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## To cite this version:

Geneviève van Maele-Fabry, Laurence Gamet-Payrastre, Dominique Lison. Residential exposure to pesticides as risk factor for childhood and young adult brain tumors: A systematic review and meta-analysis. Environment International, 2017, 106, pp.69-90. 10.1016/j.envint.2017.05.018 . hal-01602578

**HAL Id: hal-01602578**

**https://hal.science/hal-01602578**

Submitted on 26 May 2020

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Environment International 106 (2017) 69–90

Contents lists available at ScienceDirect

Environment International

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

Review article

# Residential exposure to pesticides as risk factor for childhood and young adult brain tumors: A systematic review and meta-analysis

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ARTICLE INFO

*Keywords:*
Child
Brain tumors
Residential exposure
Pesticides
Systematic review
Meta-analysis

ABSTRACT

*Background:* Accumulating evidence suggests a positive association between exposure to non-agricultural pesticides and childhood brain tumors (CBT).

*Objective:* (1) To conduct a systematic review and meta-analysis of published studies on the association between residential/household/domestic exposure to pesticides and childhood brain tumors. (2) To clarify variables that could impact the results.

*Methods:* Publications in English were identified from a MEDLINE search through 28 February 2017 and from the reference list of identified publications. Risk estimates were extracted from 18 case-control studies published between 1979 and 2016 and study quality assessments were performed. Summary odds ratios (mOR) were calculated according to fixed and random-effect meta-analysis models. Separate analyses were conducted after stratification for study quality, critical exposure period, exposure location, specific exposures, pesticide category, application methods, type of pest treated, type of CBT, child's age at diagnosis and geographic location.

*Results:* Statistically significant associations were observed with CBT after combining all studies (mOR: 1.26; 95% CI: 1.13–1.40) without evidence of inconsistency between study results or publication bias. Specifically, increased risks were observed for several groupings and more particularly for gliomas and exposure involving insecticides. Statistical significance was also reached for high quality studies, for all exposure periods, for indoor exposure and, more particularly, during the prenatal period for all stratifications involving insecticides (except for outdoor use), for pet treatments, for flea/tick treatment, for studies from USA/Canada and studies from Europe (borderline) as well as for data from studies including children of up to 10 years at diagnosis and of up to 15 years.

*Conclusions:* Our findings support an association between residential exposure to pesticides and childhood brain tumors. Although causality cannot be established, these results add to the evidence leading to recommend limiting residential use of pesticides and to support public health policies serving this objective.

## 1. Introduction

Descriptive epidemiology of childhood brain tumor (CBT) has recently been reviewed (Johnson et al., 2014). In the United States and Canada, brain and central nervous system (CNS) tumors are the most frequent solid tumors and the second leading cause of cancer-related death in children and adolescents 0 to 19 years of age (Kaderali et al., 2009; Siegel et al., 2013). In Europe, primary tumors of the CNS are the second most common (after leukemia) and the most lethal childhood tumors in children 0 to 14 years old (Gatta et al., 2014; Steliarova-Foucher et al., 2004). CBT include several histologic subtypes, each with a different incidence rate according to age (higher incidence rates observed in children 0 to 4 years of age in USA and Europe), country (overall incidence varies from 1.12 cases to 5.26 per 100,000 persons in Kuwait and in USA), gender (more common in males) and ethnicity (for review, see Johnson et al., 2014). The higher incidence rate of childhood brain tumors occurring before the age of 5 suggests that both prenatal and early postnatal exposures may be especially important.

Improved survival after a diagnosis of CNS tumor recorded over the past 40 years can mainly be attributed to earlier detection and advances in treatment (e.g., surgical techniques, rational use of postoperative radiation and chemotherapy) (Arndt et al., 2007; Wells and Packer,

*Abbreviations:* ASTRO, astroglial brain tumors; CBT, childhood brain tumor; CNS, central nervous system; CYPs, cytochrome P450s; 95% CI, 95% confidence interval; 2,4-D, 2,4-dichlorophenoxy acetic acid; ICCC, international classification of children cancer; ICD, international classification of diseases; MA, meta-analysis; mOR, summary odd ratio estimate; OC, organochlorine; OP, organophosphorus; OR, odds ratio; PNET, primitive neuroectodermal tumors; SE, standard error; 95% UI, 95% uncertainty interval

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http://dx.doi.org/10.1016/j.envint.2017.05.018
Received 20 September 2016; Received in revised form 19 May 2017; Accepted 19 May 2017
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2015).

However, despite these medical progresses and decades of epidemiological research, the etiology of CBT remains largely unclear. A multifactorial process involving genetic and environmental factors is the most likely explanation. It has been suggested that associations with parental exposure to toxicants during pregnancy may differ with polymorphisms in genes metabolizing these toxicants. As an example, positive associations were observed between both paternal and maternal smoking during pregnancy and childhood brain tumors such that children with a greater PAH activation genotype were at a higher risk relative to children with wild type genotype (Barrington-Trimis et al., 2013). Dubuc and collaborators recently reviewed major cytogenetic and genomic aberrations associated with the most common pediatric brain tumors (medulloblastoma, ependymoma, supratentorial primitive neuroectodermal tumors, and pilocytic astrocytoma) and described advances in the understanding of the epigenetics of brain tumors (Dubuc et al., 2010, 2012). Established CBT risk factors are limited to ionizing radiation exposure and to some cancer syndromes including neurofibromatosis types 1 and 2, tuberous sclerosis, nevoid basal cell carcinoma, Turcot, Cowden, hereditary retinoblastoma and Rubinstein-Taybi syndromes. Many potential risk factors have been studied with inconclusive results, including anthropometric factors (birth weight, birth length, head circumference, maternal age), developmental and birth characteristics (birth defects, premature birth, parity, single or multiple birth, as examples), parental exposures during pregnancy (smoking, alcohol, vitamin intake, folic acid intake, medication, dietary N-nitroso compounds), parental occupational exposures (electromagnetic fields, pesticides), head injuries, allergic conditions (atopy), infectious exposures (Johnson et al., 2014; Vienneau et al., 2016).

For years, pesticides have been specifically scrutinized in this respect. Several literature reviews on pesticide exposure and childhood cancer have been published the last ten years (Infante-Rivard and Weichenthal, 2007; Infante-Rivard, 2008; Nasterlack, 2006, 2007; Turner et al., 2010; Van Maele-Fabry et al., 2010, 2011, 2013; Wigle et al., 2009, as examples). Environmental exposure to pesticides is of particular concern for children as they are particularly vulnerable due to physiological and behavioral characteristics (greater food or fluids intake per body weight, "hand-to-mouth" activity, as examples) that can increase the dose and toxicity as compared to adults (Karr et al., 2007; Moya et al., 2004; Roberts et al., 2012). Children can be exposed to pesticides indirectly from parental pesticide exposure via occupational and para-occupational ("take-home") exposure. Two meta-analyses (MA) suggest some support for a positive association between paternal and parental occupational exposure to pesticides and childhood brain tumors, respectively (Van Maele-Fabry et al., 2013; Vinson et al., 2011). Children can also be directly exposed to pesticides from residential/household/domestic uses. The main sources of such pesticide exposures include professional pest control services, indoor uses (in homes, schools, and other buildings), outdoor uses (in garden, public areas, agricultural application drift), handling treated or contaminated pets or others (use of insecticidal shampoos for lice infestation, as examples) (Zahm and Ward, 1998). Indoor broadcast applications can leave lingering residues in the air, carpet, toys and house dust (Deziel et al., 2015). The present work analyzes the possible association between residential/household/domestic exposure to pesticides and childhood brain tumors.

While most epidemiological studies on the relationship between childhood pesticide exposure and brain cancer were considering parental occupational exposures, there were fewer studies assessing residential exposures. Several were of small size and the results were inconsistent. Recently, three MA combined results on childhood brain tumors following residential exposure to pesticides (Chen et al., 2015; Kunkle et al., 2014; Vinson et al., 2011). Two of which examined the association with several childhood cancers, including brain cancer (Chen et al., 2015; Vinson et al., 2011) and one focused on childhood brain cancer with regard to parental farm-related pesticide exposure during pregnancy (Kunkle et al., 2014). Very few results from Vinson et al. (2011) related CBT to residential exposures, most of them focusing on occupational exposures and occupational or residential exposures combined. The MA of Chen et al. (2015) concerned exclusively postnatal exposure (children as exposure group); and in the MA of Kunkle et al. (2014), only scarce data for non-agricultural exposure are reported.

The purpose of our study is to systematically review and to meta-analyze the available epidemiological data on the relationship between residential pesticide exposure and childhood brain tumors. We aim to enhance our understanding of the potential involvement of residential exposure in the etiology of CBT by exploring several variables as potential sources of heterogeneity in results: the quality of the studies, the sources of pesticide exposure and exposure location, critical exposure periods, specific pesticide category, application methods, type of pest treated, specific exposures, type of CBT, child age at diagnosis and geographic location.

## 2. Materials and methods

The systematic review and MA was conducted according to the protocol described in details in previous publications by our group (Van Maele-Fabry et al., 2010, 2011, 2013) and followed the available guidelines, including PRISMA (Liberati et al., 2009) and PRISMA-P (Moher et al., 2015) statements for reporting systematic review and MA. It has to be stressed that these guidelines do not cover all the complexities associated with reporting systematic reviews in the pediatric population. A study protocol for the development of guidelines for conducting and reporting of systematic reviews and MA in newborn and child health research (PRISMA-Children [C] and PRISMA-Protocol for Children [P-C]) is being developed and the final statements are expected to be published in 2017 (Kapadia et al., 2016).

### 2.1. Study identification and selection

#### 2.1.1. Study identification

The search strategy was designed to identify all English-language observational studies on childhood brain tumors and residential pesticide exposure published in the open literature in peer-reviewed journals. An electronic search on MEDLINE (National Library of Medicine, Bethesda, MD) was conducted for the period 1966 to 28 February 2017 using "(pesticides OR herbicides OR insecticides OR fungicides) AND ((children OR childhood) AND brain tumors) AND (residential OR domestic OR household)". This was supplemented by single or multiple combinations of the words pesticide(s), herbicides, insecticides, fungicides, child, children, childhood, infant, newborn, preschool child, adolescent, youth, teenage, tumors, cancer, neoplasm, astroglial, astrocytomas, glial, primitive neuroectodermal, embryonal, intracranial, residential, household, domestic, indoor, outdoor with no restriction of publication type or publication date. The reference lists of the relevant publications and review papers were also checked for additional studies.

#### 2.1.2. Study selection

Studies using a cohort and a case-control design, that referred to children exposed to pesticides from residential use (indoor or outdoor), with (subtypes of) brain tumors as the outcome were considered eligible. Studies not published in English, published in the grey literature, that did not report original results (reviews, MA, case-reports, comments, letters, editorials, and abstracts), experimental and ecological studies, focusing only on genetic data, that clearly examined a specific cancer type other than brain cancer as well as those dealing with no residential exposure, e.g. exposure resulting from agricultural drift or those reporting data for farm-related exposures were excluded.

The screening step was performed by evaluating the titles and abstracts of the studies identified by the electronic search. The full text of

potentially relevant studies was then examined. We excluded redundant studies (with subjects already included in another more complete or more recent study examining a greater number of subjects or with longer follow-up duration) to preserve the assumption of independence. Studies combining adults and children with no separate reporting of children data as well as studies providing insufficient data to determine an estimator of relative risk and its confidence intervals for childhood brain tumors were also excluded from the MA.

### 2.2. Data extraction

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

An overall MA including data from all case-control studies was performed and is illustrated by a forest plot. In subgroup analyses, summary estimates were calculated for stratifications defined by study quality (high quality, low quality), exposure windows (prenatal, childhood), exposure location (indoor, outdoor), specific exposure (professional pest exterminator, pet treatments), biocide category (insecticides, herbicides, fungicides), application methods (spray/bomb, strip, collar, shampoo), type of pest treated (termite, lice, flea/tick), brain tumor type (gliomas, embryonal tumors), geographic location (USA/Canada, Europe, others), age at diagnosis (0–10 years, 0–15 years, 0 up to > 15 years).

### 2.3. Quality assessment

Study quality was assessed for all included studies by two authors (GVM-F and LG-P) by using a modified version of the Downs and Black (1998) checklist (Supplemental Material Table 1). Because this tool was developed mainly for randomized clinical trials, the checklist was modified by Wigle et al. (2009) by adding new assessment factors focusing on the quality of exposure assessment (robustness of exposure measurement, variability of exposure intensity or duration, and specificity) and the ability to identify exposure windows (preconception, pregnancy, childhood). Before conducting the quality assessment, both reviewers discussed the individual items of the checklist to clarify their interpretation and differences in quality assessment were resolved by consensus.

### 2.4. Statistical analysis

Odds ratios of individual case-control studies were combined. Summary risk estimates were calculated according to a fixed-effect model (the Mantel-Haenszel method), which assumes that results across studies differ only by sampling error, and to the random effect model described by DerSimonian and Laird (1986), which incorporates the additional variability due to between-study variance.

The between-study heterogeneity was assessed using chi-square-based Q-test and the $I^2$ statistic. A low $P$ value from the chi-squared test indicates statistically significant heterogeneity, and, the $I^2$ statistic lying between 0% and 100%, a value of 0% indicates no observed heterogeneity and larger values show increasing heterogeneity (Deeks et al., 2011; Higgins et al., 2003). Potential sources of heterogeneity were evaluated by subset analyses.

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

To determine the robustness of the findings as well as to determine whether some of the selections made had a major effect on the results, sensitivity analyses were conducted by:

- performing the MA of all studies using both fixed and random effect methods;
- removing studies with partial redundancy (Pogoda and Preston-Martin, 1997 and Searles Nielsen et al., 2010, alternately)
- omitting the studies reporting extreme risk estimator values (the highest [Gold et al., 1979] and the lowest [Searles Nielsen et al., 2005]);
- re-estimating the mOR after including data from different sources of comparison (friends or cancer controls in Davis et al., 1993 and normal or cancer controls in Gold et al., 1979)
- re-estimating the mOR while dropping one study out at a time and examining whether any study disproportionately influenced the results.

## 3. Results

### 3.1. Study selection and characteristics

A total of 18 studies were identified for inclusion in the MA after the selection process as reported in the flow-diagram of Fig. 1. After adjusting for duplicates, 198 studies were retained for further evaluation. Of these, 144 were excluded after preliminary screening as they did not fulfil the inclusion criteria with regards to the language (not in English; $n = 12$), the study design (not cohort nor case-control studies; $n = 47$), the exposure (not residential, combining occupational and residential exposures, not pesticides; $n = 21$), the population (not children, combining data for children and adults; $n = 3$), outcome (no brain tumors data, $n = 39$). Experimental/mechanistic/genetic studies were also excluded ($n = 4$) as well as exposure studies ($n = 11$). Seven additional studies were off topic. After this screening process based essentially on titles and abstracts, 40 studies were retained for further evaluation. Of these, 36 were excluded for the reasons reported in Fig. 1.

No cohort study fulfilling the inclusion criteria was retrieved. The 18 studies finally selected for the review were all case-control studies (Bunin et al., 1994; Chen et al., 2016; Cordier et al., 1994; Davis et al., 1993; Gold et al., 1979; Greenop et al., 2013; Howe et al., 1989; Kuijten et al., 1990; Leiss and Savitz, 1995; McCredie et al., 1994; Pogoda and Preston-Martin, 1997; Preston-Martin et al., 1982; Rosso et al., 2008; Schüz et al., 2001; Searles Nielsen et al., 2005; Searles Nielsen et al., 2010; Shim et al., 2009; Spix et al., 2009). Table 1 provides the main characteristics of the studies included in the analysis. These studies were published between 1979 and 2016, twelve were from USA, 3 from Europe, 2 from Australia and 1 from China. Children and young adults included in these studies were diagnosed with brain tumors between 0 and 10 years (6 studies), 0 to 15 years (7 studies) and 0 to > 15 years of age (5 studies). Exposure data varied greatly among studies. Exposure occurred prenatally ($n = 13$) and postnatally ($n = 12$), pesticides were used indoor ($n = 14$) and outdoor ($n = 6$). The great majority of studies reported data for insecticide use ($n = 10$) while use of herbicides and fungicides was less addressed ($n = 3$ and $n = 2$, respectively). Most studies presented data for brain tumors in general and only 6 specified the type of brain tumors. The number of variables that were adjusted/matched for were also very different from one study to another (Table 1).

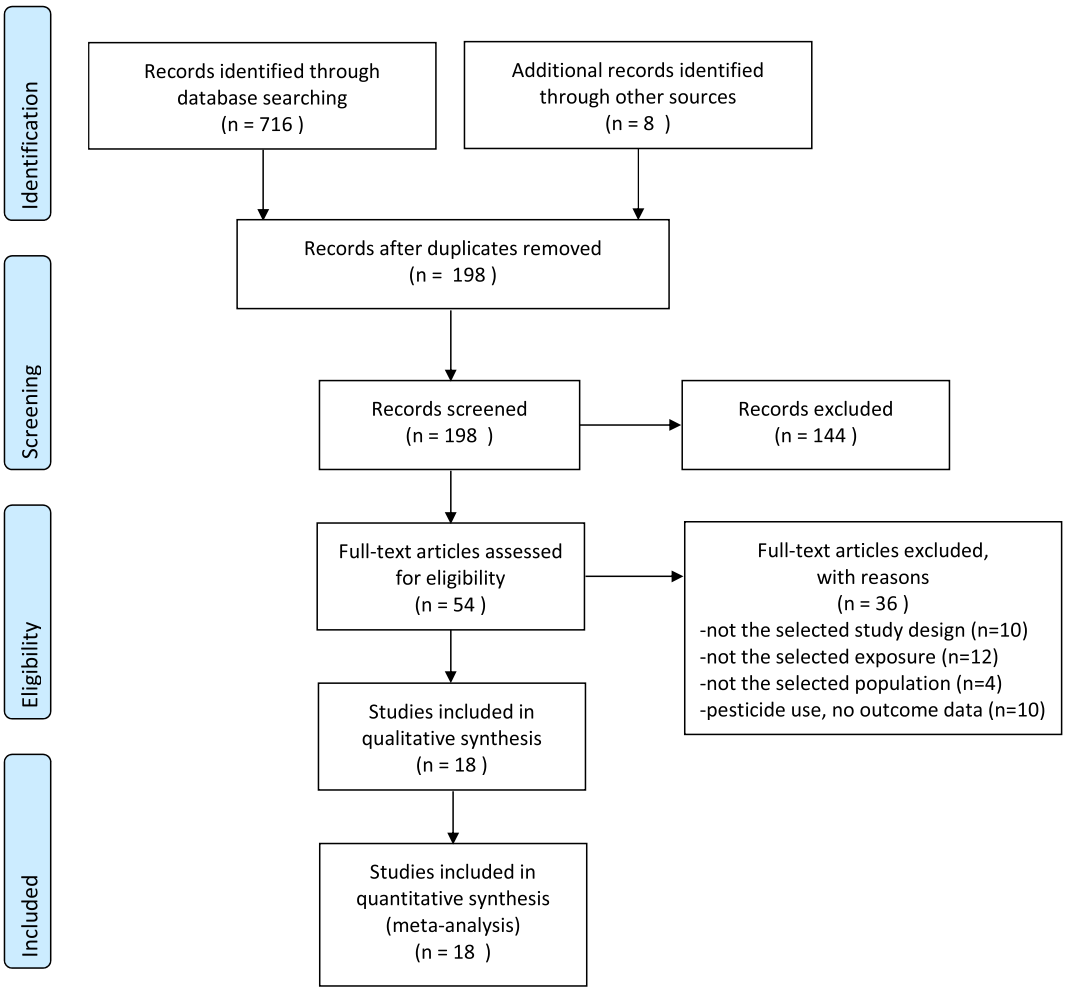


**Fig. 1.** Prisma flow diagram (Liberati et al., 2009) summarizing the search strategy for meta-analysis of residential pesticide exposure and childhood brain tumors.

### 3.2. Quality assessment

Quality scores are presented in Supplemental Material Table 2. Total scores ranged from 6.5 to 15.5 with a median value of 10.5 (maximum score of 20). No tendency to higher quality scores was observed in more recent studies. Compared with lower total quality score studies, those with higher total scores tended to have higher scores for factors related to exposure measurement and, to a lesser degree, to bias control (Supplemental Material Table 2).

### 3.3. Synthesis of results

The results of the MA are reported in Fig. 2 and in Table 2. A statistically significant association between residential exposure to pesticides and childhood/young adults brain tumors was observed, without evidence of inconsistency between studies, when the main data of all studies ($n$ = 18) were combined (mOR: 1.26, 95% CI: 1.13–1.40; $I^2$: 0%). A forest plot of these studies is shown in Fig. 2. Estimated effects of all studies except three (Howe et al., 1989; Bunin et al., 1994; Searles Nielsen et al., 2005) were on the same side of the unit line and the confidence intervals overlap to a large extent. This plot shows a low level of heterogeneity.

Subgroup analyses were also performed within strata hypothesized a priori to influence the overall result as well as the indicators of between study results heterogeneity and inconsistency. These data are reported in Table 2. With the exception of the combined data for the fungicides category and for the lice as pest treated, all summary risks (mOR) were higher than 1 and for the majority of stratifications, no indication of between study inconsistency ($I^2$: 0%) was observed. Statistical significance was reached for several groupings. Significant increased risks were observed for high quality studies, both exposure time windows (prenatal, childhood). Indoor exposure, and more particularly during the prenatal period, showed a significantly increased risk. All stratifications involving insecticides showed statistically significant increased risks, except outdoor insecticides (insecticides [all studies, prenatal, childhood]; indoor insecticides). The highest mORs were observed for the specific exposure “pet treatments” and for the type of pest treated “Flea/tick”. Significant increased risks were also observed when combining studies reporting data on gliomas (gliomas all studies and prenatal), for the stratification by geographic location when grouping studies from USA/Canada and studies from Europe (borderline) as well as for data from studies including children of up to 10 years at diagnosis and of up to 15 years.

### 3.4. Publication bias

A funnel plot of ln(OR) versus 1/SE for the MA including all studies for residential exposure to pesticides and childhood brain tumors was constructed (Fig. 3). Assessment of publication bias using the funnel plot did not demonstrate any obvious publication bias: the visual inspection of this figure does not clearly detect asymmetry arising from a lack of small studies with low risk estimators. The statistical analysis provided by the linear regression method of Egger et al. (1997) did not yield evidence of asymmetry (intercept: 1.023; 95% CI: −0.6129 to 2.659) ($p > 0.20$).

**Table 1**
Summary from relevant case-control studies dealing with residential exposure to pesticides and childhood brain tumor.

| References/geographic location/ study design/period of diagnosis | Child's age | Exposure category (source of exposure data) | Exposed person | Period of exposure | Tumor type° (source of tumor definition) | Number of exposed cases/controls | Odd ratio°° (95% CI) | Adjustment/matching |
|---|---|---|---|---|---|---|---|---|
| Bunin et al., 1994<br>USA/Canada<br>Population-based case-control study<br>"Children's Cancer Group"<br>1986–1989 | < 6 years | Household exposures: | Mother | Pregnancy | ASTRO | 34/26 | 1.5 (0.8–2.7) | Matching by race, birth year, telephone area code and prefix.<br>ASTRO: adjusted for income level; PNET: unadjusted |
| | | - Use of insect sprays or pesticides | | | | | | |
| | | - At least weekly | | | | 8/4 | 2.2 (0.6–7.4) | |
| | | - Home pest extermination | | | | 24/31 | 0.7 (0.4–1.4) | |
| | | Household exposures: | Mother | Pregnancy | PNET | | | |
| | | - Use of insect sprays or pesticides | | | | 31/39 | 0.7 (0.4–1.4) | |
| | | - At least weekly | | | | 5/5 | 1.0 (0.2–4.9) | |
| | | - Home pest extermination | | | | 34/33 | 1.0 (0.6–1.9) | |
| | | Household exposures: | Mother | Pregnancy | CBT | | | |
| | | - Use of insect sprays or pesticides | | | | 65/65 * | 1.0 (0.68–1.47) * | |
| | | - At least weekly | | | | 13/9 * | 1.46 (0.62–3.47) * | |
| | | - Home pest extermination | | | | 58/64 * | 0.89 (0.60–1.31) * | |
| | | (Questionnaire: parental telephone interviews) | | | (Biopsy [not for all cases]; pathologist) | | | |
| Chen et al., 2016<br>Shanghai (East China)<br>Hospital-based case-control study<br>2012–2015 | 0–14 years | Household exposures: Types of pesticides | Family use | After conception | CBT | 63/47 | 1.68 (1.06–2.6) | Matching by sex, age, province of residence.<br>Adjusted for age, sex, household income, maternal education level, and province of residence |
| | | - Mosquitocide | | | | | | |
| | | - Cockroach killer | | | | 58/40 | 1.83 (1.13–2.95) | |
| | | - Rodenticide | | | | 23/26 | 0.92 (0.50–1.70) | |
| | | - Mothproof agent | | | | 75/70 | 1.25 (0.81–1.93) | |
| | | - Flea/tick killer (questionnaire: mother interview at the hospital) | | | (Pediatric neurosurgery of 2 children's medical centers in Shanghai) | 19/16 | 1.29 (0.64–2.60) | |
| | | Urinary pyrethroid-total metabolites quartiles (*cis*-DCCA + *trans*-DCCA + 3-PBA):<br>Q1 (< 0.82 μg/g creatinine) | | | | 20/42 | Referent | |
| | | Q2 (0.82 to < 1.65 μg/g creatinine) | | | | 23/43 | 1.12 (0.54–2.34) | |
| | | Q3 (1.65 to < 4.25 μg/g creatinine) | | | | 46/43 | 2.25 (1.14–4.42) | |
| | | Q4 (> 4.25 μg/g creatinine)<br>Remark: also data for the three individual metabolites quartiles | | | | 72/42 | 3.60 (1.87–6.93)<br>[*p*-trend: 0.009] | |
| Cordier et al., 1994<br>France (Paris, Ile de France)<br>Part of a multicentric population-based case-control | 0–15 years | House treated with pesticides | Mother | Pregnancy (1 month before pregnancy to birth) | CBT | 18/21 | 1.8 (0.8–4.1) | Frequency-matched for year of birth. Adjusted for child's age and sex and for maternal age |

*(continued on next page)*

**Table 1** *(continued)*

| References/geographic location/ study design/period of diagnosis | Child's age | Exposure category (source of exposure data) | Exposed person | Period of exposure | Tumor type° (source of tumor definition) | Number of exposed cases/controls | Odd ratio°° (95% CI) | Adjustment/matching |
|---|---|---|---|---|---|---|---|---|
| study (SEARCH) coordinated by IARC 1985–1987 | | | Child | Childhood (at least 1 month total before the age limit) | | 31/36 | 2.0 (1.0–4.1) | |
| | | Rem: homes treated for pests by professional exterminators: OR = 0.9 (questionnaire: mothers, face to face interviews, completed with fathers acting as interpreter if mothers could not understand French) | | | (Hospital records; CAT-scan for all cases but not biopsy for all [73%]) | | | |
| Davis et al., 1993 Missouri (USA) Population-based case-control study 1985–1989 | 0–10 years | Pesticides used for nuisance pests | Family use | Pregnancy | CBT | 30/nr | 1.8 (0.8–4.0) | Adjusted for child's age at diagnosis, child's exposure to environmental tobacco smoke, family income, father's and mother's education, family member in the construction industry, time between diagnosis and interview |
| | | | | 0–6 months (birth to 6 months) | | 28/nr | 1.9 (0.8–4.3) | |
| | | | | 7-diagnosis | | 38/nr | 3.4 (1.1–10.6) | |
| | | Pesticides used on pets | | Pregnancy | | 11/nr | 0.9 (0.4–2.0) | |
| | | | | 0–6 months | | 10/nr | 1.0 (0.4–2.5) | |
| | | | | 7-diagnosis | | 21/nr | 1.1 (0.5–2.6) | |
| | | Insecticides used in the garden or orchard | | Pregnancy | | 11/nr | 1.5 (0.6–3.9) | |
| | | | | 0–6 months | | 7/nr | 2.3 (0.7–8.3) | |
| | | | | 7-diagnosis | | 22/nr | 1.6 (0.7–3.6) | |
| | | Herbicides used on the yard | | Pregnancy | | 12/nr | 1.1 (0.5–2.5) | |
| | | | | 0–6 months | | 15/nr | 1.7 (0.7–3.9) | |
| | | | | 7-diagnosis | | 30/nr | 2.4 (1.0–5.7) | |
| | | Application methods: | | | | | | |
| | | - Spray (bomb) | | Pregnancy | | 5/nr | 2.1 (0.5–8.3) | |
| | | - Strip | | Pregnancy | | 8/nr | 5.2 (1.2–22.2) | |
| | | - Collar (flea collar used on pets) | | Pregnancy | | 16/nr | 1.0 (0.4–2.1) | |
| | | - Shampoo: Kwell® [lindane] used on lice | | 7-diagnosis | | 7/nr | 4.6 (1.0–21.3) | |
| | | - Shampoo used on pets | | Pregnancy | | 10/nr | 0.8 (0.3–1.9) | |
| | | Type of pest treated: | | | | | | |
| | | - Termites | | 7-diagnosis | | 12/nr | 1.4 (0.5–3.9) | |
| | | - Lice | | 7-diagnosis | | 8/nr | 1.3 (0.4–4.1) | |
| | | - Flea/tick (collar used on pets) | | Pregnancy | | 16/nr | 1.0 (0.4–2.1) | |
| | | (Questionnaire: mother telephone interview + mailed packet containing a handout to improve recall) | | | (population-based Missouri Cancer Registry [MCR]; 89% histologically confirmed) | (2 control groups: friends and cancer co. data reported for friends co) | | |
| Gold et al., 1979 Baltimore, [Maryland] (USA) Exploratory case-control study 1965–1975 | < 20 years | Extermination for insects in the household (insecticides) | Child | Prior to diagnosis | CBT | Discordant pairs (case-control) 16 (+ −)/7 (− +) | 2.3 (0.94–5.57) * | Matched on sex, date of birth, race. |
| | | (Questionnaire: parental interview on exposure to several possible | | | (Hospital diagnostic listings, death certificates, hospital | (2 control groups: normal [non- | | |

(continued on next page)

**Table 1** *(continued)*

| References/geographic location/ study design/period of diagnosis | Child's age | Exposure category (source of exposure data) | Exposed person | Period of exposure | Tumor type° (source of tumor definition) | Number of exposed cases/controls | Odd ratio°° (95% CI) | Adjustment/matching |
|---|---|---|---|---|---|---|---|---|
| | | etiologic agents) | | | tumor registries, and pathology, radiotherapy and clinical oncology records) | diseased] children and cancer children, data reported for normal co) | | |
| Greenop et al., 2013 Australia (all 10 pediatric oncology centers), Nationwide case-control study "Aus-CBT, The Australian Study of Childhood Brain Tumors" 2005–2010 | 0–14 years | Professional pest control treatment in the home or garden: any treatment | Mother | Before (the year before pregnancy) | CBT | 72/187 | 1.54 (1.07–2.22) | Matched on age, sex, State of residence. Adjusted for matching variables, year of birth, maternal age, child's ethnicity, parental education, maternal pre-pregnancy folate supplementation |
| | | | | Pregnancy (during) | | 46/116 | 1.52 (0.99–2.34) | |
| | | | | 0–3 months | | nr | 0.76 (0.27–2.15) | |
| | | | | 4–6 months | | nr | 1.30 (0.68–2.50) | |
| | | | | 7–9 months | | nr | 2.13 (0.99–4.60) | |
| | | | | Prenatal (before + during pregnancy) | | 118/303 | 1.26 (0.96–1.65) * | |
| | | | Child | After birth | | 93/303 | 1.04 (0.75–1.43) | |
| | | Treatment in this period only | Mother | Before | | 23/46 | 1.90 (1.08–3.36) | |
| | | | | Pregnancy | | 5/18 | 1.02 (0.35–3.00) | |
| | | | Child | After birth | | 44/165 | 0.84 (0.56–1.26) | |
| | | Person home during treatment | Father | Before | | 12/29 | 1.79 (0.85–3.80) | |
| | | | Mother | Before | | 23/81 | 1.13 (0.66–1.96) | |
| | | | | Pregnancy | | 19/49 | 1.53 (0.83–2.82) | |
| | | | | Prenatal | | nr | 1.23 (0.75–2.01) | |
| | | | Child | After birth | | 38/9 | 1.63 (1.02–2.60) | |
| | | Any treatment | Mother | Before | Gliomas: low-grade | 33/187 | 1.58 (0.97–2.57) | |
| | | | | Pregnancy | | 22/116 | 1.54 (0.87–2.71) | |
| | | | Child | After birth | | 44/303 | 0.99 (0.64–1.53) | |
| | | | Mother | Before | Gliomas: high-grade | 7/187 | 2.99 (0.99–9.02) | |
| | | | | Pregnancy | | 6/116 | 4.58 (1.39–15.14) | |
| | | | Child | After birth | | 7/303 | 1.25 (0.45–3.43) | |
| | | | Mother | Before | EP (ependymomas | 6/187 | 2.34 (0.74–7.42) | |

*(continued on next page)*

**Table 1** *(continued)*

| References/geographic location/ study design/period of diagnosis | Child's age | Exposure category (source of exposure data) | Exposed person | Period of exposure | Tumor type° (source of tumor definition) | Number of exposed cases/controls | Odd ratio°° (95% CI) | Adjustment/matching |
|---|---|---|---|---|---|---|---|---|
| | | | | Pregnancy | | 3/116 | 1.90 (0.45–7.97) | |
| | | | | Prenatal | | 9/303 | 1.48 (0.61–3.61) * | |
| | | | Child | After birth | | 6/303 | 1.32 (0.44–3.99) | |
| | | | Mother | Before | All gliomas (low-grade + high-grade + EP) | 46/187 | 1.27 (0.87–1.87) * | |
| | | | | Pregnancy | | 31/116 | 1.38 (0.88–2.16) * | |
| | | | | Prenatal | | 77/303 | 1.31 (0.95–1.82) * | |
| | | | Child | After birth | | 57/303 | 0.97 (0.69–1.38) * | |
| | | | Mother | Before | Embryonal tumors | 18/187 | 1.13 (0.58–2.20) | |
| | | | | Pregnancy | | 14/116 | 1.58 (0.76–3.27) | |
| | | | | Prenatal | | 32/303 | 1.45 (0.89–2.35) * | |
| | | | Child | After birth | | 28/303 | 1.17 (0.66–2.05) | |
| | | | Mother | Before | Germ cell tumors | 4/187 | 0.91 (0.22–3.67) | |
| | | | | Pregnancy | | 0/116 | nd | |
| | | | Child | After birth | | 3/303 | 0.31 (0.07–1.39) | |
| | | Type of pest treated: | | | | | | |
| | | - Any termite treatment | Mother | Pregnancy | CBT | 4/18 | 1.06 (0.33–3.41) | |
| | | - Any general treatment for spider/insects | Mother | Pregnancy | CBT | 31/86 | 1.50 (0.90–2.48) | |
| | | (Questionnaires: written and telephone interviews) | | | (pediatric oncology centers) | | | |
| Howe et al., 1989 Toronto and municipality of York: southern Ontario (Canada) Exploratory case-control study 1977–1983 | < 20 years | Contact with herbicide, insecticide, etc. (Questionnaires: in person interviews with the mothers and whenever possible when the father was present) | Child | Prior to diagnosis | CBT (hospital diagnostics, histologically verified) | 19/38 | 0.94 (0.466–1.90) | Adjusted for age at diagnosis |
| Kuijten et al., 1990 Pennsylvania, New Jersey and Delaware (USA) Population-based case-control study 1980–1986 | < 15 years | Exposure to household insecticides (Questionnaire: mothers and fathers interviews; if father unavailable, proxy interview with the mother) | Mother | Prenatal (1 month before pregnancy until child's birth) | ASTRO (tumor registries of 8 hospitals) | Discordant pairs (case-control) 38 (+ −)/33 (− +) | 1.2 (0.7–1.9) | Matched for age, race, telephone area code and exchange |
| Leiss and Savitz, 1995 Denver area [Colorado] (USA), Population-based case-control study 1976–1983 | < 15 years | Use of home pest extermination [residence ever exterminated for insects or pests so that family had to leave the house for a few hours] | Mother | Exposure period 1 [3 months prior to birth] | CBT | 8/27 | 1.3 (0.7–2.1) | Matched by age, sex, geographic location (telephone exchange area). Adjusted for age at diagnosis, father's education, per capita income, residential stability, mother's age, maternal race, |

*(continued on next page)*

**Table 1** *(continued)*

| References/geographic location/ study design/period of diagnosis | Child's age | Exposure category (source of exposure data) | Exposed person | Period of exposure | Tumor type° (source of tumor definition) | Number of exposed cases/controls | Odd ratio°° (95% CI) | Adjustment/matching |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | maternal smoking, wire code and/ or year of diagnosis when these factors proved to be confounders |
| | | | Child | Exposure period 2 [birth through 2 yrs. prior to diagnosis] | | 12/45 | 1.4 (0.6–2.7) | |
| | | | Child | Exposure period 3 [2 yrs. prior diagnosis through diagnosis] | | 5/22 | 1.1 (0.4–3.0) | |
| | | Yard treatment [ever treated with insecticides or herbicides] | Mother | Exp. per. 1 | | 12/79 | 0.6 (0.3–1.1) | |
| | | | Child | Exp. per. 2 | | 17/118 | 0.5 (0.2–0.9) | |
| | | | Child | Exp. per. 3 | | 16/98 | 0.5 (0.4–0.8) | |
| | | Pest strips [ever used "hanging pest strips in the home"] | Mother | Exp. per. 1 | | 10/26 | 1.5 (0.9–2.4) | |
| | | | Child | Exp. per. 2 | | 13/47 | 1.4 (0.7–2.9) | |
| | | | Child | Exp. per. 3 | | 9/37 | 1.8 (1.2–2.9) | |
| | | (Questionnaire: parental interviews) | | | (Colorado Central Cancer Registry and area hospital records) | | | |
| McCredie et al., 1994 New South Wales: Sydney, Wollongong, Newcastle (Australia) Part of a multicentric population-based case-control study (SEARCH) coordinated by IARC 1985–1989 | < 15 years | House treated for pests | Family | In month before and during pregnancy | CBT (primary malignant brain tumors or cranial nerves) | 20/24 | 2.0 (1.0–3.9) | Matched by sex and age. Adjusted for father's schooling |
| | | Professional pest exterminators | Family | In month before and during pregnancy | | 15/24 | 1.31 (0.64–2.65) * | |
| | | (Questionnaire: mother face-to-face interview + some fathers) | | | (NSW Central Cancer Registry + histological confirmation of the diagnosis) | | | |
| Pogoda and Preston-Martin, 1997 Los Angeles County [California], (USA) Population-based case-control study: Los Angeles County component of the "US West Coast childhood brain tumor study" 1984–1991 | < 19 years | Nuisance pest | Mother | Prenatal | CBT (primary tumor of the brain, cranial nerves, or cranial meninges) | 106/97 | 1.1 (0.8–1.7) | Adjusted for the matching variables: gender, age, birth year |
| | | Type of lawn and garden pesticide: | | | | | | |
| | | - Insecticides | | | | 26/20 | 1.3 (0.7–2.4) | |
| | | - Herbicides | | | | 2/3 | 0.9 (0.1–6.1) | |
| | | - Fungicides | | | | 0/2 | nd | |
| | | Type of pest treated: | | | | | | |
| | | - Termite | | | | 5/2 | 2.7 (0.5–14.2) | |
| | | - Lice | | | | 2/0 | nd | |
| | | - Snail killer | | | | 21/18 | 1.1 (0.6–2.1) | |
| | | - Flea/tick | | | | 76/53 | 1.7 (1.1–2.6) | |
| | | Application methods: | | | | | | |
| | | - Spray/fogger | | | | 17/6 | 10.8 (1.3–89.1) | |
| | | - Shampoo/dip | | | | 47/33 | 1.2 (0.6–2.5) | |
| | | - Collar | | | | 54/39 | 1.1 (0.5–2.1) | |
| | | Nuisance pest | Child | Childhood | | 150/146 | 1.0 (0.6–1.5) | |
| | | Type of lawn and garden pesticide: | | | | | | |
| | | - Insecticides | | | | 57/47 | 1.2 (0.8–2.0) | |

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**Table 1** *(continued)*

| References/geographic location/ study design/period of diagnosis | Child's age | Exposure category (source of exposure data) | Exposed person | Period of exposure | Tumor type° (source of tumor definition) | Number of exposed cases/controls | Odd ratio°° (95% CI) | Adjustment/matching |
|---|---|---|---|---|---|---|---|---|
| | | - Herbicides | | | | 4/4 | 1.2 (0.3–4.9) | |
| | | - Fungicides | | | | 1/8 | 0.12 (0.02–0.95) * | |
| | | Type of pest treated: | | | | | | |
| | | - Termite | | | | 23/32 | 0.7 (0.4–1.3) | |
| | | - Lice | | | | 38/50 | 0.6 (0.4–1.0) | |
| | | - Snail killer | | | | 41/38 | 1.0 (0.6–1.8) | |
| | | - Flea/tick | | | | 106/102 | 1.0 (0.7–1.4) | |
| | | (Questionnaire: in-person interview of the mothers and follow-up of the population-based case-control study by phone interview between 1994 and 1995) | | | (From cancer registry in each area) | | | |
| Preston-Martin et al., 1982 Los Angeles County [California], (USA) Population-based case-control study 1972–1977 | < 25 years | Pesticides used often or occasionally | Mother | Index pregnancy | CBT (tumor of the brain or cranial meninges) | Discordant pairs (case-control): 42(+ −)/29 (− +) | 1.45 (0.90–2.33) * | Matched on sex, race and birth year |
| | | Home treated by exterminators | | | | 10 (+ −)/10 (− +) | 1.0 (0.42–2.40) * | |
| | | Had contact with pesticides often or occasionally | Child | Childhood | | 26 (+ −)/24 (− +) | 1.08 (0.62–1.89) * | |
| | | Home treated by exterminators | | | | 36 (+ −)/42 (− +) | 0.86 (0.55–1.34) * | |
| | | (Questionnaire: telephone interview of the mother) | | | (from The Los Angeles County Cancer Surveillance Program; microscopically confirmed) | | | |
| Rosso et al., 2008 USA/Canada Comprehensive case-control study: "Children's Cancer Group protocol E21" 1991–1997 | < 6 years | Fathers' hobbies: gardening or lawn care using insecticides (whether or not) | Family (?) | Prenatal (one month before and during pregnancy) | MB (medullo-blastoma) or PNET | 105/67 | 1.6 (1.0–2.4) | Matched on area code, race, date of birth. Adjusted for father's race, geographic location, date of interview, child's age at interview, proxy interview conducted, child's gender, father's smoking status, child's birth season |
| | | < 1/month | | | | 82/49 | 1.7 (1.0–2.7) | |
| | | > 1/month | | | | 23/18 | 1.3 (0.6–2.7) | |
| | | Lawn care | Child | After birth (from birth until reference age) | | 111/70 | 1.7 (1.1–2.6) | |
| | | < 1/month | | | | 79/52 | 1.6 (1.0–2.7) | |
| | | > 1/month | | | | 31/18 | 1.8 (0.9–3.6) | |
| | | (questionnaire: telephone interview of the mother and as many fathers as possible | | | (registered with the Children's Cancer Group) | | | |
| Schüz et al., 2001 (Lower Saxony in the northwestern part of Germany [LS study] as well as in West Germany [WG study]) Pooling of 2 population-based case-control studies 1988–1993; 1992–1994 | < 15 years | Use of household insecticides: | Child | Before diagnosis | CBT (all CNS tumors) | 22/96 | 1.38 (0.84–2.25) | Matched on gender, age-group, year of birth. Adjusted for degree of urbanization and socioeconomic status |
| | | - 1/year | | | | | | |
| | | - > 1/year | | | | 38/164 | 1.19 (0.81–1.77) | |
| | | - All (1/year and > 1/year) | | | | 60/260 | 1.24 (0.92–1.67) * | |
| | | Use of household insecticides: | | | ASTRO | 8/96 | 2.45 (1.09–5.47) | |

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**Table 1** *(continued)*

| References/geographic location/ study design/period of diagnosis | Child's age | Exposure category (source of exposure data) | Exposed person | Period of exposure | Tumor type° (source of tumor definition) | Number of exposed cases/controls | Odd ratio°° (95% CI) | Adjustment/matching |
|---|---|---|---|---|---|---|---|---|
| | | - 1/year | | | | | | |
| | | - > 1/year | | | | 6/164 | 0.58 (0.23–1.49) | |
| | | - All | | | | 14/260 | 1.15 (0.65–2.04) * | |
| | | Use of household insecticides: | | | EP | 2/96 | 1.51 (0.34–6.79) | |
| | | - 1/year | | | | | | |
| | | - > 1/year | | | | 5/164 | 1.69 (0.63–4.54) | |
| | | - All | | | | 7/260 | 1.37 (0.61–3.08) * | |
| | | Use of household insecticides: | | | Gliomas (ASTRO + EP) | 21/260 | 1.21 (0.75–1.96) * | |
| | | - All | | | | | | |
| | | Use of household insecticides: | | | MB | 5/96 | 1.14 (0.44–2.95 | |
| | | - 1/year | | | | | | |
| | | - > 1/year | | | | 8/164 | 1.06 (0.49–2.28) | |
| | | - All | | | | 13/260 | 1.07 (0.59–1.93) * | |
| | | Use of pesticides in garden | | | CBT | 60/290 | 0.94 (0.68–1.29) | |
| | | | | | ASTRO | 16/290 | 0.91 (0.48–1.71) | |
| | | | | | EP | 5/290 | 0.71 (0.27–1.89) | |
| | | | | | Gliomas | 21/290 | 1.05 (0.65–1.67) * | |
| | | | | | MB | 13/290 | 0.81 (0.43–1.53) | |
| | | (Questionnaire: mailed and subsequent telephone interview of both parents when possible) | | | (German Childhood Cancer Registry) | | | |
| Searles Nielsen et al., 2005 Seattle-Puget Sound region of Washington State (USA) Population-based case-control study 1984–1991 | < 20 years | Home pesticide treatment | Mother or children | Pregnancy or childhood before diagnosis | CBT (primary tumors of the brain, cranial nerves or meninges) | 20/57 | 0.62 (0.33–1.15) * | Matched by sex and age |
| | | (Questionnaire: interview of the mother) | | | (Cancer incidence registry affiliated with the NCISEERP) | | | |
| Searles Nielsen et al., 2010 Seattle-Puget Sound region of Washington State, San Francisco-Oakland area and Los Angeles county of California (USA) Population-based case-control study "U.S. West Coast CBT Study" 1984–1991 | ≤ 10 years | Chemical treatment of home for insect pests | Family | Pregnancy (1 month before conception until birth) | CBT (primary tumors of the brain, cranial nerves or meninges) | 55/60 | 1.41 (0.93–2.15) * | Matched by age and sex |
| | | | | Childhood (birth until diagnosis) | | 46/94 | 0.60 (0.40–0.92) * | |
| | | Insecticides for home, yard, garden, pets or lice | | Pregnancy | | 61/48 | 1.05 (0.47–2.33) * | |
| | | | | Childhood | | 60/46 | 1.45 (0.69–3.05) * | |
| | | Fleas or ticks | | Pregnancy | | 33/19 | 1.77 (0.89–3.54) * | |
| | | | | Childhood | | 33/22 | 1.47 | |

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**Table 1** *(continued)*

| References/geographic location/ study design/period of diagnosis | Child's age | Exposure category (source of exposure data) | Exposed person | Period of exposure | Tumor type° (source of tumor definition) | Number of exposed cases/controls | Odd ratio°° (95% CI) | Adjustment/matching |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | (0.75–2.88) * | |
| | | Nuisance pests | | Pregnancy | | 43/39 | 0.90 (0.46–1.76) * | |
| | | | | Childhood | | 41/40 | 0.74 (0.38–1.41) * | |
| | | (Questionnaire: maternal in-person interview of the mother) | | | (SEER registries) | | | |
| Shim et al., 2009 Florida, New Jersey, New York excluding NY city, Pennsylvania "U.S. Atlantic Coast Childhood Brain Cancer Study" 1993–1997 | < 10 years | Ever used pesticides for gardens and lawns (application by anyone including professionals): | Parental + others | 2-yr period before child's birth | First primary brain cancer: ASTRO | Discordant pairs (case-control): 52(+−)/39(−+) | 1.3 (0.9–2.0) | Matched by race, birth year, state of residence at the time of case diagnosis. Adjusted for maternal education |
| | | - Insecticides | | | | | | |
| | | | | | PNET | 25(+−)/23(−+) | 1.1 (0.6–1.9) | |
| | | | | | Other types | 26(+−)/23(−+) | 1.2 (0.7–2.0) | |
| | | | | | CBT (Astro + PNET + others) | 103(+−)/85(−+) * | 1.21 (0.91–1.62) * | |
| | | - Herbicides | | | ASTRO | 53(+−)/27(−+) | 1.9 (1.2–3.0) | |
| | | | | | PNET | 26(+−)/24(−+) | 1.0 (0.6–1.8) | |
| | | | | | Other types | 25(+−)/28(−+) | 1.0 (0.6–1.8) | |
| | | | | | CBT | 104(+−)/79(−+) * | 1.32 (0.96–1.76) * | |
| | | - Fungicides | | | ASTRO | 13(+−)/7(−+) | 1.8 (0.7–4.6) | |
| | | | | | PNET | 8(+−)/6(−+) | 1.3 (0.5–3.8) | |
| | | | | | Other types | 11(+−)/5(−+) | 2.6 (0.9–7.6) | |
| | | | | | CBT | 32(+−)/18(−+) * | 1.78 (1.00–3.17) * | |
| | | Father applied pesticides for garden and lawns: | Father | | ASTRO | 28(+−)/26(−+) | 1.0 (0.6–1.8) | |
| | | - Insecticides | | | | | | |
| | | | | | PNET | 20(+−)/19(−+) | 1.0 (0.5–1.9) | |
| | | | | | Other types | 20(+−)/10(−+) | 2.3 (1.0–5.0) | |
| | | | | | CBT | 68(+−)/55(−+) * | 1.24 (0.87–1.76) * | |
| | | - Herbicides | | | ASTRO | 40(+−)/20(−+) | 2.0 (1.2–3.4) | |
| | | | | | PNET | 21(+−)/18(−+) | 1.1 (0.5–2.0) | |
| | | | | | Other types | 15(+−)/18(−+) | 1.0 (0.5–2.0) | |
| | | | | | CBT | 76(+−)/56(−+) * | 1.36 (0.96–1.92) * | |
| | | - Fungicides | | | ASTRO | 3(+−)/1(−+) | 3.1 (0.3–30.0) | |
| | | | | | PNET | 4(+−)/1(−+) | 3.6 (0.4–32.6) | |
| | | | | | Other types | 8(+−)/3(−+) | 3.3 (0.9–13.0) | |
| | | | | | CBT | 15(+−)/5(−+) * | 3.00 (1.09–8.25) * | |
| | | Mother applied pesticides for garden and lawns: | Mother | | ASTRO | 18(+−)/18(−+) | 1.0 (0.5–1.9) | |
| | | - Insecticides | | | | | | |
| | | | | | PNET | 6(+−)/8(−+) | 0.7 (0.3–2.2) | |
| | | | | | Other types | 10(+−)/12(−+) | 0.9 (0.4–2.2) | |
| | | | | | CBT | 34(+−)/38(−+) * | 0.90 (0.56–1.42) * | |
| | | - Herbicides | | | ASTRO | 13(+−)/7(−+) | 1.9 (0.7–4.8) | |
| | | | | | PNET | 6(+−)/7(−+) | 0.8 (0.3–2.5) | |

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**Table 1** *(continued)*

| References/geographic location/ study design/period of diagnosis | Child's age | Exposure category (source of exposure data) | Exposed person | Period of exposure | Tumor type° (source of tumor definition) | Number of exposed cases/controls | Odd ratio°° (95% CI) | Adjustment/matching |
|---|---|---|---|---|---|---|---|---|
| | | | | | Other types | 5(+ −)/13(− +) | 0.4 (0.1–1.1) | |
| | | | | | CBT | 24(+ −)/27(− +) * | 0.89 (0.51–1.54) * | |
| | | - Fungicides | | | ASTRO | 10(+ −)/6(− +) | 1.7 (0.6–4.8) | |
| | | | | | PNET | 5(+ −)/3(− +) | 1.6 (0.4–6.9) | |
| | | | | | Other types | 9(+ −)/3(− +) | 3.4 (0.9–12.6) | |
| | | | | | CBT | 24(+ −)/12(− +) * | 2.00 (1.00–4.00) * | |
| | | (Questionnaire: telephone interview of the mother) | | | (cancer registries) | | | |
| Spix et al., 2009<br>41 administrative districts in the vicinity of 16 nuclear power plants (West-Germany)<br>Case-control study<br>1993–2003 | < 5 years | Exposure to herbicides or pesticides in residence, garden or agriculture | Birth weight < 2500 g | Since conception | CBT (central nervous system tumor) | 14/65 | 0.39 (0.18–0.83) | Matching criteria: nuclear power plant region, sex, age, year of diagnosis |
| | | | All weights | | | 88/204 * | 1.29 (0.67–2.49) * | |
| | | (Questionnaire: telephone interview of the mother) | | | (German Childhood Cancer Registry) | | | |

Abbreviations: yr(s), year(s); nr, information not reported; nd, not defined (could not be calculated); co: controls; Study: Aus-CBT, The Australian Study of Childhood Brain Tumors; CAT-scan, computer-assisted tomography-scan; *cis*-DCCA, *cis*-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid; *trans*-DCCA, *trans*-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid; 3-PBA, 3-phenoxybenzoic acid; NCISEERP, National Cancer Institute's Surveillance, Epidemiology and End Results Program; NSW, New South Wales; SEER, Surveillance, Epidemiology and End Results: ASTRO, astroglial tumors, astrocytomas; CBT, cranial/childhood brain tumor; CNS, central nervous system tumors; EP, ependymomas; MB, medulloblastoma; PNET, primitive neuroectodermal tumors; ICCC, the International Classification of Childhood Cancer; ICD, the International Classification of Diseases; ICD-O, the International Classification of Diseases for oncology.

Notes

°: Tumor types included in the studies:

Bunin et al., 1994: ICD-O site code 191. Astrocytoma (astrocytic glioma, glioblastoma multiforme, mixed glioma with astrocytic elements or glioma not otherwise specified); PNET (medulloblastoma, CNS neuroblastoma, ependymoblastoma, pineoblastoma); CBT (astrocytoma + PNET).

Chen et al., 2016: childhood brain tumors (glioma, medulloblastoma, choroid plexus papilloma, craniopharyngioma, ependymoma, teratoma, pineoblastoma, primitive neuroectodermal tumor).

Cordier et al., 1994: intracranial tumor (astrocytoma, medulloblastoma, ependymoma, other gliomas, neuroblastoma, other types and unspecified).

Davis et al., 1993: ICD-O site code 191. Astrocytomas, medulloblastomas and a mix of other cancer types.

Gold et al., 1979: astrocytoma, medulloblastoma, ependymoma, pontine glioma, glioblastoma multiforme, optic gliomas, other cell types and unspecified cell types.

Greenop et al., 2013: low grade gliomas, high grade gliomas, embryonal tumors (including medulloblastomas, primitive neuroectodermal tumors [including pineal], atypical teratoid rhabdoid tumors.

Howe et al., 1989: malignant tumors (ICD-O; 1976) except melanotic neuroectodermal tumors (benign) and neoplasms uncertain. Glyoma, ependymoma, astrocytoma, spongioblastoma glioblastoma oligodendroglioma, medulloblastoma, neuroblastoma, meningioma (! = toutes les tumeurs observes dans l'étude, pas seulement suite à exposition aux pesticides!

Kuijten et al., 1990: Astrocytomas [astrocytoma, glioblastoma multiforme, mixed glioma with astrocytic elements or brainstem glioma].

Leiss and Savitz, 1995: Brain tumors.

McCredie et al., 1994: Primary malignant brain tumors (ICD-9 191) or cranial nerves (ICD-9 192.0).

Pogoda and Preston-Martin, 1997: astroglial tumor, PNET, other glial tumor (ICD-O; 1976).

Preston-Martin et al., 1982: astrocytomas, medulloblastomas, glioblastomas, ependymomas, gliomas of other or unspecified types, meningiomas, neuromas, gangliogliomas, tumors of other or unspecified types.

Rosso et al., 2008: medulloblastoma and primitive neuroectodermal tumor.

Schüz et al., 2001: astrocytomas, medulloblastomas, ependymomas, other types of glioma, other or unspecified types of CNS tumors (according to the classification by Birch and Marsden, 1987).

Searles Nielsen et al., 2005, 2010: ICD-O; WHO 1976, codes 191.0-192.1.

Shim et al., 2009: ICD-O, topography codes C71.0-C71.9, including all morphologic codes with a behaviour code of 3, excluding lymphoma.

Spix et al., 2009: ICCC, 1996.

°°: all ORs were reported for exposed vs non exposed individuals. Gold et al. (1979) and Preston-Martin et al. (1982) reported ratios of discordant pairs and OR and/or 95% CI were calculated for inclusion in the MA.

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

### 3.5. Sensitivity analyses

The results of the sensitivity analyses are reported in Table 3. None of the sensitivity analyses performed calls into question the robustness of the results. Very similar values were obtained whatever the statistical pooling model used (random, fixed). Rerunning the MA after removing the study with partial redundancy, those reporting extreme risk estimators as well as including data from other control groups did not substantially modify the results of the MA. The assessment of the influence of individual studies by dropping the respective study off before pooling risk estimators indicated that the summary risk ratio is not dominated by a single study.

## 4. Discussion

### 4.1. Summary of evidence

In this MA, we studied the relationship between residential pesticide exposure and childhood brain tumors investigated in several case-control studies, often with inconclusive individual results. Overall, the summary risk of developing a brain tumor among children after residential exposure to pesticides is statistically significantly increased, with no indication of between study heterogeneity or inconsistency (Fig. 2). The consistency of the results may be somewhat surprising due to the differences in study population, in exposure and timing of exposure, and in methods to ascertain the disease. The homogeneity of observed associations should, therefore, be interpreted with caution. The consistency in findings across studies could be due to a shared bias or unmeasured confounding, but a uniform bias or confounding moving risk estimators in the same direction in almost all studies appears unlikely.

We also examined the impact of several variables including the study quality, the sources of pesticide exposure, the critical exposure periods, the exposure location, the specific pesticide category, the application method, the type of pest treated, specific exposures, the type of CBT, the child age at diagnosis and the geographic location on the results to enhance our understanding of the potential involvement of residential pesticide exposure in the etiology of CBT (Table 2 and Supplemental Material Table 2). Statistically significant positive associations were observed for studies with the higher quality, for both exposure time windows (prenatal, childhood), for indoor use of pesticides and particularly prenatally, for studies from USA/Canada as well as from Europe (borderline). We observed the strongest associations for pet treatments and for treatment against flea/tick but these associations were based on small numbers of studies. Significant increased risks were observed for all stratifications involving insecticides (except outdoor insecticides), whatever the exposure windows and in particular following indoor use. The risk of gliomas, more specifically following prenatal exposure, was also significantly increased. Children diagnosed with a CBT before 10 or before 15 years showed a significant increased risk while no significant increase was observed for children/young adults diagnosed up to later than 15 years. In all the statistically significant associations, there is little evidence of heterogeneity.

### 4.2. Comparison with others MA

Our results reinforce and greatly extend the relevant but scarce data reported in the existing MA (Chen et al., 2015; Kunkle et al., 2014; Vinson et al., 2011) with regard to residential pesticide exposure and childhood brain tumors. As most of the study results by Vinson et al. (2011) combined occupational and domestic pesticide exposure data, the only relevant results for domestic exposure are those reported for “parents' use of pesticides in the home or garden”. Unfortunately, these meta-analytic data could not be compared with ours because of the inclusion by these authors of several risk estimators issued from the same study and because data for non-significant associations were not provided. In spite of these differences, our observations are in agreement with the following statements of these authors: exposure to household and garden pesticides appears to be a risk factor for the development of brain cancer in children and the risk was increased with paternal exposure during the prenatal period. The MA of Kunkle et al. (2014) focused on parental farm-related pesticide exposure but the few data reported for non-agricultural exposure are in fair agreement with the results of the present MA. Statistically significant increased risks were observed for maternal exposure during pregnancy as well as for childhood exposure. Chen et al. (2015) restricted their analysis to exposure during childhood and summary odds ratios concerning CBT were reported for indoor and for outdoor pesticide exposures with a stratification for outdoor herbicide and yard insecticides exposures. Despite some methodological differences in the inclusion and exclusion criteria, our results for the corresponding stratifications (A.8, A.11, A.22, A.23) are in concordance with those of Chen et al. (2015), showing no statistically significant increased risks of CBT for these stratifications.

### 4.3. Strengths of the study

Of particular interest is the coherence between the present results for brain tumors following domestic/residential exposure and that of the MA on childhood brain tumors following parental occupational exposure to pesticides (Van Maele-Fabry et al., 2013). In both cases, significantly positive associations between pesticide exposure and childhood brain tumors were reported when combining all studies and significant increased risks were observed for prenatal exposure, whatever the exposed parent and particularly for childhood gliomas. No indication of between study results heterogeneity and inconsistency were reported for all these associations, suggesting that combining the data was appropriate. These results support the hypothesis that pesticide exposure could be an etiologic factor for childhood brain tumors.

An additional strength of the present MA is the lack of evidence of publication bias upon visual inspection of funnel plot and statistical analysis. Selection bias due to the non-inclusion of non-English language studies can be excluded as its relates to only 12 studies out of the 198 records screened in the study selection process and none of them would have been eligible according to inclusion criteria other than language. The possible impact of non-inclusion of unpublished small studies or of non-English language studies has already been analyzed in MA on pesticide exposure and childhood cancers. Turner et al. (2010) included such studies in their MA and observed that when restricting to studies published in English in the peer-reviewed literature only, the magnitude of the association observed between residential pesticide exposure and childhood leukemia tended to strengthen and heterogeneity to reduce. Van Maele-Fabry et al. (2010) showed that rerunning the MA on occupational parental exposure to pesticides and childhood leukemia including unpublished studies did not substantially modify the results. Although a publication bias cannot be totally ruled out, after applying conventional tests, the association observed in the present MA does not appear to have been significantly influenced by publication bias.

The association among the 9 studies with higher total quality scores [ > median] showed a statistically significant increased risk of CBT; while no significantly increased risk was observed after combining results from the 9 studies with lower total quality scores [≤ median].

All performed sensitivity analyses confirmed the robustness of the results and no single study dominated the association between residential pesticide exposure and childhood brain tumors.

### 4.4. Limitations of the study

#### 4.4.1. Recall bias

All studies included in the MA are of case-control design with self-reported retrospective exposure assessment raising the question of

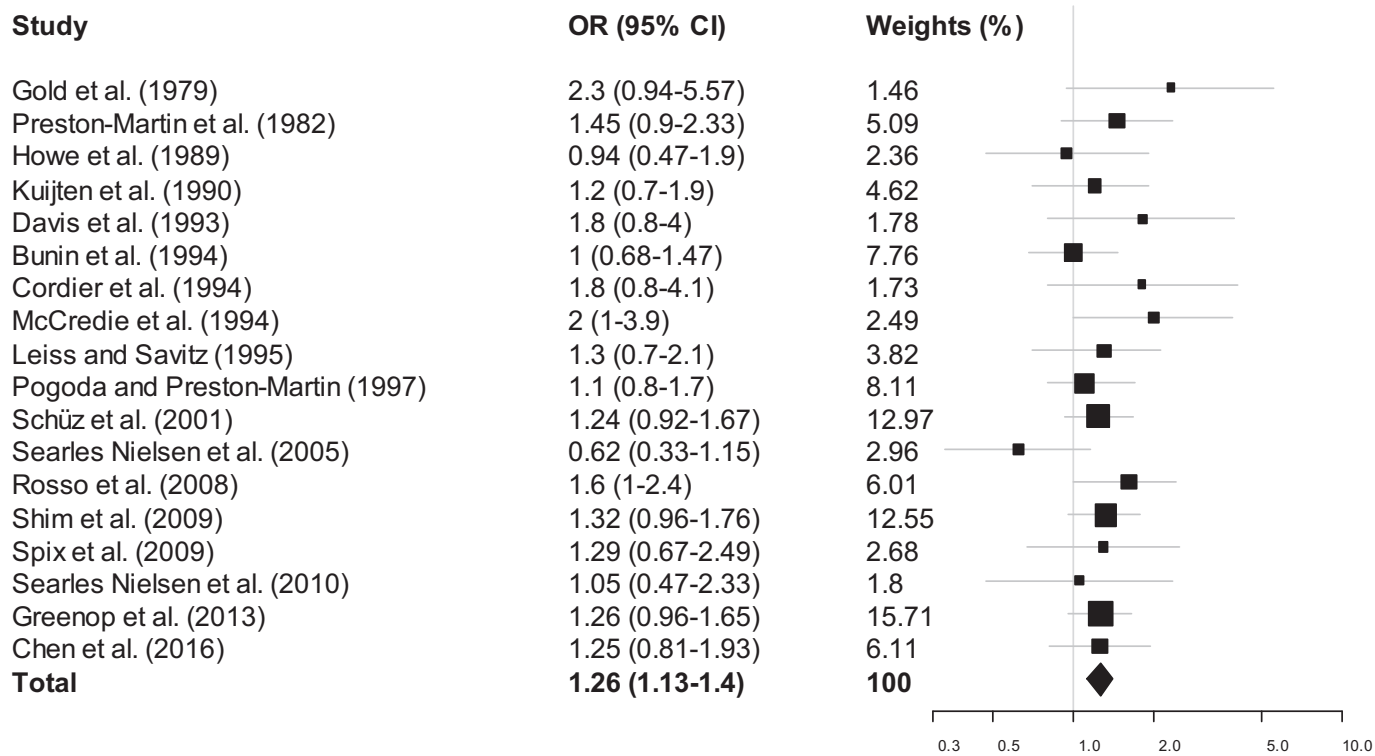


**Fig. 2.** Forest plot of case-control studies on childhood brain tumors following residential exposure to pesticides.
*Note.* Odds ratio (OR) and 95% confidence intervals (CIs) of case-control studies included in the meta-analysis "all studies" are presented. Each estimator was assigned a weight ($w_i$)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

recall bias (also called reporting bias or differential recall). Recall bias due to differences in the accuracy of parental recall or report between case and control groups, can distort the measure of association between exposure and disease and lead to an over- or underestimation of the risk. An overestimation of the risk may be due to over reporting exposure by case parents considering residential pesticide exposure a relevant risk factor or to some control parents less carefully or thoroughly answering the questionnaire. An underestimation may occur if case parents do not want to be considered responsible for causing the disease of their children. In both cases, this differential exposure misclassification might produce biased risk estimates. Potential for differential exposure misclassification has been evaluated by Vienneau et al. (2016) in a case-control study on childhood brain tumors for maternal exposures during pregnancy (e.g. smoking and working) by using two independent sources of exposure data (interview and birth registry data) and by analysing agreement between the two data sources. Their comparison indicated some potential for differential exposure misclassification and thus potentially biased risk estimates when relying on interview data alone (Vienneau et al., 2016). In a case-control study of childhood leukemia, Slusky et al. (2012) assessed the reliability of maternal reports regarding the use of household pesticides. The reliability for all pesticides, based on two repeated in-person interviews and assessed by three reliability measures did not differ significantly for cases and controls. The authors concluded that their results indicate that the reliability of maternal-reported household pesticide use was similar among cases and controls, suggesting that differential recall of maternal reported household use of pesticides may not be substantial (Slusky et al., 2012). Although there may be some differential exposure misclassification, authors of a validation study on risk factors for leukemia in children suggested that non-differential misclassification of exposure may be of greater concern (Infante-Rivard and Jacques, 2000). However, it is noteworthy that in this study, parental recall bias was not assessed for pesticide exposure but for the following variables: reported distance from home to power lines compared with measured distance and reported prenatal radiographic examinations compared with hospital medical record data

Our results showing that the magnitude of the associations with pesticide use varies by histological type of childhood brain tumors (statistically significant increased risk observed for gliomas but not for embryonal tumors), provide some evidence that differential recall bias is not likely to explain observed pesticide associations. If more accurate reporting by case parents caused a significant positive association, the risk estimates would be expected to be elevated for all histological types.

#### 4.4.2. Pesticide exposure assessment

Pesticide exposure assessment remains a key element in epidemiological studies and especially for residential exposure of children. Assessment of residential exposure is challenging because it is self-reported by the parents and information is provided only on broad pest categories (insecticides, herbicides). In addition, it can be difficult to disentangle the potential effects of individual pest categories as often people use multiple types. While the use of insecticides can be common, the use of herbicides and fungicides are often rarer and few users of these do not also use insecticides. Type of pests treated are remembered more easily by the parents than specific compounds and the general population is typically less able to report histories of use of individual pesticides than occupational groups. Various methods have been employed to improve recall of residential pesticide use such as queries about specific pests treated (in general and also home by home), lifetime use of pest treatments along a timeline to establish temporal associations with pesticide exposure (reviewed by Guha et al., 2013). Combined techniques were also analyzed: self-reported data complemented by pesticide concentrations in carpet dust (Deziel et al., 2015), web surveys versus telephone interviews (Wu et al., 2013), self-report and household inventory to collect information on the presence of specific active ingredients of stored pesticide products (Guha et al., 2013). Others authors have developed a "pesticide-exposure matrix" to

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

| Stratification | N. | Summary | | Homogeneity | | | |
|---|---|---|---|---|---|---|---|
| | Studies | Odds Ratios | 95% CI | Cochran's Q ($\chi^2$ Woolf) | *P*-value | $I^2$ | 95% UI |
| Residential exposure | | | | | | | |
| All studies (A.1)[(a)] | 18 | **1.26** | 1.13–1.40 | 14.362 | 0.641 | 0 | 0–41 |
| Study quality | | | | | | | |
| (A.2) high quality (> median) | 9 | **1.27** | 1.11–1.44 | 1.896 | 0.984 | 0 | 0–0 |
| (A.3) low quality (< median) | 9 | 1.26 | 0.98–1.61 | 12.416 | 0.134 | 36 | 0–70 |
| Exposure time windows | | | | | | | |
| (A.4) Prenatal | 13 | **1.29** | 1.14–1.46 | 6.803 | 0.870 | 0 | 0–23 |
| (A.5) childhood[(b)] | 12 | **1.26** | 1.10–1.45 | 9.716 | 0.556 | 0 | 0–53 |
| Exposure location | | | | | | | |
| Indoor exposure | | | | | | | |
| (A.6) All studies | 14 | **1.23** | 1.09–1.40 | 14.342 | 0.350 | 9 | 0–47 |
| (A.7) Prenatal | 10 | **1.26** | 1.08–1.46 | 7.734 | 0.561 | 0 | 0–56 |
| (A.8) Childhood | 9 | 1.09 | 0.88–1.35 | 15.186 | 0.0556 | 47 | 0–76 |
| Outdoor exposure | | | | | | | |
| (A.9) All studies | 6 | 1.13 | 0.89–1.44 | 8.110 | 0.150 | 38 | 0–76 |
| (A.10) Prenatal | 5 | 1.20 | 0.90–1.61 | 6.289 | 0.179 | 36 | 0–76 |
| (A.11) Childhood | 5 | 1.16 | 0.78–1.73 | 11.939 | 0.0178 | 67 | 13–87 |
| Specific exposure | | | | | | | |
| (A.12) Professional pest extermination | 5 | 1.15 | 0.95–1.40 | 2.512 | 0.643 | 0 | 0–67 |
| (A.13) Pet treatments | 2 | **1.43** | 1.02–2.01 | 0.193 | 0.661 | 0 | ND |
| Pesticide biocide category | | | | | | | |
| Insecticides | | | | | | | |
| (A.14) All studies | 10 | **1.23** | 1.06–1.42 | 7.540 | 0.581 | 0 | 0–55 |
| (A.15) Prenatal | 6 | **1.26** | 1.04–1.54 | 0.940 | 0.967 | 0 | 0–0 |
| (A.16) Childhood | 7 | **1.32** | 1.09–1.59 | 2.754 | 0.839 | 0 | 0–36 |
| Herbicides | | | | | | | |
| (A.17) All studies | 3 | 1.28 | 0.97–1.70 | 0.289 | 0.865 | 0 | 0–28 |
| (A.18) Prenatal | 3 | 1.28 | 0.97–1.70 | 0.289 | 0.865 | 0 | 0–28 |
| (A.19) Childhood | 2 | 1.55 | 0.74–3.21 | 0.173 | 0.677 | 0 | ND |
| Fungicides | | | | | | | |
| (A.20) All studies | 2 | 0.54 | 0.04–7.05 | 6.883 | 0.0087 | 86 | 41–96 |
| Exposure location and biocide category | | | | | | | |
| (A.21) Indoor insecticides | 6 | **1.31** | 1.09–1.56 | 1.949 | 0.856 | 0 | 0–35 |
| (A.22) Outdoor insecticides | 3 | 1.24 | 0.97–1.60 | 0.209 | 0.901 | 0 | 0–1 |
| (A.23) Outdoor herbicides | 3 | 1.28 | 0.97–1.70 | 0.289 | 0.866 | 0 | 0–28 |
| Application methods | | | | | | | |
| (A.24) Spray/bomb | 3 | 1.99 | 0.61–6.46 | 5.515 | 0.0634 | 64 | 0–90 |
| (A.25) Strips | 2 | 2.29 | 0.72–7.28 | 2.506 | 0.113 | 60 | 0–91 |
| (A.26) Collar | 2 | 1.06 | 0.61–1.82 | 0.029 | 0.865 | 0 | ND |
| (A.27) Shampoo | 2 | 1.03 | 0.59–1.81 | 0.464 | 0.496 | 0 | ND |
| Type of pest treated | | | | | | | |
| (A.28) Termite | 3 | 1.42 | 0.71–2.86 | 0.808 | 0.668 | 0 | 0–74 |
| (A.29) Lice | 2 | 0.73 | 0.38–1.41 | 1.468 | 0.226 | 32 | ND |
| (A.30) Flea/tick | 3 | **1.46** | 1.05–2.05 | 1.401 | 0.496 | 0 | 0–85 |
| Brain tumor type | | | | | | | |
| Gliomas | | | | | | | |
| (A.31) All studies | 5 | **1.30** | 1.09–1.55 | 0.409 | 0.982 | 0 | 0–0 |
| (A.32) Prenatal | 4 | **1.31** | 1.08–1.59 | 0.310 | 0.958 | 0 | 0–0 |
| (A.33) Childhood | 2 | 1.05 | 0.79–1.39 | 0.535 | 0.535 | 0 | ND |
| Embryonal tumors | | | | | | | |
| (A.34) All studies | 4 | 1.07 | 0.81–1.41 | 3.327 | 0.344 | 10 | 0–86 |
| (A.35) Prenatal | 3 | 1.04 | 0.69–1.57 | 3.327 | 0.190 | 40 | 0–82 |
| (A.36) Childhood | 2 | 1.12 | 0.74–1.69 | 0.046 | 0.831 | 0 | ND |
| Geographic location | | | | | | | |
| (A.37) USA/Canada | 12 | **1.22** | 1.06–1.40 | 11.645 | 0.391 | 6 | 0–61 |
| (A.38) Europe | 3 | ***1.29*** | 1.00–1.68 | 0.705 | 0.703 | 0 | 0–71 |
| (A.39) Australia | 2 | 1.42 | 0.95–2.12 | 1.529 | 0.216 | 35 | ND |
| Age at diagnosis | | | | | | | |
| (A.40) 0–10 years | 6 | **1.28** | 1.06–1.55 | 3.538 | 0.618 | 0 | 0–64 |
| (A.41) 0–15 years | 7 | **1.30** | 1.11–1.52 | 2.426 | 0.877 | 0 | 0–28 |

*(continued on next page)*

**Table 2** *(continued)*

| Stratification | N. | Summary | | Homogeneity | | | |
|---|---|---|---|---|---|---|---|
| | Studies | Odds Ratios | 95% CI | Cochran's Q ($\chi^2$ Woolf) | *P*-value | $I^2$ | 95% UI |
| (A.42) 0- > 15 years (up to 25 years) | 5 | 1.12 | 0.79–1.59 | 7.344 | 0.119 | 46 | 0–80 |

*Abbreviations*: N. Studies, number of studies; 95% CI, 95% confidence interval; summary odds ratios are in bold when the 95% CI do not include 1 and in bold italics for borderline CI values (1.00–…); 95% UI, 95% uncertainty interval; ND, not defined (could not be calculated); statistical pooling using fixed model when $I^2 \leq 25\%$.

Studies included in the meta-analyses:

(A.1) Bunin et al. (1994); Chen et al. (2016); Cordier et al. (1994); Davis et al. (1993); Gold et al. (1979); Greenop et al. (2013); Howe et al. (1989); Kuijten et al. (1990); Leiss and Savitz (1995); McCredie et al. (1994); Pogoda and Preston-Martin (1997); Preston-Martin et al. (1982); Rosso et al. (2008); Schüz et al. (2001); Searles Nielsen et al. (2005); Searles Nielsen et al. (2010); Shim et al. (2009); Spix et al. (2009).

(A.2) Chen et al. (2016); Davis et al. (1993); Greenop et al. (2013); Leiss and Savitz (1995); Pogoda and Preston-Martin (1997); Preston-Martin et al. (1982); Schüz et al. (2001); Searles Nielsen et al. (2010); Shim et al. (2009).

(A.3) Bunin et al. (1994); Cordier et al. (1994); Gold et al. (1979); Howe et al. (1989); Kuijten et al. (1990); McCredie et al. (1994); Rosso et al. (2008); Searles Nielsen et al. (2005); Spix et al. (2009).

(A.4) Bunin et al. (1994); Cordier et al. (1994); Davis et al. (1993); Greenop et al. (2013); Kuijten et al. (1990); Leiss and Savitz (1995); McCredie et al. (1994); Pogoda and Preston-Martin (1997); Preston-Martin et al. (1982); Rosso et al. (2008); Searles Nielsen et al. (2010); Shim et al. (2009); Spix et al. (2009).

(A.5) Chen et al. (2016); Cordier et al. (1994); Davis et al. (1993); Gold et al. (1979); Greenop et al. (2013); Howe et al. (1989); Leiss and Savitz (1995); Pogoda and Preston-Martin (1997); Preston-Martin et al. (1982); Rosso et al. (2008); Schüz et al. (2001); Searles Nielsen et al. (2010).

(A.6) Bunin et al. (1994); Chen et al. (2016); Cordier et al. (1994); Davis et al. (1993); Gold et al. (1979); Greenop et al. (2013); Kuijten et al. (1990); Leiss and Savitz (1995); McCredie et al. (1994); Pogoda and Preston-Martin (1997); Preston-Martin et al. (1982); Schüz et al. (2001); Searles Nielsen et al. (2005); Searles Nielsen et al. (2010).

(A.7) Bunin et al. (1994); Cordier et al. (1994); Davis et al. (1993); Greenop et al. (2013); Kuijten et al. (1990); Leiss and Savitz (1995); McCredie et al. (1994); Pogoda and Preston-Martin (1997); Preston-Martin et al. (1982); Searles Nielsen et al. (2010).

(A.8) Chen et al. (2016); Cordier et al. (1994); Davis et al. (1993); Greenop et al. (2013); Leiss and Savitz (1995); Pogoda and Preston-Martin (1997); Preston-Martin et al. (1982); Schüz et al. (2001); Searles Nielsen et al. (2010).

(A.9) Davis et al. (1993); Leiss and Savitz (1995); Pogoda and Preston-Martin (1997); Rosso et al. (2008); Schüz et al. (2001); Shim et al. (2009); Spix et al. (2009).

(A.10) Davis et al. (1993); Leiss and Savitz (1995); Pogoda and Preston-Martin (1997); Rosso et al. (2008); Shim et al. (2009).

(A.11) Davis et al. (1993); Leiss and Savitz (1995); Pogoda and Preston-Martin (1997); Rosso et al. (2008); Schüz et al. (2001).

(A.12) Bunin et al. (1994); Greenop et al. (2013); Leiss and Savitz (1995); McCredie et al. (1994); Preston-Martin et al. (1982).

(A.13) Davis et al. (1993); Pogoda and Preston-Martin (1997).

(A.14) Chen et al. (2016); Davis et al. (1993); Gold et al. (1979); Kuijten et al. (1990); Leiss and Savitz (1995); Pogoda and Preston-Martin (1997); Rosso et al. (2008); Schüz et al. (2001); Searles Nielsen et al. (2005); Searles Nielsen et al. (2010); Shim et al. (2009).

(A.15) Davis et al. (1993); Kuijten et al. (1990); Leiss and Savitz (1995); Pogoda and Preston-Martin (1997); Rosso et al. (2008); Searles Nielsen et al. (2010); Shim et al. (2009).

(A.16) Chen et al. (2016); Davis et al. (1993); Gold et al. (1979); Leiss and Savitz (1995); Pogoda and Preston-Martin (1997); Rosso et al. (2008); Schüz et al. (2001); Searles Nielsen et al. (2010).

(A.17) Davis et al. (1993); Pogoda and Preston-Martin (1997); Shim et al. (2009).

(A.18) Davis et al. (1993); Pogoda and Preston-Martin (1997); Shim et al. (2009).

(A.19) Davis et al. (1993); Pogoda and Preston-Martin (1997).

(A.20) Pogoda and Preston-Martin (1997); Shim et al. (2009).

(A.21) Chen et al. (2016); Gold et al. (1979); Kuijten et al. (1990); Leiss and Savitz (1995); Schüz et al. (2001); Searles Nielsen et al. (2010).

(A.22) Davis et al. (1993); Pogoda and Preston-Martin (1997); Rosso et al. (2008); Shim et al. (2009).

(A.23) Davis et al. (1993); Pogoda and Preston-Martin (1997); Shim et al. (2009).

(A.24) Bunin et al. (1994); Davis et al. (1993); Pogoda and Preston-Martin (1997).

(A.25) Davis et al. (1993); Leiss and Savitz (1995).

(A.26) Davis et al. (1993); Pogoda and Preston-Martin (1997).

(A.27) Davis et al. (1993); Pogoda and Preston-Martin (1997).

(A.28) Davis et al. (1993); Greenop et al. (2013); Pogoda and Preston-Martin (1997).

(A.29) Davis et al. (1993); Pogoda and Preston-Martin (1997).

(A.30) Chen et al. (2016); Davis et al. (1993); Pogoda and Preston-Martin (1997).

(A.31) Bunin et al. (1994); Greenop et al. (2013); Kuijten et al. (1990); Schüz et al. (2001); Shim et al. (2009).

(A.32) Bunin et al. (1994); Greenop et al. (2013); Kuijten et al. (1990); Shim et al. (2009).

(A.33) Greenop et al. (2013); Schüz et al. (2001).

(A.34) Bunin et al. (1994); Greenop et al. (2013); Schüz et al. (2001); Shim et al. (2009).

(A.35) Bunin et al. (1994); Greenop et al. (2013); Shim et al. (2009).

(A.36) Greenop et al. (2013); Schüz et al. (2001).

(A.37) Bunin et al. (1994); Davis et al. (1993); Gold et al. (1979); Howe et al. (1989); Kuijten et al. (1990); Leiss and Savitz (1995); Pogoda and Preston-Martin (1997); Preston-Martin et al. (1982); Rosso et al. (2008); Searles Nielsen et al. (2005); Searles Nielsen et al. (2010); Shim et al. (2009).

(A.38) Cordier et al. (1994); Schüz et al. (2001); Spix et al. (2009).

(A.39) Greenop et al. (2013); McCredie et al. (1994).

(A.40) Bunin et al. (1994); Davis et al. (1993); Rosso et al. (2008); Searles Nielsen et al. (2010); Shim et al. (2009); Spix et al. (2009).

(A.41) Chen et al. (2016); Cordier et al. (1994); Greenop et al. (2013); Kuijten et al. (1990); Leiss and Savitz (1995); McCredie et al. (1994); Schüz et al. (2001).

(A.42) Gold et al. (1979); Howe et al. (1989); Pogoda and Preston-Martin (1997); Preston-Martin et al. (1982); Searles Nielsen et al. (2005).

[a] Where results were reported for several domestic exposure categories, the most global values for house treatments were selected: use of insect sprays or pesticides (Bunin et al., 1994), pesticide used for nuisance pests (Davis et al., 1993), professional pest control treatment in the home or garden: any treatment (Greenop et al., 2013), home pest extermination (Leiss and Savitz, 1995), nuisance pest (Pogoda and Preston-Martin, 1997), pesticides used often or occasionally (Preston-Martin et al., 1982), insecticides for home, yard, garden, pets or lice (Searles Nielsen et al., 2010), ever used herbicides for gardens and lawns (application by anyone including professionals) (Shim et al., 2009). Where results were not reported for pesticides overall but for insecticides, herbicides and fungicide, the value for insecticides was used. Where results were reported by types of pest treated, the value for the higher number of exposed cases was used (Chen et al., 2016).

Where results were reported for central nervous system overall (or for cranial brain tumor) as well as for specific cell types tumors (astrocytoma/astroglial, ependymoma, primitive neuroectodermal tumors, medulloblastomas, other glial tumors, other specified intracranial and intraspinal neoplasma, as examples), the overall results were selected here. Where overall results were not presented, they were calculated from the data for specific cell types tumors. Where results were reported for maternal and for childhood exposures, the value for maternal exposure before child birth (prenatal) was used.

Gold et al. (1979) matched cases to controls from 2 independent sources: cancer controls and normal (cancer-free) controls. Data for normal controls were included in the summary odd

ratio. Davis et al. (1993) used controls from 2 independent sources: cancer controls and friends of childhood brain cancer cases as controls. Data for friends controls were included in the meta-odd ratio. Schüz et al. reported risks of CNS tumors based on use of household insecticides 1/year and > 1/year. Overall data were calculated by combining these two exposure frequencies and were included in the summary odd ratio. Shim et al. (2009) presented data for pesticide applications by anyone (including mother, father, professionals and others) and by the father and by the mother. Data for applications by anyone were selected.

[b] Exposure during childhood was assessed by Davis et al. (1993) for the first six months and for seven months of age to the diagnosis of cancer. Data for the first six months of age were included in the summary odd ratio. In the study of Greenop et al. (2013), included data are for children who are known to have been exposed when any professional pest control treatment had been carried out in the house or garden. Leiss and Savitz (1995) reported data for several sources of exposure and exposure periods. Home extermination data in the period from birth through 2 years prior to diagnosis was used.

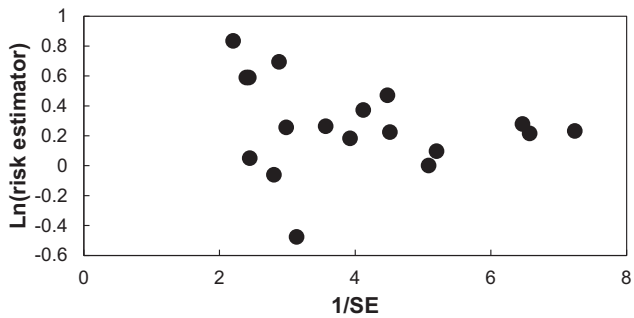


**Fig. 3.** Case-control studies of residential pesticide exposure and childhood brain tumors: funnel plot of natural logarithms of risk estimates (OR) vs the inverse of their standard errors (1/SE) (lnOR of the 18 case-control studies combined = 0.228).

assist investigators to link the self-reported type of pest treated with specific chemicals in 4 years (1976, 1980, 1990, 2000). For each pest-year combination, the matrix lists the active ingredients that were on the market and provides a rough estimate of the probability that a product containing each ingredient was used (Colt et al., 2007). A review of measurements that can be used to characterize exposures, including biological markers, personal and indoor sampling techniques, collection of dust, surface and dermal wipe samples and dietary assessment tools has been done by Bradman and Whyatt (2005)

Only two studies included in our MA reported risk estimators for specific compounds (Davis et al., 1993; Chen et al., 2016). Statistically significant increased risks were observed following residential exposure to diazinon and to lindane (Kwell® shampoo) and non-significant increase for chlordane and carbaryl (Davis et al., 1993). Chen et al. (2016) evaluated pyrethroid pesticide exposure by urinalysis of 3 nonspecific metabolites of pyrethroids (*cis*-DCCA, *trans*-DCCA and 3-PBA). *Trans*-DCCA, 3-PBA and the sum of the three metabolites were positively associated with the increased risk of CBT. However, it has to be stressed that urinary levels of the pyrethroid metabolites were not associated with self-reported use of household pesticides (Chen et al., 2016). Some other authors reported pesticides most likely to be used for different treatments: chlordane, heptachlor, diazinon and chlorpyrifos for home extermination, carbaryl, diazinon and 2,4-D as yard insecticides and dichlorvos in pest strips (Leiss and Savitz, 1995). Pogoda and Preston-Martin (1997) presented a list of the most common chemicals in different types of flea/tick products in California. Chlorpyrifos and diazinon, two organophosphorus (OP) insecticides were reported as being the two most common residential insecticides by Searles Nielsen et al. (2005). Chemicals approved for extermination of termites and other pests in Australia, including bifenthrin, fipronil, deltamethrin, chlorpyrifos, permethrin and imidacloprid, as well as chemicals used exclusively for termite treatments including arsenic trioxide, hexaflumuron and chlorfluazuron, were listed by Greenop et al. (2013). This very scarce information did not allow to draw conclusions for specific compounds.

We then attempted to assess CBT risk from types of pests treated (termite, lice, flea/tick) as well as from the application methods (spray/bomb, strips, collar, shampoo). Once again we were limited by the scarcity of available information and only results from 2 to 3 studies per stratification could be combined. The single mOR that showed a statistically significant increased risk of CBT was the treatment against flea/ticks. Chen et al. (2016) found that exposure to both mosquitocide and cockroach killer was related to the significantly increased risk of CBT.

#### 4.4.3. Outcome misclassification

Outcome misclassification is another issue. The tumor types were characterized in different ways in the primary studies: one of them reported "brain tumors" without any specification of the included tumors (Leiss and Savitz, 1995), others focused on specific tumor types like astrocytomas (Kuijten et al., 1990) and embryonal tumors (Rosso et al., 2008). Others specified several histologic subcategories without referring to international classification of disease codes [ICD] (Chen et al., 2016; Cordier et al., 1994; Gold et al., 1979; Greenop et al., 2013; Preston-Martin et al., 1982; Rosso et al., 2008), referring to ICD codes (Bunin et al., 1994; Davis et al., 1993; Howe et al., 1989; McCredie et al., 1994; Pogoda and Preston-Martin, 1997; Searles Nielsen et al., 2005, 2010; Shim et al., 2009), to international classification of children cancer [ICCC groups] (Spix et al., 2009) or to other classifications like the classification of Birch and Marsden (1987) (Schüz et al., 2001). The inconsistent tumor characterization among studies can be a source of outcome misclassification bias. It is possible that exposure to pesticides may be associated with only a subset of childhood brain tumors. Stratification of the studies by brain tumor types revealed a significantly increased risk for the gliomas, and especially for exposure during pregnancy, but not for embryonal tumors.

#### 4.4.4. Critical exposure time windows

The inability of our results to highlight a specific critical period may be partially explained by the fact that in most studies, those who use pesticides prenatally also likely use them postnatally.

### 4.5. Hill consideration

While the meta-analytical results of the present paper reveal an association, MA has a limited, although legitimate, role to play in causal inference. Distinguishing between association and causation is a fundamental scientific concern with important implications for public health (Weed, 2010). Several criteria proposed by Hill (1965) and adapted by Rothman and Greenland (1998) to facilitate the causality assessment may be of great interest for evaluating the body of evidence of the present association.

#### 4.5.1. Strength

The observed associations between residential exposure and CBT are small, the great majority of summary odds ratios remaining lower than 1.5. However, according to Rothman and Greenland (1998), weakness does not mean absence of causality and the strength of a factor depends on the relative prevalence of its causal complement. The causes of CBT are most likely multi-factorials and genetic factors, as an example, may be considered as a causal complement that plays key roles in the development of CBT. Because these are not measured, only weak associations are observed (Infante-Rivard and Weichenthal, 2007).

#### 4.5.2. Consistency

As detailed above (see § "Comparison with others MA"), in spite of methodological differences, our observations are in fair agreement with those made by other authors reporting data with regards to residential exposure to pesticides and CBT (Chen et al., 2015; Kunkle et al., 2014;

**Table 3**
Sensitivity analyses.

| Rerunning MA | N. | Summary | | Homogeneity | | | |
|---|---|---|---|---|---|---|---|
| | Studies | Odd ratio | 95% CI | Cochran's Q ($\chi^2$ Woolf) | *P*-value | $I^2$ | 95% UI |
| Statistical pooling using | | | | | | | |
| - Random effect model | 18[a] | 1.25 | 1.15–1.37 | 14.362 | 0.641 | 0 | 0–41 |
| - Fixed model | 18 | 1.26 | 1.13–1.40 | | | | |
| - Excluding study(ies) | | | | | | | |
| - With partial redundancy[b] | | | | | | | |
| Pogoda and Preston-Martin (1997) | 17 | 1.27 | 1.14–1.42 | 13.843 | 0.610 | 0 | 0–44 |
| Searles Nielsen et al. (2010) | 17 | 1.26 | 1.13–1.40 | 14.166 | 0.586 | 0 | 0–45 |
| - Reporting extreme risk estimators values | | | | | | | |
| Gold et al. (1979) and Searles Nielsen et al. (2005)[c] | 16 | 1.27 | 1.14–1.42 | 7.619 | 0.938 | 0 | 0–6 |
| - Higher precision values | | | | | | | |
| Greenop et al. (2013), Schüz et al. (2001), Shim et al. (2009)[d] | 15 | 1.25 | 1.08–1.43 | 14.238 | 0.432 | 2 | 0–54 |
| - One study at a time | | | | | | | |
| Gold et al., 1979 | 17 | 1.25 | 1.12–1.39 | 12.560 | 0.705 | 0 | 0–38 |
| Preston-Martin et al., 1982 | 17 | 1.25 | 1.12–1.39 | 13.994 | 0.599 | 0 | 0–44 |
| Howe et al., 1989 | 17 | 1.27 | 1.13–1.41 | 13.684 | 0.622 | 0 | 0–43 |
| Kuijten et al., 1990 | 17 | 1.26 | 1.13–1.41 | 14.328 | 0.574 | 0 | 0–45 |
| Davis et al., 1993 | 17 | 1.25 | 1.12–1.39 | 13.581 | 0.630 | 0 | 0–42 |
| Bunin et al., 1994 | 17 | 1.28 | 1.15–1.43 | 12.903 | 0.680 | 0 | 0–39 |
| Cordier et al., 1994 | 17 | 1.25 | 1.12–1.39 | 13.605 | 0.628 | 0 | 0–43 |
| McCredie et al., 1994 | 17 | 1.24 | 1.11–1.38 | 12.522 | 0.707 | 0 | 0–38 |
| Leiss and Savitz, 1995 | 17 | 1.25 | 1.12–1.40 | 14.347 | 0.642 | 0 | 0–46 |
| Pogoda and Preston-Martin, 1997 | 17 | 1.27 | 1.14–1.42 | 13.843 | 0.610 | 0 | 0–44 |
| Schüz et al., 2001 | 17 | 1.26 | 1.12–1.41 | 14.354 | 0.572 | 0 | 0–46 |
| Searles Nielsen et al., 2005 | 17 | 1.28 | 1.15–1.43 | 9.296 | 0.901 | 0 | 0–16 |
| Rosso et al., 2008 | 17 | 1.24 | 1.11–1.38 | 13.114 | 0.664 | 0 | 0–40 |
| Shim et al., 2009 | 17 | 1.25 | 1.11–1.40 | 14.245 | 0.580 | 0 | 0–45 |
| Spix et al., 2009 | 17 | 1.26 | 1.13–1.40 | 14.356 | 0.572 | 0 | 0–46 |
| Searles Nielsen et al., 2010 | 17 | 1.26 | 1.13–1.40 | 14.166 | 0.586 | 0 | 0–45 |
| Greenop et al., 2013 | 17 | 1.26 | 1.12–1.41 | 14.361 | 0.572 | 0 | 0–46 |
| Including data from other control groups[e] | | | | | | | |
| Cancer controls (Davis et al., 1993; Gold et al., 1979) | 17 | 1.24 | 1.11–1.38 | 11.750 | 0.815 | 0 | 0–28 |

*Abbreviations*: N. Studies, number of studies; 95% CI, 95% confidence interval; summary odds ratios are in bold when the 95% CI do not include 1; 95% UI, 95% uncertainty interval; statistical pooling using fixed model when $I^2 \leq 25\%$.

[a] The 18 included studies are as in Table 2 (A.1).

[b] Partial redundancy exist between the study of Pogoda and Preston-Martin (1997) and that of Searles Nielsen et al. (2010) as some data for children born in California or Washington States with genotyping data included in the study of Searles Nielsen et al. (2010) are from children also participating in the study of Pogoda and Preston-Martin (1997) involving only children from Los Angeles County.

[c] Extreme risk estimator values were: OR: 0.62, 95% CI: 0.33–1.15 (Searles Nielsen et al., 2005) and OR: 2.3, 95% CI: 0.94–5.57 (Gold et al., 1979).

[d] The higher precision values were 17%, 14% and 13% for the studies of Greenop et al. (2013), Schüz et al. (2001) and Shim et al. (2009), respectively.

[e] Gold et al. (1979) matched cases to controls from 2 independent sources: cancer controls and normal (cancer-free) controls and Davis et al. (1993) used cancer controls and friends of childhood brain cancer cases as controls. Data for non-cancer controls were included in the overall summary OR and are replaced by data for cancer controls in the present sensitivity analysis. Risk estimator values for cancer controls were: OR: 1.2, 95% CI: 0.55–2.59 (Gold et al., 1979) and OR: 1.2, 95% CI: 0.5–2.9 (Davis et al., 1993).

Vinson et al., 2011). In addition, our companion meta-analytic study on the association between parental occupational exposure to pesticides and risk of childhood brain tumors also reported statistically significant increased risks, among others, when combining all case-control and cohort studies, for prenatal exposure windows, for either exposed parent and for astroglial brain tumors (Van Maele-Fabry et al., 2013). For childhood CBT in general, the statistically significant associations between pesticide exposure during pregnancy (via parental occupational exposure or via residential exposure) and CBT observed in the different MA tends to increase the body of evidence of an association.

#### 4.5.3. Specificity

The low prevalence of childhood CBT as well as the imprecise exposure assessment limit the ability to associate specific pesticide exposures with specific childhood cancer. The etiology of CBT is largely unknown and likely multifactorial and conversely, pesticide exposure is not uniquely associated with CBT. However, in such a case, the specificity criterion does not confer greater validity to causality.

#### 4.5.4. Temporality

While it is obvious that exposure must occur before cancer develops, it is not clear when (in which time window) these exposures must occur in order to exert their action: prior to conception, during pregnancy or during childhood (Infante-Rivard and Weichenthal, 2007). In the present MA, significant increased risk was observed for both prenatal and during childhood exposure time windows. However, prenatal exposure appears more specifically associated with CBT for indoor exposure as well as for gliomas as CBT type agreeing with various experimental data showing that embryonic development is a critical window of exposure to contaminants. For example, Srivastava et al. (2015) have suggested a link between exposure to lindane during pregnancy and fetal effects. Another study showed that during a critical developmental window centered around the immediate perinatal period, Chlorpyrifos elicits immediate and persistent effects on expression of biomarkers for synaptic development and integrity (Aldridge et al., 2005).

#### 4.5.5. Biological gradients

Some authors assessed exposure-response gradients based on crude substitute of exposure measures. Increasing risk was observed with increasing exposure for 2 of the 3 measures of dose-response (number of pets treated, time spent with treated pets) reported by Pogoda and Preston-Martin (1997). Prenatal exposure to flea/tick products

produced a borderline statistically significant increased risk of CBT when products were used on more than one pet and when all subjects were considered. Statistical significance was achieved among children diagnosed at younger ages (< 5 years) (Pogoda and Preston-Martin, 1997). No dose-response relationship were observed by Rosso and collaborators (Rosso et al., 2008) or by Schüz and collaborators (Schüz et al., 2001) in their analyses of frequency of hobby participation (< 1/month, > 1/month) or of use of household insecticides (1/year, > 1/year), respectively. More recently, Chen et al. (2016) analyzed the association of urinary pyrethroïd metabolites quartiles with CBT and showed that, for 2 metabolites (*trans*-DCCA, 3-PBA) and for the sum of the 3 studied metabolites, children in the higher quartile had a nearly 3-fold increased risk of CBT compared with those in the lowest quartile after adjusting for confounding factors. The urinary levels of the pyrethroid metabolites were, however, not associated with self-reported use of household pesticides. These limited observations do not provide enough support to a positive exposure-response relationship between residential exposure to pesticides and childhood brain tumors.

#### 4.5.6. Plausibility

Pesticide contamination of indoor as well as outdoor environments has been documented by numerous studies reporting dust samples containing several pesticides (organochlorine, organophosphorus and pyrethroid compounds, as examples) (Hwang et al., 2008; Jiang et al., 2016; Mahler et al., 2009; Raffy et al., 2017; Regueiro et al., 2007; Rudel and Perovich, 2009; Smith et al., 2016; Starr et al., 2008).

Ubiquity of indoor pesticides is a major concern for children during the pre- and postnatal periods. Brain development is characterized by periods of rapid growth and maturation during which it is particularly sensitive to toxic substances, including pesticides (Lee et al., 2015; Win-Shwe et al., 2013).

The developing foetus may be particularly vulnerable to OP compounds absorbed from the maternal blood supply (Bradman et al., 2003; Lassiter et al., 1998; Whyatt and Perera, 1995). The concentration of OP in foetal tissues can be greater than in the exposed mother (Akhtar et al., 2006; Hunter et al., 1999). OP compounds can induce developmental neurotoxic effects in experimental animals, when exposure occurs during a period of rapid brain growth and maturation (Lee et al., 2015; Mullins et al., 2015). Prenatal OP exposure induced long-term impairments of the brain cytoarchitecture and microtubule agency (Chen et al., 2014). Exposure to chlorpyrifos during the perinatal period, elicited immediate and persistent effects on expression of biomarkers of synaptic development and integrity (Aldridge et al., 2005).

Carbamates are supposed to have similar effects and behaviour than OP. They accumulate in brain in a dose-related manner (Herr et al., 2010). Exposure to carbamate during a critical window of neonatal brain development may lead to adverse effects in offspring. Neonatal exposure of mice to a single dose of carbaryl (0.5, 5.0 or 20.0 mg/kg body weight) led to changes in protein levels in the developing brain and to persistent impairments of behaviour and cognitive function at adult age (Lee et al., 2015).

The central nervous system (CNS) is the target of OC pesticides as these compounds can cross the blood brain barrier (Corrigan et al., 2000; Fleming et al., 1994; Richardson et al., 2014). Experimental studies supported the link between exposure to lindane during pregnancy and foetal effects. Lindane induced neurobehavioral toxicity by several mechanisms, such as alterations of neurotransmitter levels and altered expression of cytochrome P450s (CYPs) (Anand et al., 1998; Johri et al., 2008; Parmar et al., 2003; Rivera et al., 1998; Srivastava et al., 2015). As the CYPs are not fully developed in the foetus and developing animals (Moscovitz and Aleksunes, 2013), lindane may not be well detoxified when exposure occurs during gestation, resulting in deleterious effects in the offspring.

Some pyrethroid insecticides such as deltamethrin are highly lipophilic compounds and can penetrate the brain. Exposure to increasing dose of an environmentally-relevant mixture of five pyrethroids in adult rats is associated with increased concentration of pyrethroid in blood and brain (Hughes et al., 2016; Kim et al., 2008, 2010). Experimental data support the involvement of pyrethroid insecticides in brain diseases in offspring upon maternal exposure. Maternal exposure to deltamethrin altered the structural and functional development of rat cerebellum during postnatal life (Kumar et al., 2013). Oral administration of low doses of cypermethrin to pregnant Wistar rats produced a dose-dependent increase in the expression of xenobiotic metabolizing cytochrome P450 (CYP1A, 2B- and 2E1) in the brain and liver of offsprings postnatally. This persistent increase in CYPs was associated with accumulation of cypermethrin in the brain of exposed offsprings (Singh et al., 2013).

Thus, some pesticides commonly found in home dust (OP, pyrethrinoid, OC and carbamate, as examples) are suggested to reach the brain and can induce CNS damage. Neonatal exposure to these compounds can induce changes in brain structure and/or function. Moreover, most of these compounds (OP/OC/PYR/Carbamate) are prooxidants and can alter key enzymes of signalling pathways involved in the regulation of cell proliferation and survival (INSERM, 2013). All these data strengthen the evidence of a relationship between childhood exposure to indoor pesticides and CBT as shown in this MA. More data are, however, needed to better identify the involved compounds and to confirm their involvement in the etiology of brain cancer. Focusing on the critical windows of exposure and on realistic doses of pesticides will contribute to a better understanding of the impact of pesticide exposure on children health.

## 5. Conclusion

The present systematic review and a MA of case-control studies have revealed a positive association between residential exposure to pesticides and childhood brain tumors, more particularly indoor exposure, involving insecticides and with gliomas as outcome. Several factors argue in favor of residential pesticide exposure as an etiological factor or at least as a contributing risk factor for childhood brain tumors, including the consistency of between-study results, the lack of or very low heterogeneity, the absence of evidence of publication bias and the biological plausibility. As it cannot be excluded that the large number of comparisons could result in some statistically significant findings by chance, the consistency of the results of the present MA with those observed in our companion MA on parental occupational exposure to pesticides and childhood brain tumors strongly supports the evidence of a relationship between pesticide exposure and childhood brain cancer. However, formal causality of pesticide exposure in childhood brain tumors cannot be established mainly due to the rarity of the disease, the absence of positive exposure-response relationship, the few available data on specific histological types of brain tumors as well as the lack of precise measurements of specific pesticides. There is a need for future studies to improve exposure assessment through specific pesticide exposure questions, use of biomarkers and semi-quantitative measures of specific pesticides in environmental or biological specimens that can allow confirming information obtained through questionnaires. As a critical role of genetic factors in the etiology of several cancers becomes evident, future research focusing on the interaction between genetic and environmental factors and attempts to correlate improved exposure data with genetic predisposition and defined subtypes of CBT would be of great interest. To this end, well-designed studies including an international consortium of researchers to collect sufficient cases in a reasonable amount of time are required. While awaiting results of such studies, prevention may be the most relevant option, and efforts should be made to limit childhood exposure. Public health policies should be developed for that purpose, including educational measures to increase the awareness of the population, and particularly of young couples, women of childbearing age or pregnant women about the potential impact of residential pesticide use on children heath.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.envint.2017.05.018.

## Acknowledgements

This study was funded by "The French National Research Program for Environmental and Occupational Health of Anses with the support of the Cancer TMOI of the French National Alliance for Life and Health Sciences (AVIESAN) (2014–2016)".

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