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Exposure to pesticides and risk of childhood cancer: a meta-analysis of recent epidemiological studies

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ABSTRACT

Objectives The authors performed a meta-analysis of case–control and cohort studies to clarify the possible relationship between exposure to pesticides and childhood cancers.

Methods Two cohort and 38 case–control studies were selected for the first meta-analysis. After evaluating homogeneity among studies using the Cochran Q test, the authors calculated a pooled meta-OR stratified on each cancer site. The authors then constructed a list of variables believed to play an important role in explaining the relation between parental exposure to pesticide and childhood cancer, and performed a series of meta-analyses. The authors also performed a distinct meta-analysis for three cohort studies with RR data.

Results Meta-analysis of the three cohort studies did not show any positive links between parental pesticide exposure and childhood cancer incidence. However, the meta-analysis of the 40 studies with OR values showed that the risk of lymphoma and leukaemia increased significantly in exposed children when their mother was exposed during the prenatal period (OR=1.53; 95% CI 1.22 to 1.91 and OR=1.48; 95% CI 1.26 to 1.75). The risk of brain cancer was correlated with paternal exposure either before or after birth (OR=1.49; 95% CI 1.23 to 1.79 and OR=1.66; 95% CI 1.11 to 2.49). The OR of leukaemia and lymphoma was higher when the mother was exposed to pesticides (through household use or professional exposure). Conversely, the incidence of brain cancer was influenced by the father's exposure (occupational activity or use of household or garden pesticides).

Conclusion Despite some limitations in this study, the incidence of childhood cancer does appear to be associated with parental exposure during the prenatal period.

What this paper adds

The aim of our study was to perform a meta-analysis of case–control and cohort studies to clarify the possible relationship between exposure to pesticides and childhood cancer sites. Our results from OR values show that the risk of brain cancer, leukaemia and lymphoma in childhood is significantly associated with parental exposure and that the prenatal period is a critical window of exposure to these compounds. All the results presented in our manuscript as well as those published elsewhere add to the evidence leading us to recommend minimising parental occupational exposure to pesticides

INTRODUCTION

Childhood cancer is the second leading cause of death among children aged 5–14 years after accidental causes in Europe and the USA (NCI, http://www.cancer.gov).[1 2] Among the 12 major types of childhood cancer, the leukaemia group has the highest incidence (40% of all cancers); cancers of the brain, lymphomas and cancers of central nervous system account for more than 25% of new cases; neuroblastoma, Wilms' tumour and sarcoma are less common.[3–5] In the USA and Europe, there is concern that overall rates of childhood cancer have been increasing since 1970.[6] The risk factors for childhood cancer are largely unknown. A few conditions such as Down's syndrome, other specific chromosomal and genetic abnormalities, and exposure to ionising radiation are known risk factors, but they explain only a small percentage of cases.[7 8] Early-life exposure to environmental contaminants is suspected to be responsible for initial anomalies occurring in utero and leading to cancer.[9 10]

Pesticides are among the suspected environmental factors, as they may promote cellular and molecular events, that is, chromosomal aberrations, oxidative stress, cell signalling disturbances or mutations, that could be linked to increased cancer risk.[11–13] In a review of epidemiological studies in 1997, Daniels *et al*[14] showed that frequent occupational exposure to pesticides or use of pesticides in the home was associated with childhood leukaemia, brain cancer and increased risk of Wilms' tumour, Ewing's sarcoma and germ-cell tumours. Living on a farm, a proxy for pesticide exposure, was also associated with increased risk of a number of childhood cancers in studies investigating associations between pesticide exposure and childhood cancers.[14] Another review of epidemiological studies and childhood cancers[15] revealed conflicting evidence across studies with regard to cancer types as well as to risk factors, and no clear data exist regarding the most critical exposure period for the occurrence of cancer.

The aim of our study was to perform a meta-analysis of case–control and cohort studies in a comprehensive overview of all available knowledge and to clarify the possible relationships between exposure to pesticides and childhood cancers. We focused on the site of the cancer, the period and the duration of exposure among studies that have calculated their evaluation of risk with

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OR. The subjects considered were reported to have been potentially exposed to pesticides after birth, during pregnancy, before conception or 'ever.' The type of exposure covered occupational exposure (farmers or chemical-industry employees), home and garden use as well as exposure due to the proximity of the home to an agricultural area. We have also separately performed a meta-analysis with three cohorts that have evaluated the RR.

MATERIALS AND METHODS

Study identification

We started our study with a review of epidemiological literature on PubMed (http://www.ncbi.nlm.nih.gov). An electronic search using the terms 'pesticides' AND 'childhood cancer' was initially undertaken to find a list of relevant articles. This was supplemented by various combinations of the following keywords: fungicide, herbicide, insecticide, cancer risk, childhood tumour, leukaemia, lymphoma, brain tumour, neonatal exposure, residential exposure, occupational exposure, household pesticides, germ cell tumour and childhood sarcoma haematopoietic cancers, using the AND operating term to complete the search. As a result, we compiled a set of epidemiological studies (published between 1985 and 2008) on the impact of childhood exposure on the risk of developing cancer at any site.

Selection of studies

Studies were excluded if:

- they were not published in English;
- they did not provide sufficient data (for example information was missing on the number of cases and controls, the period of exposure, the person exposed);
- an insufficient number of cases or controls were included (fewer than five) because statistical analyses are less robust;
- they included data resulting from accidental exposure.

Studies were included in the analysis when they complied with the following inclusion criteria:

- case–control or cohort studies with calculation of ORs and RRs
- were published in peer reviewed journals;
- were published between 1985 and 2008;
- included any site of childhood cancer;
- referred to the period of exposure (preconception and/or fetal and/or postnatal and 'ever' exposure, the latter corresponding to an unspecified period).
  - In the case of prenatal exposure, we also included data concerning exposure before conception. The OR was determined after gathering all data related to the exposure of the mother, father and both parents. When considering exposure before pregnancy, the authors included the two parents, and when considering exposure during pregnancy, they included only the mothers.
  - In the case of postnatal exposure, parents had either agricultural or non-agricultural occupations or used pesticides at home or in the garden. In some studies, exposure was due to the use of professional pest control services (indoor or outdoor).
  - Data concerning exposure classified as 'ever' (corresponding to an unspecified period of exposure by authors) were kept aside and analysed separately.
- Parents had either agricultural (farmers, farm workers) or non-agricultural occupations (chemical industry, pest controller).
- In some studies, exposure concerned the use of professional pest-control services (indoor or outdoor).

All identified studies were reviewed by two reviewers, and only studies that met the inclusion criteria were retained.

Data extraction (tables 1a and b (online) in additional data)[16–59]

The following general and methodological information was abstracted from each paper: name of authors, country and year of publication, type of epidemiological study (cohort or case–control), age and sex of children, site of cancer observed, person exposed (mother, father, both parents or child), characteristics of the type of exposure (eg, occupational/non-occupational), period (eg, pre- or postnatal, preconception, both), duration (eg, lifelong or occasional) and frequency, type and value of the calculated risks (OR or RR) with their 95% CIs, statistical method used in each study, data concerning the identity of pesticides and the number of cases and controls exposed or not, when these data were available. Articles that met the criteria of exclusion and inclusion were tabulated in an Excel spreadsheet for use in the meta-analysis. Table 1 (online) lists the most relevant and helpful information for the reader: type of cancer, age of the children, period of diagnosis, type, period and frequency of exposure, pesticide used, and estimated ORs with their 95% CIs. The main childhood cancers examined were cancers of the central nervous system (including astrocytoma, medulloblastoma, ependymoma and glioma), germ-cell tumours, leukaemia (plus different subtypes: lymphoblastic acute leukaemia (LAL), lymphoblastic non-acute leukaemia, acute leukaemia (AL)), non-Hodgkin's lymphoma, kidney tumours, Hodgkin's disease, soft-tissue sarcoma, Ewing's sarcoma and neuroblastoma.

Data analysis

Statistical pooling

Because the method used in our meta-analysis cannot mix OR and RR values in the determination of the pooled OR, we performed two separate meta-analysis; the first using the 304 ORs listed in table 1a (online) (additional data)[16–56] and another using the RRs values of three studies[57–59] listed at the end of table 1a (online).

The calculation of pooled ORs and pooled RRs was performed using the same method described below.

Each manuscript generally assessed several sources of exposure so that several ORs or RR were provided in the same article. When the ORs or RRs were calculated for different subpopulations of the same sample, we considered them separately, and all were taken into account in the meta-analyses.

To calculate the pooled-estimates (meta-OR or meta-RR) and their CI, we first used a fixed-effect model (Mantel–Haenszel method[60]). As the homogeneity hypothesis did not appear to be suitable, we used a random-effect model. The estimation was made according to the DerSimonian and Laird method. For each model, a test for overall effect was performed. The p values showed a significant effect of exposure on cancer risk in both cases.

In the Mantel–Haenszel fixed-effect model the estimated pooled OR or RR $\hat{\theta}$ equals $\hat{\theta}=\sum\theta_i\omega_i/\sum\omega_i$ where θ_i is the OR for the ith study and its weight $\omega_i=b_ic_i/N_i$; a_i and b_i are the number of persons exposed to pesticides and who had or did not develop a cancer respectively; and c_i and d_i are people who were not exposed (or controls), who had or did not have a cancer respectively. N_i is the total number of persons included in each study.

Because of the heterogeneity of our studies, the random-effect model was more appropriate. Using this model, the estimate of the pooled effect and its CI incorporate additional variability due to between-study variance (τ^2). As detailed by DerSimonian and

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Laird,[61] an estimator of τ^2 is defined as $\hat{\tau}^2 = \max$, where $Q = \sum w_i \hat{\theta}_i^2 - (w_i \hat{\theta}_i)^2 / \sum w_i$, and K represents the total number of studies.

In the DerSimonian and Laird method,[61] the estimated pooled OR $\hat{\theta}$ equals $\hat{\theta} = \sum \theta_i \omega_i^* / \sum \omega_i^*$ where θ_i is the OR for ith study and its weight $w_i^* = (\hat{var}(\hat{\theta}_i) + \hat{\tau}^2)^{-1}$. Evaluation of homogeneity was performed using the same method for the calculation of pooled OR and RR.

The next step was to determine the degree of homogeneity among the studies. The test for this hypothesis is based on the Cochran Q test with a degree of freedom equal to the number of studies minus 1 and tests the null hypothesis that the within-study estimates of ORs are homogenous across all the studies.[62] The p value (we considered $p<0.05$ to be statistically significant) indicates the presence or not of heterogeneity among the studies. When the hypothesis of homogeneity among studies appeared to be invalid, we worked with a random-effect model[61] that incorporates the estimation of the pooled effect size, and its CI incorporates the additional variability due to between-study variance,[62] although there are some limitations to the use of a random-effect model.[63]

Analysis

We calculated a meta-OR or a meta-RR for types of cancer. It is worth noting that this method accounts for the weight of each study.[60 62] To investigate possible sources of heterogeneity, we stratified the studies into each site or subtype of cancer as cited by the authors, non-Hodgkin's and Hodgkin's lymphoma, leukaemia (acute lymphoblastic and myeloid leukaemia AML, ALL, LANL), brain cancer, germ-cell tumours, kidney cancer, Ewing's sarcoma and neuroblastoma, and performed a meta-analysis for each. We defined a list of parameters including the exposure setting (occupational/non-occupational, eg, living in an agricultural area, use of pesticides in the home or garden) and the period of exposure (eg, pre- or postnatal or 'ever'), and performed a meta-analysis for each parameter concerned.

Publication bias

We explored the effect of the study size by plotting the logarithm of the estimator of OR versus its SE. Publication bias is characterised by asymmetry of the funnel plot determined by the Egger test.[64] We used the Duval and Tweedie[65] non-parametric 'trim and fill' method of accounting for publication bias in meta-analyses. The method, a rank-based data-augmentation technique, formalises the use of funnel plots, estimates the number and outcomes of missing studies, and adjusts the meta-analysis to incorporate the theoretical missing studies.

Software

All analyses were conducted using Stata/IC 10 (Stata Corporation, PC).

RESULTS

In our PubMed search, we identified 50 articles related to childhood cancer and pesticides. According to our selection criteria (described in Materials and methods), 40 epidemiological studies (two cohorts and 38 case–control studies with OR values[16–56]) were eligible based on inclusion and exclusion criteria, and were selected for the meta-analysis.[5 6] In these studies, 62 risk estimates were identified from both cohort and case–control studies (table 1 (online)). Among all the values included, 96 showed a significant positive association between exposure to pesticides and childhood cancers. Briefly, 36 OR concerned the risk of Hodgkin's and non-Hodgkin's lymphoma, 110 the risk of leukaemia (acute, lymphoid and myeloid), 95 the risk of brain tumour, 18 the risk of germ-cell tumour, and six, nine and four the risk of renal tumour, Ewing's sarcoma and neuroblastoma respectively. Except data from Cordier *et al*,[25] Valery *et al*[26] and Olshan *et al*,[42] most studies provided information on who was exposed (both parents, father, mother or child), the period and the length of exposure. Also, in most studies, the authors provided precise information on the type of exposure (occupational or the use of pesticides in the home or garden, environmental exposure due to living close to an agricultural area, or the intervention of a pest controller outside or inside the home). Fourteen studies[23 27 31 32 34–37 46 49 52–54 66] mentioned the class of pesticides used. Briefly, eight concerned the use of an insecticide, herbicide or fungicide by the parents at home or in the garden; three concerned the professional use of an insecticide, herbicide or fungicide, and two concerned herbicide spraying by a pest controller. Two studies were performed in a population living near an intensive agriculture area where insecticides, herbicides and fungicides were used. Three studies corresponded to cohort studies with RR values.[57–59]

EXPOSURE TO PESTICIDES AND INCIDENCE OF EACH TYPE OF CHILDHOOD CANCER

The separate meta-analysis of the three cohort studies with RR data did not show any positive link between pesticide exposure of parents and leukaemia (seven values, fixed model, OR=0.95; 95% CI 0.81 to 1.11), lymphoma (four values, random model OR=1.08; 95% CI 0.71 to 1.65) and brain cancer (eight values, random model OR=1.035; 95% CI 0.80 to 1.34) incidences.

However, different results were obtained in the meta-analysis of the 40 studies with OR values. Bias was observed only in data on brain tumours as shown by the asymmetry of the funnel plot in figure 1. To correct for this publication bias, we applied the 'trim and fill' method.[65] To make the funnel plot symmetrical, the method added 12 studies presumed to be missing. The corresponding OR decreased from 22% to 17% after application of the 'trim and fill' method but was still significant (OR=1.17; 95% CI 1.09 to 1.26). The hypothesis of a positive correlation between exposure to pesticides and the incidence of childhood brain cancer was still relevant. To explain the remaining heterogeneity after exploration of the publication bias, we performed a stratified analysis by type or subtype of cancer. For most cancers, the results demonstrated differences in effect among the OR (data not shown). A random model was used for analysis, except for germ-cell tumours and renal tumours for which a fixed model was used. For non-Hodgkin's lymphoma and Hodgkin's lymphoma, 36 OR were analysed, 110 OR for leukaemia (acute, lymphoid or myeloid), 95 OR for brain cancer, 18 OR for germ cell tumours, eight OR for renal cancer, nine OR for Ewing's sarcoma and four OR for neuroblastoma. Tests using Cochran Q statistics demonstrated a high heterogeneity, and the hypothesis of an identical effect for all studies was rejected. A meta-analysis revealed a significant increase in the incidence of lymphoma (OR=1.37; 95% CI 1.22 to 1.54), leukaemia (OR=1.23, 95% CI 1.14 to 1.32), brain tumour (OR=1.22; 95% CI 1.13 to 1.31), Ewing's sarcoma (OR=2.01, 95% CI 1.45 to 2.79) and neuroblastoma (OR=1.70; 95% CI 1.14 to 2.51) in children. The incidence of germ-cell tumours in the exposed population did not decrease significantly (OR=0.95; 95% CI 0.86 to 1.03), and there was a slight non-significant increase (OR=1.14; 95% CI 0.98 to 1.33) in the incidence of renal tumours.

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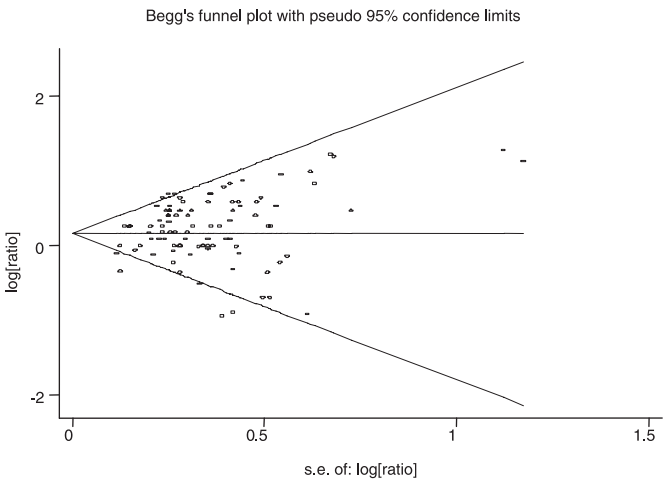


Figure 1 Begg's funnel plot with pseudo-confidence limits of 95% concerning brain cancer. To assess publication bias, we explored the effect of study size by plotting the logarithm of the estimated OR versus its SE. Publication bias is characterised by asymmetry of the funnel plot determined by the Egger test.

As the heterogeneity of each type and subtype of cancer was still significant, we defined other variables (the period of exposure, the type of exposure and the type of pesticide used) to investigate possible sources of heterogeneity.

EFFECT OF THE PERIOD OF EXPOSURE ON CHILDHOOD CANCER

We performed a more detailed analysis of the period of exposure of children, and in each case we calculated the meta-OR by stratifying the data as a function of the person exposed (mother, father or child). The results are presented in figure 2 and table 1. The prenatal period appears to be a critical window of exposure for the incidence of lymphoma. Although the risk of developing this type of cancer did not change significantly when children were exposed after birth, it was significantly higher when exposure occurred during the prenatal period than during the postnatal period. Moreover, the incidence of lymphoma increased by 53% when the mother was exposed during the prenatal period (figure 2A) and, to a lesser extent, when the father was exposed during the same period (figure 2D) (OR=1.37, 95% CI 1.16 to 1.61). The duration of exposure of the mother greatly increased the risk of lymphoma developing during childhood: when exposure was reported to be 'ever,' the OR value was 1.90 (95% CI 1.14 to 3.17).

Leukaemia risk was associated with prenatal exposure of the mother and, to a lesser extent, of the father. The risk increased by 48% and 32% after prenatal exposure of the mother and the father respectively (figure 2B,C respectively). It is noteworthy that when both parents were exposed during the prenatal period, the risk of leukaemia was even higher (84%; OR=1.84; 95% CI 1.39 to 2.44). Surprisingly, postnatal exposure of the mother had a more pronounced effect on the increased risk of leukaemia in childhood (OR=2.12; 95% CI 1.17 to 3.84).

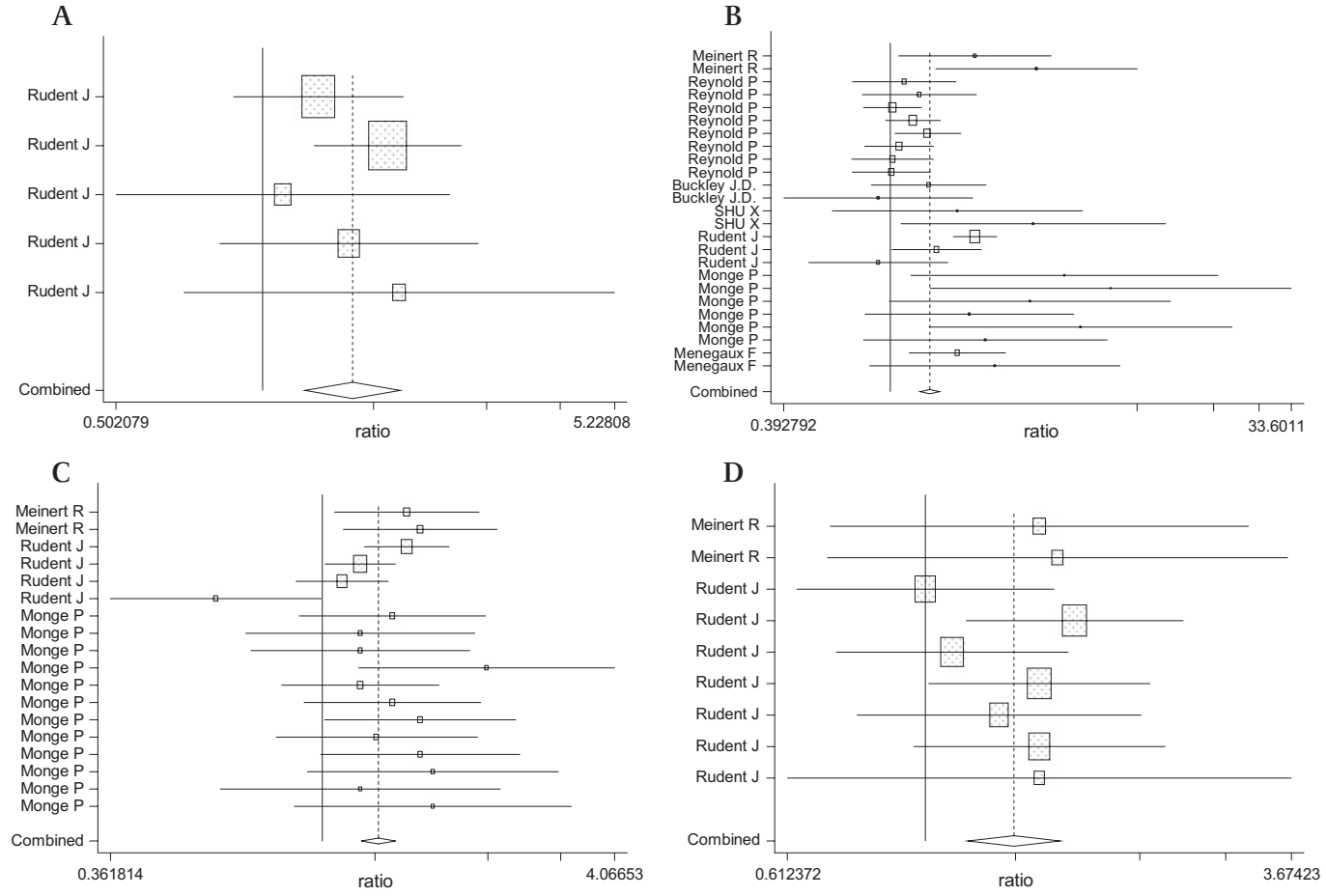


Figure 2 Forest plot of studies related to the incidence of lymphoma (A), and leukaemia (B) when mothers were exposed during the prenatal period. (C, D) Forest plots of studies related to leukaemia and lymphoma incidence respectively when the father was exposed during the prenatal period: representation of pooled OR and its 95% CI for lymphoma and leukaemia according to a fixed or random model as described in 'Materials and method' or in table 1.

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Table 1 Effect of the period of exposure on the incidence of cancers in children: number of data, model used after estimation of heterogeneity, pooled OR estimates and their 95% CI for each type of cancer

	Exposed person	Lymphoma	Leukaemia	Ewing's sarcoma	Brain
Prenatal exposure	Mother	5 (fixed) 1.53 (1.22 to 1.91) No bias	25 (random) 1.48 (1.26 to 1.75) No bias	ND	NS
	Father	9 (fixed) 1.37 (1.16 to 1.61) No bias	18 (random) 1.32 (1.20 to 1.46) No bias	ND	9 (fixed) 1.49 (1.23 to 1.79) No bias
	Father and mother	ND	4 (fixed) 1.84 (1.39 to 2.44) No bias	ND	5 (fixed) 1.37 (1.08 to 1.76) No bias
Postnatal exposure	Mother	ND	3 (fixed) 2.12 (1.17 to 3.84)	ND	ND
	Father	ND	4 (fixed) 1.33 (1.07 to 1.66) No bias	ND	2 (fixed) 1.66 (1.11 to 2.49)
	Father and mother	ND	NS	ND	ND
	Child	NS	NS	NS	21 (random) 1.16 (1.01 to 1.32)
'Ever'	Mother	6 (random) 1.90 (1.14 to 3.17) No bias	ND	NS	NS
	Father	ND	NS	ND	10 (fixed) 1.41 (1.11 to 1.79) No bias
	Father and Mother	ND	NS	ND	NS
	Child	ND	2 (fixed) 1.85 (1.15 to 2.96) Bias	ND	ND

Children were reported to be exposed 'ever' (unspecified period), after birth (postnatal exposure) or before birth (prenatal exposure) and via the father, the mother, both parents or by themselves (the child). The Cochran Q test was used to choose the appropriate model to calculate pooled ORs. In the case of heterogeneity ($p<0.05$), pooled ORs were recalculated according to the random-effect model estimated using the DerSimonian & Laird method.[61] Publication bias was characterised by asymmetry of the funnel plot according to the Egger test[64] (not shown). When there was bias, the pooled ORs were recalculated after applying the 'trim and fill' method.[62]
ND, not determined because there was no study or only one; NS, not significant.

However, this result should be interpreted with caution, since only three ORs were pooled. Table 1 also shows that the increase in incidence of brain cancers in children was more pronounced when exposure occurred during the postnatal period (OR=1.66; 95% CI 1.11 to 2.49). However, it should be noted that only two studies were taken into account for the determination of the pooled OR. Here again, the prenatal period appears to be a critical window of exposure for the incidence of cancer in the offspring (OR=1.49, 95% CI 1.23 to 1.79 when the father was exposed, and OR=1.37, 95% CI 1.08 to 1.76 when both the father and mother were exposed). It is notable that the risk of brain cancer in children mainly increased when the father was exposed rather than the mother, whose exposure only slightly and non-significantly increased the risk. Exposure of both parents also increased the risk (37%) but to a lesser extent.

Next we tried to stratify these data to identify the critical perinatal period (preconception, gestation, lactation) during which the mother's exposure to pesticides could have an impact on the health of her offspring. The results of our stratified analysis (not shown) did not reveal any difference between the three periods tested, probably due to the small number of data concerning this point.

INFLUENCE OF THE TYPE OF EXPOSURE ON THE INCIDENCE OF CHILDHOOD CANCER

We next checked whether the type of exposure (occupational, use of pesticides in the home or garden, the proximity of the home to an agricultural area) could play a role in the risk of developing these diseases. The results of this analysis are presented in table 2. No significant risk of developing lymphoma or leukaemia or a brain tumour was found in children whose parents lived in an active agricultural area. The risk of brain cancer was significantly associated with both occupational and residential exposure of fathers (figure 3A,B respectively) (OR=1.40; 95% CI 1.20 to 1.62 and OR=1.48; 95% CI 1.22 to 1.80 respectively). The risk of developing Ewing's sarcoma increased when fathers were occupationally exposed to pesticides (OR=2.34; 95% CI 1.33 to 4.12) although it should be borne in mind that only three ORs were pooled. On the other hand, the risk of lymphoma and leukaemia increased by 48 and 56% respectively when the mother used pesticides in the home or garden.

INFLUENCE OF THE CLASS OF PESTICIDES ON THE INCIDENCE OF CHILDHOOD CANCER

The last step of our meta-analysis focused on the influence of the type of pesticide on the incidence of childhood cancer. Results are presented in table 3. The risk of lymphoma was correlated with exposure to both insecticides and fungicides (OR=1.46; 95% CI 1.20 to 1.78 and OR=1.45; 95% CI 1.06 to 1.99 respectively) and, to a lesser extent, to herbicides (OR=1.31; 95% CI 1.02 to 1.67). The risk of leukaemia was associated with exposure to herbicides and, to a lesser extent, with exposure to insecticides (OR=1.26; 95% CI 1.14 to 1.39 and OR=1.17; 95% CI 1.03 to 1.33 respectively). The risk of brain cancer was also correlated with exposure to herbicides and fungicides (OR=1.31; 95% CI 1.08 to 1.60 and OR=1.32; 95% CI 1.06 to 1.65 respectively) and, to a lesser extent, with exposure to insecticides (OR=1.18; 95% CI 1.06 to 1.33).

DISCUSSION

The aetiology of childhood cancers remains largely unknown, and it has been hypothesised that environmental factors could play a role.[67] Previous excellent reviews revealed positive and

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Table 2 Effect of the type of exposure (professional or not professional) on the incidence of childhood cancer: pooled OR estimates and their 95% CI for each type of cancer

	Occupational exposure of parents to pesticides		Parents' use of pesticides in the home or garden		Living in an active agricultural zone
	Father	Mother	Father	Mother	
Lymphoma					
Test for heterogeneity	NS	ND	Fixed	Fixed	NS
OR (95% CI)			1.35 (1.13 to 1.61)	1.48 (1.23 to 1.80)	
No of data			6	10	
Leukaemia					
Test for heterogeneity	Fixed	ND	Random	Random	NS
OR (95% CI)	1.37 (1.23 to 1.52)		1.26 (1.06 to 1.49)	1.56 (1.21 to 2.02)	
No of data	21		3	9	
Brain					
Test for heterogeneity	Fixed	NS	Fixed	NS	NS
OR (95% CI)	1.40 (1.20 to 1.62)		1.48 (1.22 to 1.80)		
No of data	11		13		
Ewing's sarcoma					
Test for heterogeneity	Fixed	NS	ND	ND	ND
OR (95% CI)	2.34 (1.33 to 4.12)				
No of data	3				

Children were exposed via the professional use of pesticides by their father or mother, or via the use by the mother or father of pesticides in the home or garden or because they lived in an active agricultural area. The Cochran Q test was used to choose the appropriate model to calculate pooled ORs. In the case of heterogeneity ($p<0.05$), pooled ORs were recalculated according to the random-effect model estimated using the DerSimonian and Laird method. No bias was determined using the Egger test.
ND, not determined because there was no study or only one; NS, not significant.

negative associations between parental exposure to pesticides and the incidence of the main childhood cancers.[15 68 69] We performed a meta-analysis on 40 papers (including case–control and cohort studies) in order to update these data.

From our study, it appears that exposure to pesticides is significantly associated with an increased risk of leukaemia, lymphoma and brain cancer in children. A strong association was found between the incidence of neuroblastoma and Ewing's sarcoma and exposure to pesticides. However, our results should be interpreted with caution because of the small number of reports analysed. These cancers are rare, and a meta-analysis was performed on only four and nine datasets respectively. No correlation was found between parental exposure to pesticides and renal cancer or germ-cell tumours in children. Conversely, our results showed that the risk of leukaemia and lymphoma in children was high when their mothers were exposed during the prenatal period and when they used pesticides in the home or garden (OR=1.48 (1.26–1.75 and 1.53 (1.22–1.99) respectively). Interestingly, the incidence of childhood brain cancer was high (OR=1.49 (1.23–1.79)) when the father was exposed during the prenatal period. In addition, occupational exposure of the father as well as use of pesticides in the home or in the garden was also found to influence the risk of brain cancer in the offspring (OR=1.40 (1.20–1.62) and OR=1.48 (1.22–1.80) respectively). The proximity of the home to a farm or an active agricultural area was not associated with an increased risk of the cancers we studied.

Our results point to the prenatal period as a high-risk window of exposure to pesticides and show that exposure of both the father and mother to pesticides may be linked to the incidence of different cancer sites in childhood. This result indeed suggests that the type of pesticides used and the degree or frequency of exposure may differ depending on the gender of the parent. Moreover, exposure to household and garden pesticides appears to be a high-risk factor for the development of leukaemia, lymphoma and brain cancer in children, whereas occupational

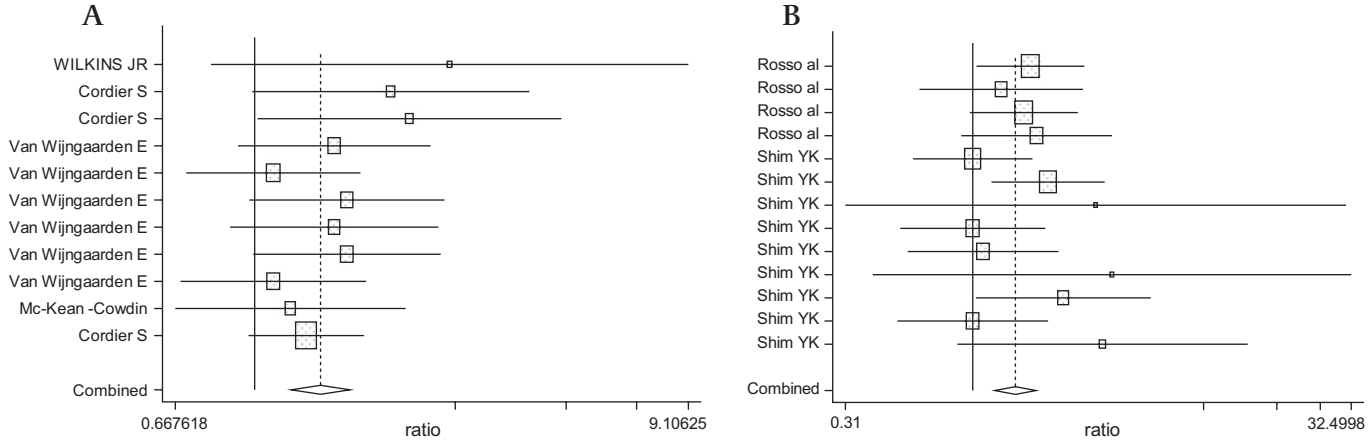


Figure 3 Forest plot of studies related to the incidence of brain cancer when the father was exposed professionally or at home (A, B respectively): representation of pooled OR and its 95% CI for brain cancer according to a fixed or random model as described in 'Materials and methods' or in table 2.

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Table 3 Influence of the class of pesticide on the incidence of childhood cancer: pooled OR estimates and their 95% CI for the incidence of leukaemia, lymphoma and brain cancer as a function of the class of pesticide (herbicide, insecticide and fungicide)

Type of cancer	Herbicide	Insecticide	Fungicide
Lymphoma			
Test for heterogeneity	Fixed	Random	Fixed
OR (95% CI)	1.31 (1.02 to 1.67)	1.46 (1.20 to 1.78)	1.45 (1.06 to 1.99)
No of data	4	11	3
Leukaemia			
Test for heterogeneity	Fixed	Random	NS
OR (95% CI)	1.26 (1.14 to 1.39)	1.17 (1.03 to 1.33)	
No of data	20	45	
Brain			
Test for heterogeneity	Random	Fixed	Random
OR (95% CI)	1.31 (1.08 to 1.60)	1.18 (1.06 to 1.33)	1.32 (1.06 to 1.65)
No of data	16	24	15

The Cochran Q test was used to choose the appropriate model to calculate pooled ORs. In the case of heterogeneity ($p<0.05$), pooled ORs were recalculated according to the random-effect model estimated using the DerSimonian and Laird method. No bias was determined using the Egger test.
NS, not significant.

exposure to pesticides is mainly positively correlated with brain cancer and Ewing's sarcoma. In the case of professional exposure, the type of pesticides used in agriculture and the degree or frequency of exposure undoubtedly differ from residential exposure.[45] Investigators in the Northern California Childhood Leukemia study included a comprehensive assessment of residential exposure to pesticides[70] and provided more precise details concerning the relationship between residential exposure to pesticides and childhood leukaemia. Stratification by biocide category showed statistically significant increased risks of childhood lymphoma and of childhood leukaemia for the group of studies on exposure to insecticides and herbicide respectively. Data on the impact of exposure to herbicides or fungicides and to the three classes of pesticides on the respective incidence of lymphoma and brain cancer were less consistent.

When assessing environmental health impacts, children, fetuses and neonates need to be distinguished from adults, as they are believed to be more vulnerable to the effects of environmental pollutants,[68] and many routes of exposure are possible. Depending on the developmental period, children could be exposed via the placenta, maternal milk, the skin and the digestive tract (WHO 2006 (principles for evaluating health risks in children associated with exposure to chemicals in Environmental Health Criteria (Unedited draft) IPCS, ed., p. 302, WHO, Geneva).[71] The lungs and/or air are also a potentially important source of exposure to pesticides used at home or when the home is located near farms or orchards. Paternal germ cells could also be the target of pesticides via a direct effect resulting in heritable genetic damage or in epigenetic changes that alter gene function.[8 72] This could explain the strong correlation between paternal exposure and the increased incidence of brain cancer. However, several other possible mechanisms could explain this association, especially indirect mechanisms such as household contamination with substances brought home on the father's clothing.[8]

Exposure to pesticides during fetal development is due to the capacity of these compounds to pass through the placental barrier and into the fetal bloodstream.[73 74] The association between the concentration of pesticides in the biological fluid and childhood health problems is well documented.[12 75–77] It is well established that the beginning of the initial event leading to some infant or young children cancers occurs in utero.[12 78] Together with the positive association revealed in our meta-analyses between parental exposure and some childhood cancers, these data lead us to suggest that pesticides present in parent tissue or fluid could be responsible for the genetic modifications in the fetus or in parental germinal cells that lead to cancer.

While our results do provide evidence of an association between pesticide exposure and the risk of some childhood cancers, some limitations of our meta-analysis have to be addressed, and many questions still remain to be answered (the vulnerable window and the frequency of exposure during the prenatal period, for example). Moreover, the use of multiple point estimates from the same publication, although independent, may lead to potential bias or heterogeneity. However, these parameters were evaluated and taken into account in the assessment of the pooled ORs throughout our analysis. One other limitation in our study could be that the assessment of potential risk factors for childhood cancers was performed from a majority of case–control studies and only two cohorts. The general limitations of case–control studies include the response bias due to the use of retrospectively collected data to assess exposure. The use of cohort approaches offers the possibility of collecting individual information on exposure to biomarkers or prospective measurement of the environmental effects of pesticides.[79] However, the incidence of a disease in a cohort is often evaluated as an RR, which is not statistically compatible with the methods used in our meta-analysis which had been validated in a previous work.[62] Indeed, we performed a separate meta-analysis of three cohort studies with RR values: (1) Kristensen *et al*,[58] who showed an association between brain cancer and factors linked to horticulture and use of pesticides; (2) Feychting *et al*,[57] who demonstrated that paternal occupational exposure to pesticides was associated with an increased risk of tumours of the nervous system; and (3) Reynolds *et al*,[59] who observed little evidence of any association between the incidence of childhood cancers and residence in an agricultural area characterised by intensive use of pesticides. The result of this meta-analysis did not show any positive correlation between parental exposure to pesticide and childhood cancer incidence. This result must be considered carefully because of the small number of data and because exposures of parents were different in these studies. On the other hand, three very recent reviews and meta-analyses[80–83] showed a significantly elevated risk of childhood leukaemia associated with paternal and maternal occupational and/or residential exposure. These studies complete and reinforce these data on the incidence of leukaemia.

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In conclusion, despite some limitations in our study, our results do provide evidence concerning the sites of childhood cancer most associated with pesticide exposure, the period and type of exposure as well as the type of pesticide that could increase the risk of developing childhood cancer. The causality of these associations is not proven, and the hypothesis of an environmental origin of some cancers requires experimental studies. Taken together with the results of our previous study,[62] the results of the present work convinced us of the need to conduct experimental studies to confirm and explain these correlations.

Competing interests None.

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Exposure to pesticides and risk of childhood cancer: a meta-analysis of recent epidemiological studies

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