1.90 (1.10–3.00)
			Maternal		6	1.90 (1.10–3.00)
Pearce et al. [56]; North of England	A. Birth certificate: paternal occupation				[Leukaemia]	OR
	B. Occupations classification focusing on *pesticides* exposure among which: farm owners and managers, forestry managers, horticulturists, gardeners, groundskeepers, horticultural trades, farm workers, forestry workers	Pesticides or herbicides	Paternal	At birth	34ca [lymphoid leukaemia]	0.38 (0.27–0.55)
					23ca	0.37 (0.24–0.57)
					[ANLL]	
					7ca	0.36 (0.17–0.77)
					[CML]	
					3ca	0.59 (0.14–2.46)
Perez-Saldivar et al. [57]; Mexico city	A. Questionnaire: parents, face-to-face interviews				[Acute leukaemia]	OR
	B. Exposure index constructed for carcinogenic agents by occupational physicians; Occupations classification among which: *farmers*	Farmers	Paternal	2 Years before conception	7ca/3co	2.91 (0.44–19.23)

Table 1 continued

Reference; geographic location	Exposure assessment A. source of exposure data B. exposure category	Occupational exposure	Parental exposure	Period of exposure considered	[Leukaemia type] Number of cases (cases/controls)	Estimator of relative risk (95% CI)
Roman et al. [58]; West Berkshire, Basingstoke, North Hampshire, UK	A. Birth certificate: paternal occupation; Questionnaire: parents, face-to-face interviews; Mothers obstetric notes; Nuclear industry records				[Leukaemia ($n = 50$) + NHL ($n = 6$)]	RR
	B. Occupations classification among which: *agriculture* workers	Agriculture	Paternal	From 3 years before birth until diagnosis	2ca/11co	1.10 (0.10–5.90)
Rudant et al. [59]; France	A. Questionnaire: mothers, phone interviews				[acute leukaemia]	OR
	B. Employment in *agricultural* occupation (ever versus never); Occupational exposure to *pesticides* (any contact versus none)	Agriculture	Paternal	During pregnancy or childhood	20ca/69 co	0.60 (0.40–1.10)
			Maternal	During pregnancy	3ca/28 co	0.20 (0.10–0.80)
		Pesticides	Maternal	During pregnancy	21ca/42 co	1.20 (0.70–2.00)
Shu et al. [60]; Shangai, China	A. Questionnaire: parents, face-to-face interviews				[Leukaemia]	OR
		Agriculture	Paternal	During pregnancy	2ca/10co	0.30 (0.10–1.60)
	B. Occupations classification among which: *agriculture workers and foresters*; Occupational exposure to chemicals among which *pesticides*		Maternal		12ca/13co	2.30 (0.90–6.30)
		Pesticides	Maternal		12ca/6co	2.60 (0.80–9.10)
					[ALL]	
		Agriculture	Maternal		6ca/13co	1.80 (0.60–5.40)
		Pesticides			7ca/6co	3.50 (1.10–11.20)
					[ANLL]	
		Agriculture	Maternal		4ca/13co	1.60 (0.40–6.30)
		Pesticides			3ca/6co	2.40 (0.50–11.00)
Van Steensel-Moll et al. [61]; The Netherlands	A. Questionnaire: parents, mailed				[ALL]	RR
	B. Occupations classification among which: *agriculture, forestry and horticulture*; Occupational exposure to agents among which: *pesticides*, *herbicides*, *insecticides*	Agriculture	Paternal	During pregnancy	35ca/39co	0.90 (0.50–1.50)
				1 Year before diagnosis	32ca/38co	0.90 (0.50–1.50)
			Maternal	During pregnancy	3ca/7co	0.40 (0.10–1.70)
				1 Year before diagnosis	3ca/8co	0.40 (0.10–1.30)
		Pesticides	Paternal	During pregnancy	36ca/35co	1.00 (0.60–1.70)
			Maternal	During pregnancy	4ca/6co	0.70 (0.20–2.50)

Table 1 continued

Reference; geographic location	Exposure assessment A. source of exposure data B. exposure category	Occupational exposure	Parental exposure	Period of exposure considered	[Leukaemia type] Number of cases (cases/controls)	Estimator of relative risk (95% CI)
Cohort						
Flower et al. [40]; Iowa, North Carolina, USA	A. Questionnaire: applicators: at enrolment and take home, spouses: take home and phone interview B. Persons applying for *pesticide application* between 1993 and 1997	Pesticides	Either	Prenatally	[Leukaemia] 9ca	SIR 0.91 (0.47–1.75)
Heacock et al. [41]; British Columbia, Canada	A. Industry records; Questionnaire: experienced workers, managers, engineers and chlorophenate distributors B. Sawmill workers occupationally exposed to *chlorophenate fungicides*, employed at least 1 year between 1950 and 1985	Pesticides	Paternal	1 Year before birth	[Leukaemia] 11ca	SIR 1.00 (0.50–1.80)
Rodvall et al. [42]; Sweden	A. Records of pesticide applicators licensed 1965–1976 B. Licensed pesticide applicators	Pesticides	Paternal	Unspecified	[Leukaemia] 8ca	SIR 0.43 (0.19–0.86)

Note: only available summary data with regard to leukaemia are reported in the table; italics highlight the occupational exposure reported in the papers

No. number; *RR* relative risk, *OR* odds ratio, *95% CI* 95% confidence interval, *ALL* acute lymphocytic leukaemia, *ANLL* acute non-lymphocytic leukaemia, *CML* chronic myeloid leukaemia, *NHL* non-Hodgkin lymphoma, *SIR* standardized incidence ratio, *NR* information not reported

[a] Discordant pairs (cases exposed-controls unexposed/cases unexposed-controls exposed)

*Number of cases and/or crude OR and/or 95% CI calculated on the basis of data in paper

**Crude OR calculated by assuming 1 instead of 0 exposed control subgroups: 3 studies reported data for insecticide exposure [4, 5, 48], 2 studies for herbicide exposure [5, 48] and 4 studies for fungicide exposure [5, 41, 44, 48]. Estimators of RR varied between 0.2 and 16.03 and included from 2 up to 68 cases.

Data synthesis

Cohort meta-analysis

The meta-rate ratio calculated for the three included cohorts was 0.77 (95% CI: 0.52–1.14) according to the fixed effect model and 0.76 (95% CI: 0.46–1.24) according to the random effect model. No evidence of heterogeneity was detected among the relative risk estimators applying the χ^2 statistic test, but the meta-analysis contains 37.03% of inconsistency in the studies' results (I^2) with an uncertainty interval of 0–80.06%. The meta-rate ratios calculated according to both models (fixed and random) were very close to each other and revealed a non-statistically significant reduced risk of leukaemia among children of parents occupationally exposed to pesticides.

Case–control meta-analyses

Table 2 summarizes the results of the different meta-analyses of case–control studies. Meta-rate ratios were calculated after classification of the studies based on the definition of parental occupational exposure (use of pesticides stipulated versus general employment in agriculture/farm), based on the parent exposed (paternal, maternal, paternal and/or maternal) and based on critical exposure windows (before, during, after pregnancy, before + during + at birth, any time/unspecified/ever) as well as based on specific types of leukaemia (ALL, ANLL) and on biocide category (insecticides, herbicides, fungicides).

While the meta-rate ratios calculated from studies stipulating occupational exposure to pesticides showed statistically significant (95% CI not including 1) increased risks of childhood leukaemia for several groupings, none were statistically significant from studies considering general occupation in farms/agriculture.

(i) Occupational exposure to pesticides

Paternal exposure

Paternal exposure: all studies. In the group "occupational exposure to pesticides", the meta-rate ratio for all paternal exposure studies was 1.14 (95% CI: 0.76–1.69). A forest plot of the 10 studies is reported in Fig. 2. The visual inspection of this figure shows that the RR estimator of the study of Ali and collaborators [44] is clearly higher than that of the other studies. This study reported a very imprecise value (weight = 0.5%). None of the studies had a particularly high weight when compared to the others. Five studies contributed each less than 10% of the total weight and 5 contributed between 11 and 20% of the total weight. The strong heterogeneity and degree of inconsistency existing among the 10 relative risk estimates (p value of 0.999×10^{-7} and I^2 of 82%) argued against an overall meta-analysis of the data. Further analyses were therefore carried out to identify the sources of heterogeneity, pooling studies according to different stratification variables (windows of exposure, leukaemia type and biocide category).

Paternal exposure: windows of exposure. Stratification of the studies (paternal exposure to pesticides) by windows of exposure strongly reduced heterogeneity and inconsistency among the studies' results for all windows except "before pregnancy + during pregnancy + at birth". Statistically significant increased meta-rate ratios were observed for the windows of exposure "before pregnancy" (mRR: 1.41; 95% CI: 1.15–1.74), "during pregnancy" (mRR: 1.36; 95% CI: 1.08–1.72) and "any time/unspecified/ever" (mRR: 1.49; 95% CI: 1.18–1.89).

Paternal exposure: leukaemia type. Stratification by type of leukaemia slightly reduced heterogeneity and inconsistency for ALL (p value of 0.108 and I^2 of 55%) but not for ANLL (p value of 0.006 and I^2 of 87%). No statistically significant increased or decreased risk was observed for ALL (mRR: 1.09; 95% CI: 0.75–1.60) or for ANLL (mRR: 0.73; 95% CI: 0.19–2.76).

Paternal exposure: biocide category. The grouping of studies according to the biocide category showed a statistically significant increased risk for each category: insecticides, herbicides and fungicides with no evidence of heterogeneity among the results of individual studies except for the fungicides ($I^2 = 57.5\%$). The highest risk was observed for this last category.

Maternal exposure

Maternal exposure: all studies. Combining the 10 studies dealing with maternal occupational exposure to pesticides yielded a statistically significant increased risk of childhood leukaemia (mRR: 1.62; 95% CI: 1.22–2.16). A forest plot for these studies is reported in Fig. 3, showing the weight applied to each study in the meta-analysis. The study of Rudant et al. [59] and that of Meinert et al. [54] contributed to 30.1% and 20.1% of the total weight, respectively. No evidence of heterogeneity was detected among the different relative risk estimators by applying the χ^2 statistic test (p value of 0.422), and the meta-analysis did

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

Stratification	No. Studies	Meta-		Homogeneity			
		Rate ratio	95% CI	χ^2 Woolf	*p*-Value	I^2	95% UI
Occupational exposure							
A. Pesticides							
Paternal							
(A.1) Pesticides all studies	10b	1.14	0.76–1.69	50.175	0.999×10^{-7}	82	68–90
Windows of exposure							
(A.2) before pregnancy	5	*1.41*	1.15–1.74	4.913	0.296	19	0–83
(A.3) during pregnancy	4a	*1.36*	1.08–1.72	2.285	0.515	0	0–80
(A.4) after pregnancy	3	1.25	0.95–1.65	0.168	0.919	0	0–0
(A.5) before + during pregnancy + at birth	3b	0.83	0.33–2.07	16.582	0.251×10^{-3}	88	0–99
(A.6) any time/unspecified/ever	6	*1.49*	1.18–1.89	5.529	0.355	10	0–77
Leukaemia type							
(A.7) ALL	3	1.09	0.75–1.60	4.447	0.108	55	0–87
(A.8) ANLL	2	0.73	0.19–2.76	7.472	0.0062	87	47–97
Biocide category							
(A.9) insecticides	2	*1.39*	1.02–1.90	0.002	0.964	0	ND
(A.10) herbicides	2	*1.51*	1.06–2.16	0.706	0.401	0	ND
(A.11) fungicides	4	*2.65*	1.05–6.67	7.063	0.07	58	0–86
Maternal							
(A.12) Pesticides all studies	10	*1.62*	1.22–2.16	9.166	0.422	2	0–63
Windows of exposure							
(A.13) before pregnancy	3	*2.24*	1.34–3.72	0.087	0.958	0	0–0
(A.14) during pregnancy	8a	*2.00*	1.11–3.62	13.042	0.071	46	0–76
(A.15) after pregnancy	3	*2.25*	1.21–4.20	0.136	0.934	0	0–0
(A.16) any time/ever	4	*2.45*	1.58–3.81	0.145	0.986	0	0–0
Leukaemia type							
(A.17) ALL	4	1.34	0.70–2.59	4.087	0.252	27	0–72
(A.18) ANLL	2	*2.68*	1.06–6.78	0.030	0.862	0	ND
Biocide category							
(A.19) insecticides	2	2.11	0.97–4.62	0.907	0.341	0	ND
Paternal and/or maternal							
(A.20) Pesticides	5	*2.00*	1.37–2.90	1.990	0.738	0	0–58
B. Farming/agriculture							
Paternal							
(B.1) all studies	12c,d	1.10	0.84–1.45	19.548	0.0519	44	0–71
Windows of exposure							
(B.2) during pregnancy	4	0.81	0.50–1.32	8.923	0.030	66	2–89
(B.3) after pregnancy	3	1.49	0.76–2.94	5.936	0.0514	66	0–90
(B.4) before + during pregnancy + at birth	3c	1.05	0.73–1.51	3.397	0.183	12	0–87
(B.5) any time/at diagnosis	4d	1.57	0.86–2.87	2.250	0.522	0	0–80
Leukaemia type							
(B.6) ALL	3	1.14	0.67–1.94	4.532	0.104	56	0–87
Maternal							
(B.7) all studies	7d,e	1.00	0.53–1.90	15.678	0.0156	62	13–83
Windows of exposure							
(B.8) during pregnancy	4	0.77	0.22–2.65	14.021	0.288×10^{-2}	79	42–92
(B.9) after pregnancy	2	0.81	0.26–2.51	2.356	0.125	58	0–90

Table 2 continued

Stratification	No. Studies	Meta-		Homogeneity			
		Rate ratio	95% CI	χ^2 Woolf	*p*-Value	I^2	95% UI
Leukaemia type							
(B.10) ALL	4e	1.40	0.82–2.41	3.550	0.314	16	0–87
Paternal and/or maternal							
(B.11) farming/agriculture	2	1.37	0.97–1.93	0.819	0.366	0	ND

No Studies number of studies, *95% CI* 95% confidence interval; meta-rate ratios are in italics when the 95% CI do not include 1, *95% UI* 95% uncertainty interval, *ND* not defined (could not be calculated)

Notes a: in the study of Monge et al. [5], exposure during pregnancy was assessed for the first, the second and the third trimesters. Data for the first trimester were included in the meta-rate ratio; b: Pearce et al. [56] matched cases to controls from 2 independent sources: cancer controls and cancer-free controls. Data for cancer-free controls were included in the meta-rate ratio; c: the analysis of Gardner et al. [46] was carried out within the sets of cases and area or local controls. Data for local controls were included in the meta-rate ratio; d: in the study of Meinert et al. [53], data for occupations with potential exposure to pesticides included farmers, gardeners, florists and the total. Data for the total were included in the meta-rate ratio; e: Van Steensel-Moll et al. [61] reported relative risks of leukaemia based on mother's occupation during pregnancy and one year before diagnosis. Data for occupation during pregnancy were included in the meta-rate ratio

Studies included in the meta-analyses

(A.1) Ali et al. [44], Buckley et al. [45], Heacock et al. [41], Infante-Rivard and Sinnett. [48], McKinney et al. [52], Meinert et al. [53], Meinert et al. [54], Monge et al. [5], Pearce et al. [56], Van Steensel-Moll et al. [61]

(A.2) Ali et al. [44], Infante-Rivard and Sinnett. [48], Meinert et al. [53], Meinert et al. [54], Monge et al. [5]

(A.3) Meinert et al. [53], Meinert et al. [54], Monge et al. [5], Van Steensel-Moll et al. [61]

(A.4) Meinert et al. [53], Meinert et al. [54], Monge et al. [5]

(A.5) Ali et al. [44], McKinney et al. [52], Pearce et al. [56]

(A.6) Ali et al. [44], Buckley et al. [45], Heacock et al. [41], Meinert et al. [53], Meinert et al. [54], Monge et al. [5]

(A.7) Infante-Rivard and Sinnett [48], McKinney et al. [52], Van Steensel-Moll et al. [61]

(A.8) Buckley et al. [45], Pearce et al. [56]

(A.9) Infante-Rivard and Sinnett [48], Monge et al. [5]

(A.10) Infante-Rivard and Sinnett [48], Monge et al. [5]

(A.11) Ali et al. [44], Heacock et al. [41], Infante-Rivard and Sinnett [48], Monge et al. [5]

(A.12) Buckley et al. [45], Infante-Rivard et al. [4], McKinney et al. [52], Meinert et al. [53], Meinert et al. [54], Menegaux et al. [55], Monge et al. [5], Rudant et al. [59], Shu et al. [60], Van Steensel-Moll et al. [61]

(A.13) Meinert et al. [53], Meinert et al. [54], Monge et al. [5]

(A.14) Infante-Rivard et al. [4], Meinert et al. [53], Meinert et al. [54], Menegaux et al. [55], Monge et al. [5], Rudant et al. [59], Shu et al. [60], Van Steensel-Moll et al. [61]

(A.15) Meinert et al. [53], Meinert et al. [54], Monge et al. [5]

(A.16) Buckley et al. [45], Meinert et al. [53], Meinert et al. [54], Monge et al. [5]

(A.17) Infante-Rivard et al. [4], McKinney et al. [52], Shu et al. [60], Van Steensel-Moll et al. [61]

(A.18) Buckley et al. [45], Shu et al. [60]

(A.19) Infante-Rivard et al. [4], Monge et al. [5]

(A.20) Abadi-Korek et al. [43], Buckley et al. [45], Laval and Tuyns [49], Meinert et al. [53], Menegaux et al. [55]

(B.1) Gardner et al. [46], Hemminki et al. [47], Lowengart et al. [50], Magnani et al. [51], McKinney et al. [52], Meinert et al. [53], Meinert et al. [54], Perez-Saldivar et al. [57], Roman et al. [58], Rudant et al. [59], Shu et al. [60], Van Steensel-Moll et al. [61]

(B.2) Hemminki et al. [47], Rudant et al. [59], Shu et al. [60], Van Steensel-Moll et al. [61]

(B.3) Magnani et al. [51], Meinert et al. [54], Van Steensel-Moll et al. [61]

(B.4) Gardner et al. [46], Magnani et al. [51], McKinney et al. [52]

(B.5) Lowengart et al. [50], Magnani et al. [51], Meinert et al. [53], Roman et al. [58]

(B.6) Magnani et al. [51], McKinney et al. [52], Van Steensel-Moll et al. [61]

(B.7) Infante-Rivard et al. [4], McKinney et al. [52], Meinert et al. [53], Meinert et al. [54], Rudant et al. [59], Shu et al. [60], Van Steensel-Moll et al. [61]

(B.8) Infante-Rivard et al. [4], Rudant et al. [59], Shu et al. [60], Van Steensel-Moll et al. [61]

(B.9) Meinert et al. [53], Meinert et al. [54]

(B.10) Infante-Rivard et al. [4], McKinney et al. [52], Shu et al. [60], Van Steensel-Moll et al. [61]

(B.11) Meinert et al. [53], Meinert et al. [54]

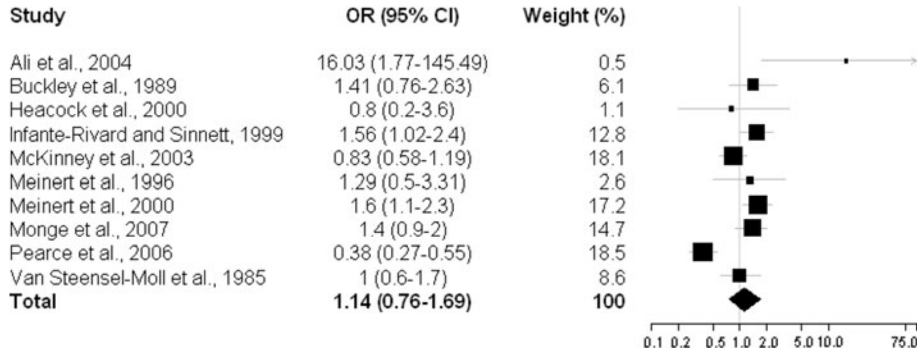


Fig. 2 Forest plot of case–control studies on childhood leukaemia following paternal occupational exposure to pesticides. *Note* Estimators of RR and 95% confidence intervals (CIs) of case–control studies included in the meta-analysis "all studies" are presented. Each estimator was assigned a weight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

only contain very weak inconsistency ($I^2 = 2\%$), although the uncertainty interval of the I^2 value was wide (95% UI: 0–63).

Maternal exposure: windows of exposure. After stratifying the data (maternal exposure to pesticides) into windows of exposure, statistically significant increased meta-rate ratios (mRR between 2.00 and 2.45) were observed for each group. Consistency in the studies' results was observed for each grouping as evidenced by p values for heterogeneity of 0.934 to 0.986 and I^2 of 0% except for the window "during pregnancy" (p value of 0.071 and I^2 of 46%).

Maternal exposure: leukaemia type. Stratification by type of leukaemia showed increased meta-rate ratios for each group (ALL: mRR = 1.34 and ANLL: mRR = 2.68) but with a statistical significance only for ANLL (95% CI: 1.06–6.78). A slight inconsistency (I^2 of 27%) was observed among the ALL studies.

Maternal exposure: biocide category. The stratification of studies according to the biocide category could only be performed for insecticides as only one study was available for the other categories (herbicides, fungicides). A non-significantly increased risk was observed after combining both studies with a maternal occupational exposure to insecticides.

Paternal and/or maternal exposure

Combining the 5 studies reporting paternal and/or maternal occupational exposure to pesticides yielded a meta-rate ratio of 2.00 (95% CI: 1.37–2.90) and did not show inconsistency in the study results (I^2 of 0%; 95% UI: 0–58).

(ii) General employment in agriculture/farm

When general employment in agriculture/farm was used as a surrogate for parental occupational exposure to pesticides, the meta-rate ratios for all paternal ($n = 12$) and all maternal ($n = 7$) studies were 1.10 and 1.00, respectively (95% CI: 0.84–1.45 and 0.53–1.90, respectively). Heterogeneity and inconsistency in the studies' results were observed in both groups (p values of 0.052 and of 0.016 for paternal and maternal studies, respectively and I^2 of 44% and 62%, respectively).

Stratifications by windows of exposure reduced heterogeneity and inconsistency only for paternal exposure, "before pregnancy + during pregnancy + at birth" and "any time/at diagnosis" but not for maternal exposure.

Stratification by type of leukaemia reduced heterogeneity and inconsistency only for ALL childhood leukaemia for maternal exposure.

Combining both studies reporting paternal and/or maternal employment in agriculture/farm yielded a meta-rate ratio of 1.37 (95% CI: 0.97–1.93) and did not show inconsistency in the studies results (I^2 of 0%).

Sensitivity analyses

Omitting the particularly high result of the study of Ali et al. [44] with imprecise value (OR: 16.03; 95% CI: 1.77–145.49; weight = 0.5%) did not substantially modify the result of the MA "pesticides all studies" (mRR: 1.06; 95% CI: 0.72–1.55 instead of mRR: 1.14; 95% CI: 0.76–1.69). Exclusion of studies with upper age limits higher than 15 years yielded similar results (data not shown). Replacing the data of Monge et al. [5] for the first trimester by the data for the second and for the third trimesters did not substantially modify the results of the meta-analyses (data not shown). Similar results were obtained by rerunning the meta-analyses after replacing the data of Pearce et al. [56] from cancer-free controls by those from cancer-controls as well as after replacing the data of Gardner et al. [46] from local controls by those from area controls (data not shown). Results of all meta-analyses performed using both fixed and random effects models were similar (data not shown).

Funnel plots and asymmetry

Funnel plots of ln(RR) versus 1/SE for the meta-analysis including all studies for maternal (Fig. 4) as well as for paternal (data not shown) occupational exposure to pesticides were constructed. The visual inspection of these figures did not clearly detect asymmetry arising from a lack of small studies with low RR estimators. The statistic analysis by the linear regression method of Egger et al. [18] did not yield evidence of asymmetry (intercept 1.748; 95% CI: −1.798 to 5.294) ($p > 0.2$) for maternal occupational exposure to pesticides. Some evidence of asymmetry was suggested for paternal exposure (intercept 6.762; 95% CI: −0.4592 to 13.98) ($p \sim 0.05$).

Discussion

This systematic review and meta-analysis examined the relevant literature (case–control and cohort studies) on the possible association between occupational parental exposure to pesticides and childhood leukaemia. Several issues have been addressed to improve the analysis of the data available: definition of pesticide exposure, exposed parent, critical windows of exposure, type of leukaemia and biocide category.

During the redaction of this paper, another independent meta-analysis on the same subject has been published [62] using a slightly different approach. This is of great interest as it allows to highlight some methodological aspects of the respective meta-analysis procedures as well as to compare the conclusions drawn by both groups.

General employment in farm/agriculture versus use of pesticides stipulated

No statistically significant association between childhood leukaemia and parental occupational exposure was observed when farming/agricultural work was used as a surrogate for pesticide exposure, whereas statistically significant increased risks were observed when grouping studies specifically considering the use of pesticides by the parents. These data support the hypothesis that parental occupational exposure to pesticides may be a risk factor for childhood leukaemia. These data also reinforce the message that farming job title has to be considered as a poor indicator of pesticide exposure (as a substantial proportion of farm jobs may not involve such exposure) and that this is likely to result in overestimation into the probability of exposure (important associations may be under-rated or remain undetected) [63]. For this reason, the following discussion will focus on the data of studies specifically considering pesticide exposure.

Maternal or paternal occupational exposure to pesticides

When combining the 10 studies dealing with maternal occupational exposure to pesticides, a statistically significant increased risk of childhood leukaemia was observed. The risk was not statistically increased when combining all studies on paternal exposure. These findings indicate that maternal occupational exposure may be of greater concern than paternal occupational exposure and are in agreement with the conclusions of other reviews [62, 64]. In our systematic review, the same number of studies addressing parental occupational exposure to pesticides has focused on paternal ($n = 10$) and on maternal exposure ($n = 10$). Several of the isolated studies reporting on maternal exposure were too small to show statistically significant increases in leukaemia risk. However, when the results of all these studies were combined, a statistically significant increased risk emerged. The consistency of the results for maternal exposure in our MA was supported by a weak degree of heterogeneity among the individual relative risk estimators. The results for paternal exposure “all studies” have to be taken with caution as the strong heterogeneity among the 10 relative risk estimators argued against an overall meta-analysis of the data.

It has to be stressed that interpretation of meta-analyses is constrained by the limitations in the original studies mainly related to exposure assessment and potential source of bias. Bias in studies of self-reported parental occupational exposure and childhood cancer may lead to an overestimation of risk estimates. Such bias may be introduced into a retrospective study because exposure is measured indirectly, is self-reported and may be differentially recalled by parents of a healthy, versus a sick, child [65]. Recall bias can be exacerbated by participation bias which is introduced when those who respond to a study differ from those who do not [66]. This point is to be taken into consideration in the interpretation of the positive associations observed in our meta-analyses.

Publication bias

The association observed in the meta-analysis including all studies for maternal occupational exposure to pesticides does not appear to have been significantly influenced by publication bias, as there was no evidence for a substantial deficit in small negative studies. However, it should be reminded that some data were omitted from the present analysis as a result of the study selection procedure: for example, published studies giving too scarce data to derive an estimator of RR and its confidence interval, studies with combined adults and children data with no separate reporting of children’s data, studies with leukaemia data

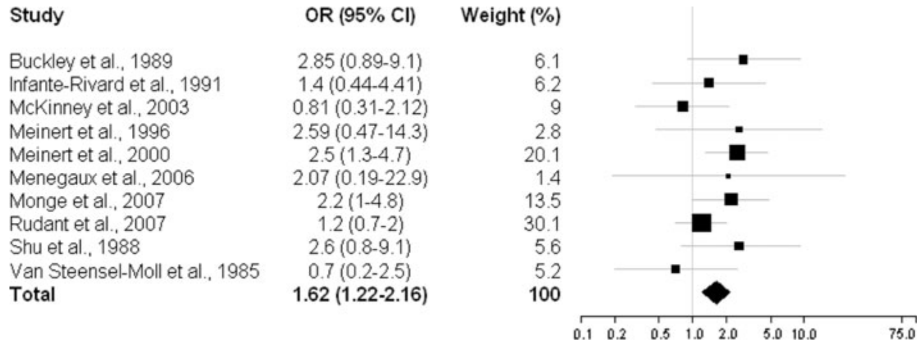
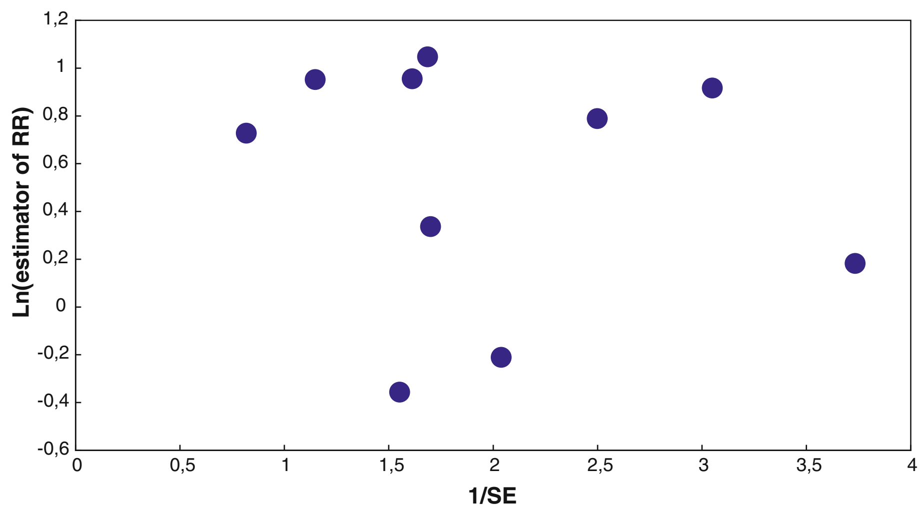


Fig. 3 Forest plot of case–control studies on childhood leukaemia following maternal occupational exposure to pesticides. *Note*. Estimators of RR and 95% confidence intervals (CIs) of case–control studies included in the meta-analysis "all studies" are presented. Each estimator was assigned a weight (w_i) equal to the inverse square of its standard error (SE): $w_i = 1/(SE)^2$

Fig. 4 Case–control studies of maternal occupational exposure to pesticides and childhood leukaemia: funnel plot of natural logarithms of relative risk (RR) estimates versus the inverse of their standard errors (1/SE) (lnRR of the 10 case–control studies combined = 0.484)



combined with other cancer types (such as lymphomas), studies ever conducted but not published for several reasons or published in other languages than English. The recent systematic review published by Wigle et al. [62] allows assessing the impact of some of these issues as these authors included unpublished studies as well as studies written in languages other than English in their MA. Two unpublished studies [67, 68] but no other language studies with regard to maternal pesticide occupational exposure and childhood leukaemia were retrieved. Rerunning our meta-analysis conducted on the corresponding exposure group including these unpublished studies did not substantially modify the results (mRR 1.64; 95% CI: 1.26–2.15 instead of mRR 1.62; 95% CI: 1.22–2.16).

The association observed in the meta-analysis including all studies for paternal occupational exposure to pesticides appears to have been significantly influenced by publication bias, indicating a potential lack of small studies with effect sizes smaller than those for larger studies. Wigle et al. [62] retrieved two unpublished studies [67, 69] with regard to paternal occupational exposure to pesticides. Rerunning our MA after including these unpublished studies did not substantially modify the results (mRR 1.17; 95% CI: 0.81–1.69 instead of mRR 1.14; 95% CI: 0.76–1.69). However, funnel plot asymmetry may also be due to other factors including study quality, methodological differences or the study population. As the study of Ali et al. [44] showed a particularly high estimator of relative risk (see forest plot of the studies for paternal occupational pesticide exposure), we reran the corresponding MA excluding this study. This did not substantially modify the results (mRR 1.06; 95% CI: 0.72–1.55 instead of mRR 1.14; 95% CI: 0.76–1.69), but evidence of funnel plot asymmetry was not observed anymore (intercept 0.692; 95% CI: −4.324 to 5.707; $p > 0.2$ instead of intercept 6.762; 95% CI: −0.4592 to 13.98; $p \sim 0.05$).

Critical windows of exposure

In assessing children's susceptibility to environmental toxicants, the influence of the exposure period on potential outcomes needs to be evaluated. There appears to be strong evidence from animal and epidemiologic studies for causal relationships between exposure preconceptionally, in utero, and during childhood, and cancer occurrence in children and adults [70]. However, the evidence is incomplete, and the comprehensive evaluation of the relative importance of specific time windows is limited by the lack of empirical evidence. The mechanism by which childhood leukaemia arises remains largely unknown but a number of recent studies support the hypothesis that it is likely to follow a multi-stage model involving gene–environment interactions. It is suggested that initiation of childhood leukaemia arises prenatally (prenatal primary event) and that exposure early in life (postnatal second event) plays an important role in its further development [71–74]. Exposure before conception and/or during pregnancy could be potentially linked to the prenatal events, whereas those risk factors associated with breastfeeding, mothers and children exposure after birth could be linked to the postnatal events. If there are discrete windows of vulnerability in the development of leukaemia, it remains critical to identify which time periods would be of the greatest importance.

Many differences in the way of reporting time windows were noted among the studies. In the present review, studies were stratified according to exposure windows (before, during, after pregnancy, before pregnancy up to birth and any time/unspecified/ever) of the father and of the mother. We found a significantly elevated risk of childhood leukaemia in association with paternal and maternal occupational exposure to pesticides prior to and during pregnancy as well as with maternal exposure after pregnancy. An increased risk was also observed for the studies reporting results for all time windows combined or unspecified. The highest statistically significant meta-RR estimators were observed for the different windows of maternal exposure to pesticides indicating that the strongest evidence of an increased risk of childhood leukaemia comes from maternal occupational exposure to pesticides. No evidence of a most crucial exposure period for later development of childhood leukaemia could be drawn from these results. It has to be stressed that the statistically significant elevated meta-rate ratios for the specified exposure time windows were higher than the meta-rate ratios of all studies combined for paternal as well as for maternal exposure. This suggests that reporting results for all time windows combined may under-rate or mask a potential association linked to specific exposure time windows.

Types of leukaemia

Most studies provided data for all leukaemia types and not for a specific type of leukaemia. As it could be hypothesized that the varying forms of leukaemia probably have different aetiologies, studies that made this distinction were used for stratification. Only a small number of studies reported data for a specified type of leukaemia, and findings should be interpreted cautiously. A statistically significant increased risk of ANLL was observed following maternal exposure to pesticide but not following paternal exposure to pesticides. Neither paternal nor maternal exposure was significantly associated with ALL. These results are in agreement with those of Wigle and collaborators [62] except for ALL and maternal pesticide exposure. The inclusion of data issued from one unpublished study [67] and of one Japanese language study [75] reporting high relative risk estimators [3.20 (0.26–170.4) and 4.0 (1.1–14), respectively] in this other meta-analysis can partially explain this discrepancy.

Biocide categories

Too few original studies have taken into account the biocide category (insecticides, herbicides, fungicides) to allow highlighting the potential existence of a relationship between parental occupational exposure to one or several categories of biocides and childhood leukaemia. Statistically significant increased risks were observed following paternal exposure to each category with an apparently higher increase for exposure to fungicides and an increase of borderline significance was observed after maternal occupational exposure to insecticides. Insufficient data were available to combine results from studies with regard to maternal occupational exposure to herbicides or fungicides.

Cohort studies

The meta-rate ratio for the three included cohort studies revealed a non-statistically significant decreased risk of leukaemia among children of parents occupationally exposed to pesticides. It can be assumed that these data mainly concern paternal exposure as 1 study reports data for parental exposure but for only 0.4% of the children was the mother the licensed pesticide applicator. These results seem to be in partial discrepancy with the case–control studies data, as the meta-rate ratio for paternal pesticide exposure "all studies" showed a non-significant increased risk. However, in both cases, results were not statistically significant. In addition, the small numbers of cases and limited statistical power or potential misclassification of exposure may have limited the ability of cohort studies to detect small increased risks.

Comparison with the other systematic review

If we compare the approaches followed in both MA [62, and the present MA], several differences appear. Two of them will be discussed here. The first main difference concerns the literature search. Wigle et al. [62] conducted a comprehensive literature search by applying their search strategy to several databases with no language restriction and included unpublished studies. We searched in one database (Medline) for published studies in English as these are likely to be more reliable than unpublished reports. The same published studies were retrieved in both works, but included studies were slightly different due to differences in the inclusion and exclusion criteria. Wigle and collaborators included three unpublished studies and one study in Japanese. We performed a sensitivity analysis by rerunning our MA for the stratifications of concern. Inclusion of these studies did not substantially change the magnitude of the associations.

The second difference between the two independent MA is the quality assessment of the included studies. Wigle et al. [62] applied a modified Downs and Black [76] tool including external and internal validity factors (bias, exposure measurement, confounding) and focusing on the quality of exposure assessment and the ability to identify exposure windows. 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 and preferred to use a simpler approach also focusing mainly on exposure and bias. In addition, the aetiology of childhood leukaemia remains largely unknown and, as a consequence, confounding factors are also largely unknown, and it is not possible to adjust for those factors. Assessment of the overall quality is made difficult if reporting of the observational study is inadequate. Even if, when conducting a systematic review, we cannot directly act on these limitations, we can still critically review the exposure information and refine the conclusions that can be drawn as much as possible. To improve the analysis of available exposure data, we decided to separate studies stipulating pesticide exposure and studies using occupation such as farming/agriculture as surrogate for exposure to limit non-differential misclassification of exposure. The quality scores attributed by Wigle et al. [62] for exposure measurement of all studies selected in our MA as reporting only data for farming/agriculture were lower than or equal to 2 on a subtotal of 8. Although the approaches followed by the authors of the two MA to exploit as much as possible the exposure data reported in the original studies were mostly similar (e.g. separate the data as a function of the parent of concern, of the exposure windows), the differences in the subgroups definitions make it impossible to systematically compare the results. However, the main conclusions of the two MA were the same, which strongly reinforce the validity of the conclusions.

Conclusions

In conclusion, our findings following the classification of the published epidemiological studies based on the type of exposure (general employment in agriculture/farm versus use of pesticides specifically considered) support the assumption that farm-related activities may be an inadequate surrogate for potential pesticide exposure that is likely to result in overestimation of the probability of exposure. There was no statistically significant association between childhood leukaemia and parental occupation as farmers among all subgroups of studies, taking into account the exposed parent, the critical windows of exposure and the types of leukaemia.

Among case–control studies in which use of pesticides was specifically considered, this systematic review and MA revealed positive associations between maternal occupational exposure and childhood leukaemia in the analyses of all studies combined and in all exposure windows considered. An increased risk was also detected in relation to maternal exposure and childhood ANLL, but this was based only on two studies.

Associations with paternal exposure to pesticides were weaker and less consistent: combining all available studies showed no statistically significant increased risk. Significantly increased risks were seen for before pregnancy, during pregnancy and unspecified exposure windows as well as for all biocide categories: insecticides, herbicides and fungicides, although also based on few studies.

No statistically significant increased risk has been observed among cohort studies. This apparent discrepancy with the results from the case–control studies may be partially explained by the specific drawbacks of each study design like recall bias in the case–control studies that may lead to an overestimation of risk estimates and like small numbers of cases, limited statistical power or potential misclassification of exposure that may have limited the ability of cohort studies to detect small risks. This once again emphasizes the need for more sophisticated exposure assessment methods in epidemiologic studies of childhood cancer. As suggested by Infante-Rivard and Weichenthal [9], exposure measures could be improved by including separate parental interviews, specific pesticide exposure questions and semi-quantitative exposure measures that can be used to confirm information obtained through questionnaires.

In spite of the above-mentioned limitations and even though statistical association is to be distinguished from causal relationship, these data provide enough evidence to recommend reducing parental, and more particularly maternal, occupational exposure to pesticides. Potentially exposed workers should be further encouraged to use protective clothing and masks and to be particularly attentive to avoid "take-home" exposure.

Acknowledgments V.M.F.G. was supported by a grant from the Belgian Ministry of Health (Grant Number 95/15 (164)).

Conflict of interest statement None

References

1. Onciu M, Pui CH (2006) Diagnosis and classification. In: Pui CH (ed) Childhood leukemias. Cambridge University Press, New York, pp 21–47
2. Belson M, Kingsley B, Holmes A (2007) Risk factors for acute leukemia in children: a review. Environ Health Perspect 115(11): 138–145
3. Linet MS, Wacholder S, Zahm SH (2003) Interpreting epidemiologic research: lessons from studies of childhood cancer. Pediatrics 112(1):218–232
4. Infante-Rivard C, Mur P, Armstrong B, Alvarez-Dardet C, Bolumar F (1991) Acute lymphoblastic leukaemia among Spanish children and mothers' occupation: a case–control study. J Epidemiol Community Health 45(1):11–15
5. Monge P, Wesseling C, Guardado J, Lundberg I, Ahlbom A, Cantor KP, Weiderpass E, Partanen T (2007) Parental occupational exposure to pesticides and the risk of childhood leukemia in Costa Rica. Scand J Work Environ Health 33(4):293–303
6. Zahm SH, Ward MH (1998) Pesticides and childhood cancer. Environ Health Perspect 106(suppl 3):893–908
7. Nasterlack M (2006) Do pesticides cause childhood cancer? Int Arch Occup Environ Health 79(7):536–544
8. Nasterlack M (2007) Pesticides and childhood cancer: an update. Int J Hyg Environ Health 210(5):645–657
9. Infante-Rivard C, Weichenthal S (2007) Pesticides and childhood cancer: an update of Zahm and Ward's 1998 review. J Toxicol Environ Health B Crit Rev 10(1–2):81–99
10. Clarke M, Oxman AD (eds) (2000) Cochrane reviewers' handbook 4.1 (update June 2000). In: Review Manager (RevMan) (computer program). Version 4.1. The Cochrane Collaboration 2000, Oxford, England
11. Lipsett M, Campleman S (1999) Occupational exposure to diesel exhaust and lung cancer: a meta-analysis. Am J Public Health 89(7):1009–1017
12. Hardy RJ, Thompson SG (1998) Detecting and describing heterogeneity in meta-analysis. Stat Med 17(8):841–856
13. Higgins JPT, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. BMJ 327(7414):557–560
14. Higgins JPT, Thompson SG (2002) Quantifying heterogeneity in a meta-analysis. Stat Med 21(11):1539–1558
15. Stewart RE, Dennis LK, Dawson DV, Resnick MI (1999) A meta-analysis of risk estimates for prostate cancer related to tire and rubber manufacturing operations. J Occup Environ Med 41(12):1079–1084
16. Dennis LK (2000) Meta-analysis for combining relative risks of alcohol consumption and prostate cancer. Prostate 42(1):56–66
17. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7(3):177–188
18. Egger M, Davey SG, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. BMJ 315 (7109):629–634
19. Fabia J, Thuy TD (1974) Occupation of father at time of birth of children dying of malignant diseases. Br J Prev Soc Med 28(2): 98–100
20. Mulder YM, Drijver M, Kreis IA (1994) Case–control study on the association between a cluster of childhood haematopoietic malignancies and local environmental factors in Aalsmeer, The Netherlands. J Epidemiol Community Health 48(2):161–165
21. Buckley JD, Buckley CM, Ruccione K, Sather HN, Waskerwitz MJ, Woods WG, Robison LL (1994) Epidemiological characteristics of childhood acute lymphocytic leukemia. Analysis by immunophenotype. Leukemia 8(5):856–864
22. Buckley JD, Meadows AT, Kadin ME, Le Beau MM, Siegel S, Robison LL (2000) Pesticide exposures in children with Non-Hodgkin lymphoma. Cancer 89(11):2315–2321
23. Gold EB, Diener MD, Szklo M (1982) Parental occupations and cancer in children. J Occup Med 24(8):578–584
24. Schüz J, Spector LG, Ross JA (2003) Bias in studies of parental self-reported occupational exposure and childhood cancer. Am J Epidemiol 158(7):710–716
25. Mutanen P, Hemminki K (2001) Childhood cancer and parental occupation in the Swedish Family-Cancer database. J Occup Environ Med 43(11):952–958
26. Peters JM, Preston-Martin S (1984) Childhood tumors and parental occupational exposures. Teratog Carcinog Mutagen 4(1):137–148
27. Alexander FE, Patheal SL, Biondi A, Brandalise S, Cabrera ME, Chan LC, Chen Z, Cimino G, Cordoba JC, Gu LJ, Hussein H, Ishii E, Kamel AM, Labra S, Magalhães IQ, Mizutani S, Petridou E, Pombo de Oliveira M, Yuen P, Wiemels JL, Greaves MF (2001) Transplacental chemical exposure and risk of infant leukemia with *MLL* gene fusion. Cancer Res 61(6):2542–2546
28. Deschamps M, Band P (1993) Study of a cluster of childhood leukemia. Health Rep 5(1):81–85
29. Infante-Rivard C, Labuda D, Krajinovic M, Sinnett D (1999) Risk of childhood leukemia associated with exposure to pesticides and with gene polymorphisms. Epidemiology 10(5):481–487
30. Infante-Rivard C (2003) Hospital or population controls for case–control studies of severe childhood diseases? Am J Epidemiol 157(2):176–182
31. Leiss JK, Savitz DA (1995) Home pesticide use and childhood cancer: a case–control study. Am J Public Health 85(2):249–252
32. Ma X, Buffler PA, Gunier RB, Dahl G, Smith MT, Reinier K, Reynolds P (2002) Critical windows of exposure to household pesticides and risk of childhood leukemia. Environ Health Perspect 110(9):955–960
33. Petridou E, Dessypris N (2000) Maternal pesticide exposure and childhood leukemia. Epidemiology 11(2):230
34. Pombo-de-Oliveira MS, Koifman S, Brazilian Collaborative Study Group of Infant Acute Leukemia (2006) Infant acute leukemia and maternal exposures during pregnancy. Cancer Epidemiol Biomarkers Prev 15(12):2336–2341
35. Schwartzbaum JA, George SL, Pratt CB, Davis B (1991) An exploratory study of environmental and medical factors potentially related to childhood cancer. Med Pediatr Oncol 19(2): 115–121
36. Olsen JH, de Nully Brown P, Schulgen G, Jensen OM (1991) Parental employment at time of conception and risk of cancer in offspring. Eur J Cancer 27(8):958–965
37. Kristensen P, Andersen A, Irgens LM, Bye AS, Sundheim L (1996) Cancer in offspring of parents engaged in agricultural activities in Norway: incidence and risk factors in the farm environment. Int J Cancer 65(1):39–50
38. Feychting M, Plato N, Nise G, Ahlbom A (2001) Paternal occupational exposures and childhood cancer. Environ Health Perspect 109(2):193–196

39. Kaatsch P, Kaletsch U, Meinert R, Miesner A, Hoisl M, Schüz J, Michaelis J (1998) German case–control study on childhood leukaemia–basic considerations, methodology and summary of results. Klin Pädiatr 210(4):185–191
40. Flower KB, Hoppin JA, Lynch CF, Blair A, Knott C, Shore DL, Sandler DP (2004) Cancer risk and parental pesticide application in children of agricultural health study participants. Environ Health Perspect 112(5):631–635
41. Heacock H, Hertzman C, Demers PA, Gallagher R, Hogg RS, Teschke K, Hershler R, Bajdik CD, Dimich-Ward H, Marion SA, Ostry A, Kelly S (2000) Childhood cancer in the offspring of male sawmill workers occupationally exposed to chlorophenate fungicides. Environ Health Perspect 108(6):499–503
42. Rodvall Y, Dich J, Wiklund K (2003) Cancer risk in offspring of male pesticide applicators in agriculture in Sweden. Occup Environ Med 60(10):798–801
43. Abadi-Korek I, Stark B, Zaizov R, Shaham J (2006) Parental occupational exposure and the risk of acute lymphoblastic leukemia in offspring in Israel. J Occup Environ Med 48(2):165–174
44. Ali R, Yu CL, Wu MT, Ho CK, Pan BJ, Smith T, Christiani DC (2004) A case–control study of parental occupation, leukemia and brain tumors in an industrial city in Taiwan. J Occup Environ Med 46(9):985–992
45. Buckley JD, Robison LL, Swotinsky R, Garabrant DH, LeBeau M, Manchester P, Nesbit ME, Odom L, Peters JM, Woods WG, Hammond GD (1989) Occupational exposures of parents of children with acute nonlymphocytic leukemia: a report from the Childrens Cancer Study Group. Cancer Res 49(14):4030–4037
46. Gardner MJ, Snee MP, Hall AJ, Powell CA, Downes S, Terrell JD (1990) Results of case–control study of leukaemia and lymphoma among young people near Sellafield nuclear plant in West Cumbria. Br Med J 300(6722):423–429
47. Hemminki K, Saloniemi I, Salonen T, Partanen T, Vainio H (1981) Childhood cancer and parental occupation in Finland. J Epidemiol Community Health 35(1):11–15
48. Infante-Rivard C, Sinnett D (1999) Preconceptional paternal exposure to pesticides and increased risk of childhood leukaemia. Lancet 354(20):1819
49. Laval G, Tuyns AJ (1988) Environmental factors in childhood leukaemia. Br J Ind Med 45(12):843–844
50. Lowengart RA, Peters JM, Cicioni C, Buckley J, Bernstein L, Preston-Martin S, Rappaport E (1987) Childhood leukemia and parents' occupational and home exposures. J Natl Cancer Inst 79(1):39–46
51. Magnani C, Pastore G, Luzzatto L, Terracini B (1990) Parental occupation and other environmental factors in the etiology of leukemias and non-Hodgkin's lymphomas in childhood: a case–control study. Tumori 76(5):413–419
52. McKinney PA, Fear NT, Stockton D, on behalf of the UK Childhood Cancer Study Investigators (2003) Parental occupation at periconception: findings from the United Kingdom Childhood Cancer Study. Occup Environ Med 60(12):901–909
53. Meinert R, Kaatsch P, Kaletsch U, Krummenauer F, Miesner A, Michaelis J (1996) Childhood leukaemia and exposure to pesticides: results of a case–control study in Northern Germany. Eur J Cancer 32A(11):1943–1948
54. Meinert R, Schüz J, Kaletsch U, Kaatsch P, Michaelis J (2000) Leukemia and non-Hodgkin lymphoma in childhood and exposure to pesticides: results of a register-based case–control study in Germany. Am J Epidemiol 151(7):639–646
55. Menegaux F, Baruchel A, Bertrand Y, Lescoeur B, Leverger G, Nelken B, Sommelet D, Hémon D, Clavel J (2006) Household exposure to pesticides and risk of childhood acute leukaemia. Occup Environ Med 63(2):131–134
56. Pearce MS, Hammal DM, Dorak MT, McNally RJQ, Parker L (2006) Paternal occupational exposure to pesticides or herbicides as risk factors for cancer in children and young adults: a case–control study from the north of England. Arch Environ Occup Health 61(3):138–144
57. Perez-Saldivar ML, Ortega-Alvarez MC, Fajardo-Gutierrez A, Bernaldez-Rios R, Del Campo-Martinez Mde L, Medina-Sanson A, Palomo-Colli MA, Paredes-Aguilera R, Martinez-Avalos A, Borja-Aburto VH, Rodriguez-Rivera Mde J, Vargas-Garcia VM, Zarco-Contreras J, Flores-Lujano J, Mejia-Arangure JM (2008) Father's occupational exposure to carcinogenic agents and childhood acute leukemia: a new method to assess exposure (a case–control study). BMC Cancer 8:7
58. Roman E, Watson A, Beral V, Buckle S, Bull D, Baker K, Ryder H, Barton C (1993) Case–control study of leukaemia and non-Hodgkin's lymphoma among children aged 0–4 years living in West Berkshire and North Hampshire health districts. BMJ 306(6878):615–621
59. Rudant J, Menegaux F, Leverger G, Baruchel A, Nelken B, Bertrand Y, Patte C, Pacquement H, Vérité C, Robert A, Michel G, Margueritte G, Gandemer V, Hémon D, Clavel J (2007) Household exposure to pesticides and risk of childhood hematopoietic malignancies: the ESCALE study (SFCE). Environ Health Perspect 115(12):1787–1793
60. Shu XO, Gao YT, Brinton LA, Linet MS, Tu JT, Zheng W, Fraumeni JF Jr (1988) A population-based case–control study of childhood leukemia in Shangai. Cancer 62(3):635–644
61. Van Steensel-Moll HA, Valkenburg HA, van Zanen GE (1985) Childhood leukemia and parental occupation. A register-based case–control study. Am J Epidemiol 121(2):216–224
62. Wigle DT, Turner MC, Krewski D (2009) A systematic review and meta-analysis of childhood leukemia and parental occupational pesticide exposure. Environ Health Perspect 117(10):1505–1513
63. MacFarlane E, Glass D, Fritschi L (2009) Is farm-related job title an adequate surrogate for pesticide exposure in occupational cancer epidemiology? Occup Environ Med 66(8):497–501
64. Brown RC (2006) Review: windows of exposure to pesticides for increased risk of childhood leukemia. Toxicol Environ Chem 88(3):423–443
65. Infante-Rivard C, Jacques L (2000) Empirical study of parental recall bias. Am J Epidemiol 152(5):480–486
66. Anderson LM, Diwan BA, Fear NT, Roman E (2000) Critical windows of exposure for children's health: cancer in human epidemiological studies and neoplasms in experimental animal models. Environ Health Perspect 108(suppl 3):573–594
67. Danila RN (1989) An epidemiologic study of acute lymphocytic leukemia in children less than sixteen years—an evaluation of potential risk factors with emphasis on farm exposures. University of Minnesota, Minnesota (cited by Wigle et al. 2009)
68. Steinbuch M (1994) The role of environmental exposures in the etiology of childhood acute myeloid leukemia. Ohio State University, OH (cited by Wigle et al. 2009)
69. Dell DM (2004) Epidemiology of childhood leukemia: environmental and genetic determinants. ProQuest Information and Learning Company, Ann Arbor; University of Pittsburgh, Pittsburgh (cited by Wigle et al. 2009)
70. Olshan AF, Anderson L, Roman E, Fear N, Wolff M, Whyatt R, Vu V, Diwan BA, Potischman N (2000) Workshop to identify critical windows of exposure for children's health: cancer work group summary. Environ Health Perspect 108(supplement 3): 595–597
71. Greaves MF, Wiemels J (2003) Origins of chromosome translocations in childhood leukaemia. Nat Rev Cancer 3(9):639–649
72. Lightfoot T (2005) Aetiology of childhood leukemia. Bioelectromagn Suppl 7:S5–S11
73. Kim AS, Eastmond DA, Preston RJ (2006) Childhood acute lymphocytic leukemia and perspectives on risk assessment of early-life stage exposures. Mutat Res 613(2–3):138–160

74. Rossig C, Juergens H (2008) Aetiology of childhood acute leukaemias: current status of knowledge. Radiat Prot Dosimetry 132(2):114–118
75. Kishi R, Katakura Y, Yuasa J, Miyake H (1993) Association of parents' occupational exposure to cancer in children (Japanese). Jpn J Ind Health 35(6):515–529
76. Downs SH, Black N (1998) The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health 52(6):377–384