Risk of Central Nervous System Tumors in Children Related to Parental Occupational Pesticide Exposures in three European Case-Control Studies

Olivia Febvey, Joachim Schüz, PhD, Helen D. Bailey, PhD, Jacqueline Clavel, MD, PhD, Brigitte Lacour, MD, Laurent Orsi, PhD, Tracy Lightfoot, PhD, Eve Roman, PhD, Roel Vermeulen, PhD, Hans Kromhout, PhD, and Ann Olsson, PhD

Objective: The aim of this study was to assess the risk of childhood central nervous system (CNS) tumors associated with parental occupational pesticide exposure. **Methods:** We pooled three population-based case-control studies from France, Germany, and the United Kingdom. Cases were children below 15 years of age with CNS tumors; controls were matched by gender and age. A general population job-exposure matrix assessed parental occupational pesticide exposure. Logistic regressions estimated odds ratios (ORs) and 95% confidence intervals (CIs). **Results:** The study included 1361 cases and 5498 controls. Prevalence of maternal occupational pesticide exposure during pregnancy was low and no association with childhood CNS tumors was detected (OR 0.76, 95% CI: 0.41 to 1.41). Around conception, OR for childhood CNS tumors associated with paternal occupational pesticide exposure was 0.71 (95% CI: 0.53 to 0.95). **Conclusion:** Our results do not suggest a role of parental occupational pesticide exposure in the etiology of childhood CNS tumors.

Childhood cancers are the second leading cause of death, after accidental causes, among children under 15 years old in high-income countries. Brain and central nervous system (CNS) tumors are a heterogeneous group of malignancies and represent the second most common form of childhood cancers after leukemia, accounting for about 20% of all pediatric tumors.[1] Incidence of childhood CNS tumors increased between 1978 and 1997 with an estimated average annual increase of 1.7% in Europe, although incidence varied according to histological subgroup.[1] Major histological subgroups of CNS tumors are astrocytomas (47%), CNS embryonal tumors [22%, including medulloblastomas and other primitive neuroectodermal tumors (PNETs)], and ependymomas (10%). The only established risk factors are therapeutic doses of X-rays to the head and certain genetic syndromes (such as neurofibromatosis, Li-Fraumeni syndrome, and tuberous sclerosis).[2] Hence, the etiology for the majority of CNS tumors remains unknown and is likely to be multifactorial and vary by histological subgroup.

The majority of histological subgroups of CNS tumors are diagnosed at an early age, suggesting that predisposing events may occur in the prenatal or postnatal period. The incidence of astrocytomas peaked at the ages of 5 and 13 years, while PNET and ependymomas mainly occur in children under 3 years old and then decrease with increasing age.[3] The brain is still developing at birth and may therefore remain vulnerable to adverse effects of carcinogens. Before conception, harmful substances may impair parental germ cells by causing DNA damage in father's sperm.[4] During pregnancy, intrauterine exposures can affect the fetus directly by crossing the placental barrier and entering the fetal blood circulation. After birth, substances may cross the blood-brain barrier of the child, which is incompletely developed and permeable up to 6 months of age.[5] Many pesticides have demonstrated neurotoxicity in humans[6] and it has been suggested that parental occupational pesticide exposure during the development of the child could increase susceptibility to CNS tumors.[7,8]

A recent meta-analysis including 16 case-control studies published between 1974 and 2010 reported an increased risk of CNS tumor with parental occupational exposure to pesticides (before conception and during pregnancy) with a summary odds ratio [SOR] of 1.30 [95% confidence interval (95% CI): 1.11 to 1.53] overall, 1.39 (95% CI: 1.10 to 1.75) for maternal exposure, and 1.19 (95% CI: 1.03 to 1.38) for paternal exposure; no heterogeneity between studies was observed in these analyses ($I^2 = 0\%$).[9] The occupational data were collected in different ways, for example, via birth records (job titles) or face-to-face interviews using standardized questionnaires or open questions; and the methods to estimate exposure included self-assessment of specific agents, job-exposure matrices (JEMs) applied to self-reported job titles, expert assessment based on individual and detailed questionnaire data, or focused on single or a group of occupations or industries.

The main aim of this paper was to examine the hypothesis that parental occupational pesticide exposure is associated with risk of CNS tumor development in children, using data from three European studies and an independently developed JEM (ALOHA JEM) to estimate the level of parental pesticide exposure based on

From the International Agency for Research on Cancer (IARC), Section of Environment and Radiation, Lyon (Febvey, Drs Schüz, Bailey, Olsson); Institut National de la Santé (INSERM) U1153, Epidemiology and Biostatistics Sorbonne Paris Cité Center (CRESS), Epidemiology of Childhood and Adolescent Cancers Team (EPICEA), Villejuif (Drs Bailey, Clavel, Lacour, Orsi); Paris-Descartes University, UMRS-1153, Epidemiology and Biostatistics Sorbonne Paris Cité Center (CRESS) (Drs Bailey, Clavel, Lacour, Orsi); RNCE - National Registry of Childhood Cancers, Villejuif (Dr Clavel); RNCE - National Registry of Childhood Cancers, Nancy, France (Dr Lacour); Epidemiology and Cancer Statistics Group, Department of Health Sciences, University of York, UK (Drs Lightfoot, Roman); Institute for Risk Assessment Sciences (IRAS), Department of Environmental Epidemiology, Utrecht University (Drs Vermeulen, Kromhout); Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, The Netherlands (Dr Vermeulen); and The Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden (Dr Olsson).

Olivia Febvey was supported by the Hospices Civils de Lyon, and the remaining coauthors contributed from their regular positions. The development of the ALOHA-JEM was supported by internal funding provided by the Institute for Risk Assessment Sciences (IRAS). The original case-control studies were supported as follows: France: INSERM, the Fondation de France, the Association pour la Recherche sur le Cancer (ARC), the Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS), the Agence Française de Sécurité Sanitaire de l'Environnement et du Travail (AFSSET), the association Cent pour sang la vie, the Institut National du Cancer (INCa), the Agence Nationale de la Recherche (ANR), and Cancéropôle Ile de France; Germany: Federal Ministry for the Environment, Nature Preservation and Nuclear Safety; UK: Leukaemia & Lymphoma Research.

The authors have no conflict of interest to declare.

Address correspondence to: Ann Olsson, PhD, International Agency for Research on Cancer, Section of Environment and Radiation, 150 cours Albert Thomas, 69372 Lyon CEDEX 08, France (Olssona@iarc.fr).

DOI: 10.1097/JOM.0000000000000852

job histories reported in the three studies. A secondary aim was to compare the prevalence of occupational pesticide exposure estimated using the ALOHA JEM with the prevalence of self-reported occupational pesticide exposure in the German study.

METHODS

Study Population

The study included three population-based case-control studies of childhood cancer, from France (diagnostic time window 2003 to 2004),[10] Germany (1988 to 1994),[11] and the United Kingdom (UK) (1991 to 1996).[12] Cases were recruited from population-based childhood cancer registries in France and Germany, and from tailored population-based referral systems in the UK. All children up to 15 years of age diagnosed with CNS tumors were included. Population-based controls were recruited in all studies and frequency-matched in the present study. Further details about ascertainment of case and control populations are given in Table 1.

Data Collection

Information about the socio-demographic characteristics and the parental occupational histories were collected through interviews conducted by trained personnel using standardized questionnaires, face-to-face, or via telephone. Both parents were interviewed when possible. In Germany, the parents were in addition shown a list of broad classes of chemicals including pesticides as one group, where they could tick whether they were exposed (yes/no) during the year before conception, during pregnancy, or any time after birth.[13]

Exposure Assessment

Parental occupational data were provided in three different coding formats, which were harmonized to a similar coding format in order to apply an existing general population JEM ALOHA[14] to assign pesticide exposure. The ALOHA JEM classifies all jobs in the International Standard Classification of Occupations from 1988 (ISCO-88)[15] into no, low, or high-exposure categories for insecticides, herbicides, fungicides, and all pesticides combined.

Job titles in the French study were initially coded according to ISCO-68, and converted into ISCO-88 using the conversion table between ISCO-68 and ISCO-88 included in the ISCO-88 documentation. Job titles in the German study were coded according to the ''Klassifizierung der Berufe, Ausgabe 1988'' (KldB-88)[16] and recoded to ISCO-88 using a conversion table provided by the Federal Employment Agency. Job titles in the UK study were coded according to the ''Standard Occupational Classification'' from 1990 (SOC-90)[17] and recoded to ISCO-88 using a conversion table provided by the Office for National Statistics. Moreover, the original text description of the job was used when there were no corresponding codes ($N = 12$ jobs coded in ISCO-68) or when there were multiple codes suggested in the conversion tables ($N = 117$).

Statistical Analyses

First, analyses were conducted for each study separately and a meta-analysis was performed to assess heterogeneity between the three studies. Second, data from the three studies were pooled in a single dataset and analyses were carried out on the pooled sample.

Study-specific odds ratios (ORs) and corresponding 95% CIs were estimated using unconditional logistic regressions adjusting for the study matching variables,[18] and included in the meta-analysis. We then estimated I^2, which described the percentage of total variation across studies due to heterogeneity. I^2 lies between 0% and 100%, with a value of 0% indicating no observed heterogeneity and larger values reflecting increasing heterogeneity.[19]

For the pooled analysis, ORs and 95% CIs were estimated using unconditional logistic regressions adjusted for sex, age, and country. The addition of the child's year of birth and parental educational level to the model did not change the results and these variables were therefore not included in the final models. The dichotomous exposure variable (never/ever) was used. Analyses were undertaken for maternal occupational exposures during pregnancy, and for paternal occupational exposures around conception (one year before pregnancy).

The most common histological subgroups of CNS tumors, that is, astrocytomas, CNS embryonal tumors, and ependymomas were analyzed separately, to investigate whether associations between pesticide exposure and histological subgroup varied. The remaining histological subgroups were combined into the ''Others'' subgroup, including other gliomas, other specified intracranial and intra-spinal neoplasms, and unspecified CNS tumors. Analyses were conducted by selecting cases from each histological subgroup and using all the controls available.

Prevalence of pesticide exposure was studied using percentages and Cohen's kappa coefficients were computed to assess agreement beyond chance between the ALOHA JEM and self-reported exposure to pesticides in the German study.

TABLE 1. Description of Case and Control Ascertainment in the Three Studies

Study (Years of Diagnosis)	Source	Participation	*N*
France (2003–2004)			
Cases	French National Registry of Childhood Solid Tumours	80%	209
Controls	List of 60,000 phone numbers provided by the French national telephone company, enriched by random generation of unlisted phone numbers. Matching criteria: frequency-matched by sex, age	71%	1681
Germany (1988–1994)*			
Cases	German Childhood Cancer Registry (GCCR)	81%	466
Controls	Population registers: two controls selected for each child, one from the same community, one from a randomly selected community in LS (LS study); one control selected for each case (WG study). Matching criteria: individually matched by sex, date of birth within one year (LS study); additionally matched by community (WG study)	69%	2456
United Kingdom (1991–1996) †			
Cases	Regional pediatric oncology units, cross-checked to regional and national cancer registries	87%	686
Controls	Population registers: two controls selected for each case. Matching criteria: individually matched by sex, date of birth, region	64%	1361

LS, Lower Saxony; WG, West Germany.
*In this pooled study of LS and WG studies, a pool of all controls irrespective of the diagnosis of the individual matched case was generated.
†England, Scotland, and Wales.

The level of significance was set at 0.05. All statistical analyses were conducted using the Stata statistical software, version 12.1 (StataCorp LP, College Station, TX).

RESULTS

Characteristics of the Study Population

General characteristics of the population are presented in Table 2. In total, 1361 children with CNS tumors and 5498 control children were included in the analyses. The children were born between 1974 and 2004, and more likely to be boys (55%). The mean age of cases at diagnosis was 6.3 years and the mean age of controls at reference date was 5.9 years. The parental mean age at birth of the child was 28.1 years for mothers and 31 years for fathers. Parental educational levels were significantly different between cases and controls, with less case parents completing tertiary education than control parents ($P < 0.001$).

The most common occupations with pesticide exposure in our study were within farming, gardening, wood work, and freight handling. Exposed parents in France and the UK were primarily farmers, gardeners, and freight handlers, while in addition parents in Germany also included carpenters and machine operators.

Overall, the most frequent histological subgroup was astrocytoma (representing 32.8% of all cases), followed by CNS embryonal tumor (27.5%) and ependymoma (11.2%). This distribution was observed in the German and UK studies, while the French study comprised more CNS embryonal tumors (47.9%) than astrocytomas (12.4%). However, only malignant CNS tumors were included in the French study, excluding low-grade astrocytomas that represent an important group of astrocytoma diagnoses.

Parental Occupational Pesticide Exposure and Risk of CNS Tumors

The prevalence of maternal occupational pesticide exposure during pregnancy was low in the three studies (about 2%), and less frequent in the UK overall (<1%) than in France and Germany. The prevalence of paternal occupational exposure to pesticides before conception was higher in Germany (11%) than the prevalence in France (6%) and in the UK (2%). Strong correlation of different types of pesticides prevented meaningful analyses by pesticide type (correlation coefficients between 0.86 and 0.97, all $P < 0.01$).

Study-Specific ORs and Meta-Analyses

Study-specific ORs are presented in Figs. 1 and 2 for both maternal and paternal occupational exposures. We observed no heterogeneity in risk between the three countries for maternal occupational pesticide exposure during pregnancy ($I^2 = 0\%$, $P = 0.47$); a positive association, albeit statistically nonsignificant,

TABLE 2. Characteristics of the Study Population

Characteristics of the Population	All studies		France		Germany		UK	
	Cases $n = 1361$	Controls $n = 5498$	Cases $n = 209$	Controls $n = 1681$	Cases $n = 466$	Controls $n = 2456$	Cases $n = 686$	Controls $n = 1361$
Sex, *n* (%)								
Boys	731 (53.7)	3004 (54.6)	125 (59.8)	932 (55.4)	262 (56.2)	1391 (56.6)	344 (50.2)	681 (50.0)
Girls	630 (46.3)	2494 (45.4)	84 (40.2)	749 (44.6)	204 (43.8)	1065 (43.4)	342 (49.9)	680 (50.0)
Age at diagnosis/reference date, mean (SD)	6.3 (4.0)	5.9 (4.1)	6.3 (3.9)	6.0 (4.3)	6.4 (4.0)	5.8 (4.0)	6.2 (4.0)	6.2 (4.0)
Parental age at birth, mean (SD)								
Mothers	27.5 (4.9)	28.3 (4.9)	30.1 (4.5)	30.1 (4.7)	27.2 (4.6)	27.7 (4.6)	26.9 (4.9)	27.3 (5.2)
Fathers	30.3 (5.8)	31.2 (5.8)	32.4 (5.8)	32.5 (5.6)	30.3 (5.6)	30.7 (5.6)	29.7 (5.8)	30.3 (6.2)
Parental educational level, *n* (%)								
Mothers								
Did not complete secondary education	467 (34.3)	1849 (33.6)	80 (38.3)	659 (39.2)	190 (40.8)	869 (35.4)	197 (28.7)	321 (23.6)
Completed secondary education	558 (41.0)	1936 (35.2)	45 (21.5)	320 (19.0)	168 (36.1)	916 (37.3)	345 (50.3)	700 (51.4)
Completed tertiary education	308 (22.6)	1577 (28.7)	84 (40.2)	701 (41.7)	85 (18.2)	546 (22.2)	139 (20.3)	330 (24.3)
Fathers								
Did not complete secondary education	468 (34.4)	2154 (39.2)	827 (49.2)	106 (50.7)	203 (43.6)	998 (40.6)	159 (23.2)	329 (24.2)
Completed secondary education	395 (29.0)	1291 (23.5)	236 (14.0)	20 (9.6)	96 (20.6)	550 (22.4)	279 (40.7)	505 (37.1)
Completed tertiary education	379 (27.9)	1622 (29.5)	601 (35.8)	81 (38.8)	118 (25.3)	657 (26.8)	180 (26.2)	364 (26.8)
Paternal occupations with pesticide exposure, *n* (%)								
Farmers and agricultural workers	30 (0.53)	217 (0.51)	8 (0.89)	75 (0.74)	13 (0.39)	128 (0.42)	9 (0.60)	14 (0.74)
Wood workers, Machine operators	19 (0.33)	135 (0.32)	0	13 (0.13)	17 (0.52)	121 (0.40)	2 (0.13)	1 (0.05)
Transport laborers, Freight handlers	6 (0.11)	59 (0.14)	0	9 (0.09)	2 (0.06)	46 (0.15)	4 (0.27)	4 (0.21)
Veterinarians, agronomy, and forestry technicians	2 (0.04)	15 (0.04)	1 (0.11)	4 (0.04)	1 (0.03)	11 (0.04)	0	0
Histological subgroups, *n* (%)								
Astrocytomas	446 (32.8)	—	26 (12.4)	—	119 (25.5)	—	301 (43.9)	—
CNS embryonal tumors	374 (27.5)	—	100 (47.9)	—	112 (24.0)	—	162 (23.6)	—
Ependymomas	152 (11.2)	—	33 (15.8)	—	50 (10.7)	—	69 (10.1)	—
Other	389 (28.6)	—	50 (23.9)	—	185 (39.7)	—	154 (22.5)	—

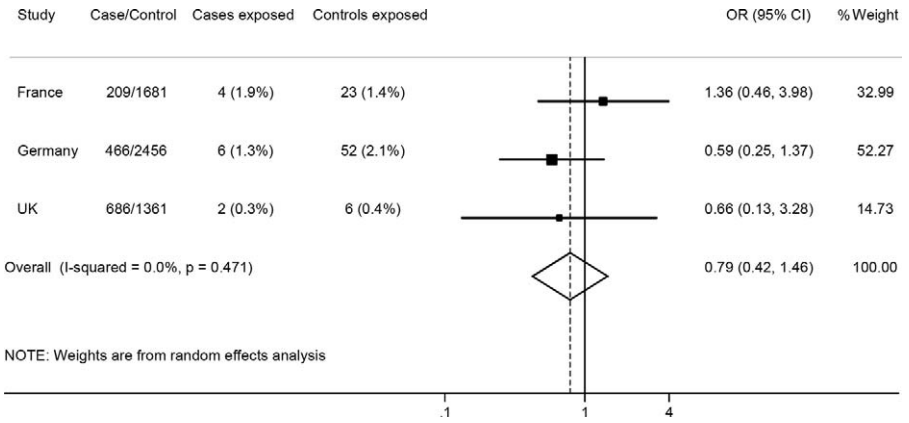

FIGURE 1. Forest plot of maternal occupational pesticide exposure during pregnancy and the risk of childhood CNS tumors.

was only found in the French study (Fig. 1). Paternal occupational pesticide exposure before conception showed substantial heterogeneity in risk across the three countries ($I^2 = 68.3\%$, $P < 0.05$); reduced risks of CNS tumors were seen in Germany and France, while there was a positive association in the UK study, although statistically nonsignificant (Fig. 2).

Pooled Analyses of the Three Studies

Risks of CNS tumors in children related to parental pesticide exposure overall and by histological subgroup are reported in Table 3.

The OR for childhood CNS tumors associated with maternal occupational pesticide exposure during pregnancy was 0.76 (95% CI: 0.41 to 1.41), based on low numbers of exposed women [12 cases (0.9%) and 81 controls (1.5%)]. There were too few exposed women to investigate level of exposure.

The OR for childhood CNS tumors associated with paternal pesticide exposure around conception was 0.71 and reached statistical significance (95% CI: 0.53 to 0.95). Results obtained for low and high levels of pesticide exposure were similar; hence, data were only presented for ever (low or high) pesticide exposure in the table.

Analyses by histological subgroups showed no statistically significant associations for either maternal occupational pesticide exposure during pregnancy or paternal exposure around conception.

Comparison of the ALOHA JEM and Self-Assessed Exposure

In the German study, we were able to study the agreement between two methods to assign parental occupational exposure to pesticides, that is, exposure to pesticides as assigned by the ALOHA JEM based on job titles collected during an interview and self-assessed occupational exposure to pesticides as reported via a self-administered questionnaire, presented in Table 4. Prevalence of maternal and paternal occupational exposures was higher according to the ALOHA JEM (2% and 11%, respectively) than self-assessed exposure (<0.5% and 3.5%, respectively). Agreement was low for both maternal and paternal exposure (Kappa Cohen coefficients: 0.05 for mothers, 0.24 for fathers).

DISCUSSION

This pooled analysis of three European case-control studies sought to investigate the association between parental occupational exposure to pesticides and subsequent risk of CNS tumors in their offspring. We did not observe any increased risk of CNS tumors in the offspring following parental occupational exposure to pesticides, overall or by histological subgroup. However, the OR for childhood CNS tumors associated with paternal occupational exposure to pesticides around conception was 0.71 and reached statistical significance (95% CI: 0.53 to 0.95).

Some studies have found an increased risk of CNS tumor with parental occupational exposure to pesticides.[20,21] Our findings, consistent with previous research,[22–24] failed to support the hypothesis that parental exposure to pesticides is associated with an increased risk of childhood CNS tumors.

A previous analysis of the same population from West Germany, when asking parents working on farms about their work-related use of pesticides during a telephone interview, also found a reduced OR (OR: 0.41, 95% CI: 0.18 to 0.93).[11] However,

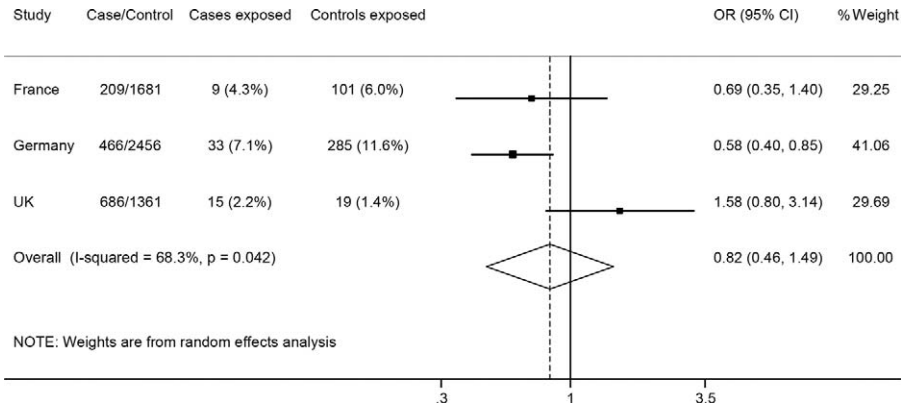

FIGURE 2. Forest plot of paternal occupational pesticide exposure before conception and the risk of childhood CNS tumors.

TABLE 3. Pooled OR (and 95% CI) for the Association Between Parental Occupational Pesticide Exposure and Risk of Childhood CNS Tumors, According to Histological Subgroup

	All CNS Tumors				Astrocytomas		Embryonal Tumors		Ependymomas		Others	
	Cases Exposed *n* (%)	Controls Exposed *n* (%)	OR*	95% CI	OR*	95% CI	OR*	95% CI	OR*	95% CI	OR*	95% CI
Mothers during pregnancy	12 (0.9)	81 (1.5)	0.76	0.41–1.41	0.46	0.11–1.90	0.67	0.21–2.13	1.71	0.53–5.53	0.75	0.27–2.06
Fathers around conception	57 (4.2)	405 (7.4)	0.71	0.53–0.95	0.87	0.53–1.43	0.68	0.40–1.17	0.44	0.16–1.20	0.73	0.46–1.16

CI, confidence interval; OR, odds ratio.
*OR adjusted for sex, age, and country.

the findings lacked precision due to the small number of exposed children.

The study from Germany was the earliest study and the prevalence of paternal occupational exposure to pesticides was higher in Germany than the prevalence in France and in the UK. The original classifications of occupations may have influenced the ISCO-88 coding and thereby the exposure assignment. The original German classification KldB-88 (around 800 codes) is more detailed than ISCO-88 (around 500 codes), resulting in a wider distribution of ISCO-88 codes within farmers/gardeners, as well as machine operators (metal- and wood-products). France also had a wide distribution of ISCO-88 codes because the original coding was ISCO-68 (around 1800 codes), and the most frequent ISCO-88 codes were within gardeners and farmers. UK was originally coded in SOC-90 (three digits) comprising relatively few codes corresponding to ISCO-88 codes (four digits), and the most frequent ISCO-88 codes were ''market gardeners and crop growers'' and ''transport laborers and freight handlers.'' Consequently, if we assume that the original data were coded correctly, the observed country differences could be explained by true differences in occupational patterns in the three studies, or by differences in the original classifications and/or the conversion tables.

We cannot rule out that our analyses have led to statistically significant results by chance. Moreover, selection bias due to nonparticipation cannot be excluded. Studies have shown that persons exposed to potentially hazardous agents may be interested in the consequences of their occupational exposures and are more likely to participate in epidemiological studies than those who are not exposed.[25] Therefore, if, for example, farmers would be more prone to participate in a study than the general population, this could influence the prevalence among controls and thereby lower the risk estimates. The participation rates in the three studies (64% to 71% among controls) were nevertheless comparable and reasonably good. In addition, using the same control set for leukemia cases in the German study showed a positive association between exposure to pesticides and risk of childhood leukemia, arguing against such a selection bias.[26] Bias could also occur due to lack of complete ascertainment of cases especially in the German study, wherein the cases of CNS tumors were reported to the German Childhood Cancer Registry (GCCR). In 1987, the level of completeness of the GCCR was around 95%, but thought to be lower for CNS tumors.[27] Because some children with CNS tumors did not require chemotherapy, they were not necessarily seen by pediatric oncologists and may therefore not have been reported to the registry. However, the German study showed no difference in cases and controls of whether children lived in urban or rural areas, making it less likely that completeness of reporting to the registry would be related to pesticide exposure.[11] In addition, we cannot exclude confounding by an unknown causative factor playing a role; no major causative factors for childhood CNS tumors have been identified, that is, factors explaining more than very small proportions of the disease. Among the few risk factors established (genetic factors, high doses of ionizing radiation), none qualifies as confounder, as their prevalence is too low to considerably impact on our OR estimation. Looking for nonpesticide-related factors among those occupations showing the reduced risk for CNS tumors in the offspring may feed into new research ideas, also taking into account that these factors would differ between Germany and the UK.

The main strength of this study was the large pooled sample of children. Identification of cases of CNS tumors was relatively

TABLE 4. Parental Occupational Exposure to Pesticides According to the ALOHA JEM and Self-Assessment, in the German Study

	Total Exposed %	Cases Exposed *n* (%)	Controls Exposed *n* (%)	OR	95% CI	Kappa*
Parental occupational pesticide exposure						
Mothers during pregnancy						
ALOHA JEM	1.98	6 (1.3)	52 (2.1)	0.59	0.25–1.37	—
Self-assessment	0.31	1 (0.2)	8 (0.3)	0.67	0.08–5.41	0.05
Fathers around conception						
ALOHA JEM	10.88	33 (7.1)	285 (11.6)	0.58	0.40–0.85	—
Self-assessment	3.52	17 (3.7)	86 (3.5)	1.10	0.65–1.88	0.24

CI, confidence interval; OR, odds ratio.
*Cohen Kappa compared with ALOHA JEM.

comprehensive, with recruitment from nationwide childhood cancer registries in the French and German studies, and through the clinical setting and cross-checking with cancer registries in the UK. The analysis by histological subgroups allowed the consideration of each subgroup as an etiological entity, but no specific association with exposure to pesticides was identified. In this study, we were able to focus on specific time periods where it is most biologically plausible that parental exposure could have an impact on an outcome in the offspring, namely close to conception for fathers and during pregnancy for mothers.

Different methods initially used to estimate pesticide exposure in the original studies include JEMs, expert assessment, and self-assessment. The ALOHA JEM assigned exposure to pesticides blinded to disease status and objectively in the same way across the three studies. In contrast to studies based on case-by-case expert assessment, the ALOHA-JEM avoided expert variability within and between studies. In addition, in case-control studies based on self-reported exposure, it has been demonstrated that cases and controls tend to remember exposures differently, which introduces differential exposure misclassification.[13]

We compared two different methods in assigning parental occupational exposure to pesticides, self-assessment, and the ALOHA JEM, which showed very low agreement (Kappa Cohen coefficients: 0.05 for mothers, 0.24 for fathers). In job categories typically associated with pesticide exposure, such as farmers, only a portion of parents reported being exposed to pesticides, while in some other more common job categories (eg, office workers) as well as among housewives, usually classified as unexposed to pesticides, ''occupational exposure'' was reported by a substantial proportion of parents, which contributed to a considerable amount of exposed cases and controls.[13] This may explain the low agreement between parental self-reported exposure and the ALOHA-JEM method in the German study. Therefore, assessing pesticide exposure via a JEM and via self-reports are two different approaches, which lead to different groups of exposed and unexposed. However, in this particular case, the results pointed in the same direction, namely no association between parental occupational exposure to pesticides and childhood CNS tumors.

This study also had several limitations. First, ORs were in opposite directions and heterogeneity between studies was substantial ($I^2 > 50\%$) for paternal occupational exposure. This is an unexpected finding reducing the value of the pooling. Second, a JEM assigns exposure at the job level and does not take into account variability between workers or between farms/companies for the same job. Third, the JEM method does not consider specific tasks and pesticides use, which could differ by crop, country, and decade. The time of the studies lasted from 1988 to 2004 and changes in pesticide use over time would have most certainly induced differences in types and levels of exposure. For instance, different application techniques, increased use of personal protective equipment, or organic farming may have changed the exposure to pesticides over time. Therefore, using the JEM to assess historical occupational exposure may have resulted in nondifferential exposure misclassification, most often leading to an attenuation of the risk. Exposure to pesticides was assigned at different time periods (around conception, during pregnancy) without information about actual duration of exposure, which prevented us from exploring the effect of cumulative exposure. Finally, multiple other possible sources of exposure have not been considered in this study. Children may indeed be exposed indirectly to pesticides from parental exposure (occupational, nonoccupational, or a combination). In addition, they can be exposed to pesticides at low levels via food, from residential applications (pets, garden), or drift from agricultural areas nearby residences or schools.

In conclusion, we did not find an association between risk of CNS tumors and maternal occupational pesticide exposure, but maternal exposure was rare (<2%). The statistically significantly reduced OR observed for paternal pesticide exposure is likely due to chance, or because of farming and other pesticide-related jobs being a surrogate of an unknown nonpesticide-related protective factor of childhood CNS tumors in some countries.

ACKNOWLEDGMENT

The authors thank Mrs Véronique Luzon for her help with the data management.

REFERENCES

1. Kaatsch P. Epidemiology of childhood cancer. *Cancer Treat Rev.* 2010; 36:277–285.
2. Kuijten RR, Bunin GR. Risk factors for childhood brain tumors. *Cancer Epidemiol Biomarkers Prev.* 1993;2:277–288.
3. Baldwin RT, Preston-Martin S. Epidemiology of brain tumors in childhood: a review. *Toxicol Appl Pharmacol*. 2004;199:118–131.
4. Anderson LM, Diwan BA, Fear NT, Roman E. Critical windows of exposure for children's health: cancer in human epidemiological studies and neoplasms in experimental animal models. *Environ Health Perspect*. 2000; 108(suppl 3):573–594.
5. Ostrea Jr EM, Bielawski DM, Posecion Jr NC, et al. Combined analysis of prenatal (maternal hair and blood) and neonatal (infant hair, cord blood and meconium) matrices to detect fetal exposure to environmental pesticides. *Environ Res*. 2009;109:116–122.
6. Bjorling-Poulsen M, Andersen HR, Grandjean P. Potential developmental neurotoxicity of pesticides used in Europe. *Environ Health*. 2008;7:50.
7. Infante-Rivard C, Weichenthal S. Pesticides and childhood cancer: an update of Zahm and Ward's 1998 review. *J Toxicol Environ Health B Crit Rev.* 2007;10:81–99.
8. Greenop KR, Peters S, Bailey HD, et al. Exposure to pesticides and the risk of childhood brain tumors. *Cancer Causes Control*. 2013;24:1269–1278.
9. Van Maele-Fabry G, Hoet P, Lison D. Parental occupational exposure to pesticides as risk factor for brain tumors in children and young adults: a systematic review and meta-analysis. *Environ Int*. 2013;56:19–31.
10. Plichart M, Menegaux F, Lacour B, et al. Parental smoking, maternal alcohol, coffee and tea consumption during pregnancy and childhood malignant central nervous system tumours: the ESCALE study (SFCE). *Eur J Cancer Prev.* 2008;17:376–383.
11. Schuz J, Kaletsch U, Kaatsch P, Meinert R, Michaelis J. Risk factors for pediatric tumors of the central nervous system: results from a German population-based case-control study. *Med Pediatr Oncol*. 2001;36: 274–282.
12. UK Childhood Cancer Study Investigators. The United Kingdom Childhood Cancer Study: objectives, materials, methods. *Br J Cancer.* 2000;82:1073–1102.
13. Schuz J, Spector LG, Ross JA. Bias in studies of parental self-reported occupational exposure and childhood cancer. *Am J Epidemiol*. 2003; 158:710–716.
14. Matheson MC, Benke G, Raven J, et al. Biological dust exposure in the workplace is a risk factor for chronic obstructive pulmonary disease. *Thorax*. 2005;60:645–651.
15. International Labour Office. *International Standard Classification of Occupations.* Geneva, Switzerland: ILO, 1988; 2015.
16. Bundesanstalt für Arbeit. *Classification of Occupations. Systematic and Alphabetical List of Professional Designations [in German].* Nürnberg, Germany: Bundesanstalt für Arbeit; 1988.
17. Office of Population Censuses, Surveys. *Standard Occupational Classification. Volume 1*. London: HMSO, 1990; 2015.
18. Breslow NE, Day NE. Statistical methods in cancer research. Volume I—the analysis of case-control studies. *IARC Sci Publ*. 1980;5–338.
19. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557–560.
20. van Wijngaarden E, Stewart PA, Olshan AF, Savitz DA, Bunin GR. Parental occupational exposure to pesticides and childhood brain cancer. *Am J Epidemiol*. 2003;157:989–997.
21. Feychting M, Plato N, Nise G, Ahlbom A. Paternal occupational exposures and childhood cancer. *Environ Health Perspect*. 2001;109:193–196.
22. Pearce MS, Hammal DM, Dorak MT, McNally RJ, Parker L. Paternal occupational exposure to pesticides or herbicides as risk factors for cancer in children and young adults: a case-control study from the North of England. *Arch Environ Occup Health*. 2006;61:138–144.

23. McKinney PA, Fear NT, Stockton D. Parental occupation at periconception: findings from the United Kingdom Childhood Cancer Study. *Occup Environ Med*. 2003;60:901–909.
24. Rodvall Y, Dich J, Wiklund K. Cancer risk in offspring of male pesticide applicators in agriculture in Sweden. *Occup Environ Med*. 2003;60:798–801.
25. Galea S, Tracy M. Participation rates in epidemiologic studies. *Ann Epidemiol*. 2007;17:643–653.
26. Meinert R, Schuz J, Kaletsch U, Kaatsch P, Michaelis J. Leukemia and non-Hodgkin's lymphoma in childhood and exposure to pesticides: results of a register-based case-control study in Germany. *Am J Epidemiol*. 2000; 151:639–646.
27. Kaatsch P, Rickert CH, Kuhl J, Schuz J, Michaelis J. Population-based epidemiologic data on brain tumors in German children. *Cancer*. 2001; 92:3155–3164.