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Occupational solvent exposure and risk of glioma in the INTEROCC study

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Background: The aetiology of glioma remains largely unknown. Occupational solvent exposure has been suggested as a putative cause of glioma, but past studies have been inconsistent. We examined the association between a range of solvents and glioma risk within the INTEROCC project, a study of brain tumours and occupational exposures based on data from seven national case–control studies conducted in the framework of the INTERPHONE study. We also investigated associations according to tumour grade.

Methods: Data from the seven countries were standardised and then combined into one aggregate data set. Pooled odds ratios (ORs) were estimated for adjusted models that included sex, age, country–region of residence and level of educational attainment. Exposures to any solvent or 11 specific solvents or subgroups were assessed using a modified version of the FINJEM job exposure matrix (JEM) specifically developed for the study, called INTEROCC-JEM.

Results: Analysis included 2000 glioma cases and 5565 controls. For glioma and ever/never exposure to any solvent, the OR was 0.91 (95% confidence interval: 0.74–1.11). All ORs were <1.0 for specific solvents/subgroups. There were no increases in risk according to high or low grade of tumour.

Conclusions: The results of this study show no consistent associations for any solvent exposures overall or by grade of tumour.

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Glioma is the most common form of malignant brain tumour, and although relatively rare, current incidence rates in the United States and other developed countries range from 5 to 7 cases per 10^5 persons-years and represent approximately 80% of all malignant brain tumours (Ohgaki, 2009; Efird, 2011; Ostrom and Barnholtz-Sloan, 2011; Ostrom *et al*, 2014). Survival rates vary according to several factors, including age at diagnosis, grade, and extent of tumour resection, with 5-year survival rates for glioblastoma of approximately 5% (Ostrom *et al*, 2014).

Few aetiologies have been mentioned: high doses of ionising radiation have been associated with glioma but other occupational, environmental, and lifestyle exposures have only shown inconsistent associations (Bondy *et al*, 2008; Gomes *et al*, 2011; Ostrom *et al*, 2014). Chlorinated industrial solvents have long been suspected as a cause of glioma due to their ability to cross the blood–brain barrier because of their high solubility in fats (Sato and Nakajima, 1979a, b). A history of allergy has been inversely associated with the disease (Turner *et al*, 2013). In 2008, the Brain Tumour Epidemiology Consortium called for increased efforts by the research community to study glioma and neurocarcinogens of which solvents are a subgroup (Bondy *et al*, 2008). Solvents are, and will probably remain, important agents in the workplace.

The term 'solvents' is generic and may include hundreds of specific chemical compounds. They are often subdivided into chlorinated solvents, for example, methylene chloride, perchlorethelyne, carbon tetrachloride, and so on; aliphatic solvents; and aromatic solvents. Solvent exposure occurs in a wide range of occupations, as they are used in many products, such as pesticides, plastics, glues, paints, lubricants, metal degreasers, fossil fuels, and many cleaning fluids. High solvent exposure occupations include painters, lacquerers, and floor layers; printers; upholsterers; footwear workers; occupations in graphics; and plastic product workers. However, there are many occupations in the building and construction and agriculture where low-level solvent exposure may be encountered. With regard to specific solvent exposures, results have been inconsistent, but methylene chloride has been associated with astrocytic brain cancer (Heineman *et al*, 1994). Many past occupational studies that investigated the generic exposure of 'solvents' were limited due to poor exposure assessment methodology, small numbers, and the presence of multiple chemical exposures (Benke *et al*, 2001).

The public health importance of this investigation is high because solvent exposure is one of the highest prevalent chemical exposures in the workplace following gases and dusts. Additionally, solvents are not well controlled in underdeveloped countries where exposure may be significantly higher. Data on the number of exposed workers exposed worldwide is not available but may be about 14% for males (based on controls in the current study).

The INTERPHONE study was conducted by an international group of researchers and commenced in 2000 to investigate the possible relationship between mobile phone use and risk of glioma, meningioma, acoustic neuroma, and malignant parotid gland tumours. The study design and epidemiological methods and a description of the INTERPHONE study population are described in detail elsewhere (Cardis *et al*, 2007). Seven of the original participating countries (Australia, Canada, France, Germany, Israel, New Zealand, and the United Kingdom) participated in the Occupational Exposure and Brain Cancer (INTEROCC) study in order to evaluate the effects of exposure to selected chemicals in the workplace—determined through the use of a job exposure matrix (JEM) (van Tongeren *et al*, 2013)—on the risk of brain cancer. For this component of the INTEROCC study in which we evaluate risk factors for glioma, a total of 2000 cases and 5565 population-based controls were included, making this the largest case–control study of glioma exploring occupational risk factors. Results of analyses of glioma risk in relation to selected combustion products, dusts and other chemical agents has been published previously (Lacourt *et al*, 2013). Other related manuscripts have examined associations between occupational solvent (McLean *et al*, 2014) and metal exposure (Sadetzki *et al*, 2016) and meningioma risk. In this paper, we examine results for occupational exposure to 11 specific solvents or solvent subgroups and glioma risk. Many past studies have not been able to address this wide range of solvents and their likely association with glioma, due to power limitations. INTEROCC provided an opportunity to address some of the limitations of previous studies by investigating exposure to various solvents with a large sample size of cases and controls and use of a JEM, based on intensive expert assessment input (Lavoué *et al*, 2012; van Tongeren *et al*, 2013). We also aimed to determine whether grade of tumour was associated with exposure to any solvents.

MATERIALS AND METHODS

Case and control ascertainment. The INTEROCC project has been previously described elsewhere (Lavoué *et al*, 2012; Lacourt *et al*, 2013; van Tongeren *et al*, 2013; McLean *et al*, 2014; Turner *et al*, 2014; Sadetzki *et al*, 2016). Briefly, included in the original INTERPHONE study questionnaire was an occupational history questionnaire capturing detailed data on job title, specific tasks, company name, a description of the activities of the company, and the start and end year of each job for all jobs held for >6 months. Subjects were recruited between the years 2000 and 2004 and were aged between 30 and 59 years in most study centres, with extensions in the age limit in Israel (18 + years), Germany (30–69 years), and the United Kingdom (18–69 years) to allow for greater ascertainment of cases. The sampling frame was centre-specific, and based on all residents in the study regions. Cases of first primary glioma were recruited rapidly using a standard protocol and diagnosis was confirmed based on histo-pathology, or unequivocal radiological diagnosis in 25% of cases. The ICD codes and definitions for high- and low-grade glioma have been previously published (Cardis *et al*, 2007). Controls were randomly selected based on locally developed sampling frames of the source population in each centre and were either individually or frequency matched to cases according to age (5-year groups), sex and study centre. The reference date for controls was calculated as the date of interview minus the median difference between the date of case diagnosis and interview by country. For this study, a total of 2054 glioma cases and 5601 controls were recruited into the study among the 7 countries, with participation rates of 68% for glioma cases and 50% for controls. Participation rates ranged from 56% of cases in Australia to 86% of cases in Israel and 31% of controls in Canada to 74% in France. Study participants were interviewed in person by trained interviewers using a computer-assisted personal interview questionnaire. Proxy respondents were permitted if the study subject had died or could not be interviewed. Written informed consent was provided by study participants prior to interview. Ethics approval was obtained from all appropriate national and regional research ethics boards, including the Ethical Review Board of IARC (Lyon) for INTERPHONE and the Municipal Institute for Medical Investigation Barcelona for INTEROCC.

Exposure assessment. The methods for the assessment of occupational chemical exposures in INTEROCC have been described elsewhere (van Tongeren *et al*, 2013). In brief, the Finnish job exposure matrix, FINJEM (Kauppinen *et al*, 1998), was modified following review by experts from the participating countries to construct the INTEROCC-JEM. INTEROCC-JEM has the same 11 categories of solvents as the original FINJEM that are chlorinated hydrocarbons, toluene, benzene, trichloroethylene, methylene chloride, gasoline, perchloroethylene, 1,1,1-trichloroethane, aromatic hydrocarbons, aliphatic and alicyclic hydrocarbons, and other organics. All reported jobs were coded in ISCO 68 with a cross-walk to the Finnish codes (van Tongeren *et al*, 2013).

Modifications to INTEROCC-JEM were based on expert input with knowledge of the solvent exposure in specific job codes by country. Validation studies involving efforts to standardise the coding from the centres were undertaken, and the results are reported elsewhere (Lavoué *et al*, 2012; van Tongeren *et al*, 2013). Past studies using the FINJEM have defined exposure on the basis of having a job code in which the proportion of exposed was $>P$, where P ranged from 5 to 50% for specific agents depending on the study (Benke *et al*, 2001). In INTEROCC, it was decided *a priori* to use a $P \geqslant 25\%$ with the INTEROCC-JEM. Participants with a cutoff proportion (P) of $P \geqslant 25\%$ in an occupational category for >1 year were deemed to be 'exposed'. The lifetime cumulative exposure index was defined among ever exposed as the sum of the product of the proportion of exposure (P), the level of exposure (L), and the duration in years for each job held by a subject (van Tongeren *et al*, 2013). The reference group consisted of those subjects with no solvent exposure, $P<5\%$. Subjects with $5\% \leqslant P < 25\%$ or who were exposed for <1 year were excluded from analyses here.

Statistical analysis. Statistical analysis was performed using conditional logistic regression models stratified by sex, age (using 5-year age groups), and country–region of residence (study site) and adjusted for level of educational attainment. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each solvent or solvent group according to categories of ever/never exposure, cumulative indices of exposure, and duration of exposure (years). Analyses were conducted for all subjects and for males and females separately. Analyses also examined high- and low-grade gliomas. Potential confounding by marital status, cigarette smoking status, allergy history (asthma, hay fever or eczema), and socioeconomic position (according to the Standard International Occupational Prestige Scale (Treiman, 1977) was assessed.

INTERPHONE included not only glioma cases but also cases of meningioma, acoustic neuroma and salivary gland tumours. Inclusion of glioma and meningioma controls in this analysis was designed to increase the statistical power of the study to test for associations between solvent exposure and glioma risk. The original analyses of mobile phone use in INTERPHONE used matched controls (and *post hoc* matched controls in the most recent paper—Turner *et al*, 2017—as the uptake of mobile phones increased very rapidly during the study period, and it was therefore essential that controls were matched as closely as possibly to cases as possible). For past occupational exposures, however, this is not so critical and the power advantages greatly outweigh the disadvantage. Because of this matching, however, the results from this paper and from the companion paper on meningioma risk (McLean *et al*, 2014) are not entirely independent as the same controls have been used in both.

Sensitivity analyses were performed examining different lag periods of exposure (1 year and 10 years), taking a 5-year lag as the standard (Checkoway *et al*, 1990), as well as with different probabilities ($P \geqslant 5$ and $\geqslant 50$) to define exposure status. Additional analyses examined associations in different time windows of exposure (5–14 years, 15–24 years, and 25+ years) in the past, among self-respondents only (proxies were excluded), excluding participants >69 years of age, excluding subjects with personal history of neurofibromatosis and/or tuberous sclerosis, or excluding participants with a poor quality interview as they were deemed by the interviewer to be reticent and uninterested. Potential effect modification by sex, age group ($\leqslant 39$, 40–49, 50–59, $\geqslant 60$), education (primary–secondary, intermediate college, or tertiary), age at first exposure (<18, 18+ years), smoking status (ever, never), and country was examined according to the likelihood ratio test. Analyses were conducted using StataCorp, 2011.

RESULTS

The study consisted of 2000 eligible cases of glioma and 5565 controls. A small number of participants ($n=54$ cases and 36 controls) were excluded owing to erroneous job history data. A description of the characteristics of the glioma cases and controls is provided in Table 1. The majority of glioma cases were men (61.3%), whereas controls were slightly more women (55.4%). The mean (s.d.) age of cases was 51.2 (12.5) years and controls 52.0 (11.5) years. Most participants had completed either a primary or secondary level of education and the majority was married. The United Kingdom, Israel, and Germany contributed the greatest number of glioma cases. Proxy respondents were used for 17.6% of cases and 0.4% of controls.

In general, the prevalence of solvent exposure was low, with a total of 9.6 of cases and 7.6% of controls ever exposed to 'any' solvent (Table 2). For specific solvents/solvent groups, 8.4 of

Table 1. Selected characteristics of glioma cases and controls, INTEROCC study, 2000–2004

	%		
	Cases ($n=2000$)	Controls ($n=5565$)	Total ($n=7565$)
Sex			
Men	61.3	44.6	49.0
Women	38.7	55.4	51.0
Age categories (years)[a]			
<25	1.8	0.6	0.9
25–29	1.8	1.3	1.4
30–39	16.5	14.3	14.8
40–49	23.2	25.0	24.6
50–59	33.9	36.4	35.7
60–69	16.8	17.2	17.2
70–74	2.9	2.5	2.6
75+	3.1	2.8	2.9
Education			
Primary–secondary	52.2	53.9	53.4
Intermediate college	19.5	18.8	19.0
Tertiary	27.6	27.2	27.3
Marital status			
Single	10.2	8.9	9.2
Married	76.8	76.4	76.5
Divorced	7.5	9.2	8.8
Widowed	4.9	5.4	5.3
Smoking status			
Current	27.6	27.0	27.1
Former	20.9	23.7	23.0
Never	51.5	49.3	49.9
Country			
Australia	13.9	12.0	12.5
Canada	8.5	11.7	10.9
France	4.7	8.5	7.5
Germany	18.3	27.6	25.1
Israel	21.6	17.7	18.8
New Zealand	3.8	2.9	3.1
United Kingdom	29.3	19.6	22.2

Note: Some column totals do not add up to total due to missing values.
[a]Age at diagnosis/reference.

Table 2. Prevalence of solvent exposure, mean cumulative exposure, and duration of exposure in glioma cases and controls and by gender, INTEROCC study, 2000–2004

Glioma cases

	All				Men				Women			
Agent	Total *n*	Ever %	Mean cumulative exposure (p.p.m.)	Mean number of years exposed	Total *n*	Ever %	Mean cumulative exposure (p.p.m.)	Mean number of years exposed	Total *n*	Ever %	Mean cumulative exposure (p.p.m.)	Mean number of years exposed
Any solvent	1840	9.6	—	—	1101	14.9	—	—	739	1.8	—	—
Aliphatic and alicyclic hydrocarbons	1721	3.4	7994	12.4	989	5.3	8677	13.5	732	0.8	2081	3.5
Aromatic hydrocarbons	1815	8.4	11 333	11.7	1081	13.3	11 747	12.2	734	1.1	3893	3.8
Benzene	1679	1.0	430	4.2	951	1.5	470	4.1	728	0.3	149	4.3
Chlorinated hydrocarbons	1666	0.2	2828	6.4	940	0.3	2828	6.4	726	0	—	—
Gasoline	1667	0.2	169	2.8	940	0.3	146	2.7	727	0.1	240	3.0
Methylene chloride	1663	0	—	—	937	0	—	—	726	0	—	—
Other organics	1706	2.5	3684	12.7	976	4.0	3893	13.6	730	0.5	1649	4.0
Perchloroethylene	1663	0	—	—	937	0	—	—	726	0	—	—
1,1,1-Trichloroethane	1664	0.1	1000	8.0	938	0.1	1000	8.0	726	0	—	—
Toluene	1718	3.2	11 535	10.4	986	5.0	12 556	11.2	732	0.8	3199	3.7
Trichloroethylene	1664	0.1	2100	7.0	938	0.1	2100	7.0	726	0	—	—

Controls

	All				Men				Women			
Agent	Total *n*	Ever %	Mean cumulative exposure (p.p.m.)	Mean number of years exposed	Total *n*	Ever %	Mean cumulative exposure (p.p.m.)	Mean number of years exposed	Total *n*	Ever %	Mean cumulative exposure (p.p.m.)	Mean number of years exposed
Any solvent	5119	7.6	—	—	2213	14.7	—	—	2906	2.2	—	—
Aliphatic and alicyclic hydrocarbons	4869	2.9	7262	10.9	1990	5.2	9078	13.4	2879	1.3	2065	3.7
Aromatic hydrocarbons	5081	6.9	10 585	11	2193	14.0	11 430	12.0	2888	1.6	4840	4.4
Benzene	4796	1.4	1054	4.7	1929	2.2	1428	5.7	2867	0.8	399	3.0
Chlorinated hydrocarbons	4743	0.3	4614	7.6	1895	0.4	6276	9.8	2848	0.2	1954	4.0
Gasoline	4755	0.5	169	4.2	1900	0.7	247	5.7	2855	0.4	83	2.7
Methylene chloride	4730	0	—	—	1887	0	—	—	2843	0	—	—
Other organics	4819	1.8	7167	13.4	1964	3.9	7799	14.9	2855	0.4	3115	4.2
Perchloroethylene	4730	0	—	—	1887	0	—	—	2843	0	—	—
1,1,1-Trichloroethane	4733	0.1	458	3.7	1889	0.1	344	2.8	2844	0	688	5.5
Toluene	4858	2.6	10 742	10.6	1990	5.2	12 744	12.4	2868	0.9	2493	3.5
Trichloroethylene	4741	0.2	3521	6.1	1894	0.4	4704	7.8	2847	0.1	1450	3.3

cases and 6.9% of controls were ever exposed to aromatic hydrocarbons, with the prevalence of exposure to the remaining solvents ranging from 0 to 3%. Cases overall tended to have greater cumulative exposure levels to aliphatic and alicyclic hydrocarbons, aromatic hydrocarbons, 1,1,1-trichloroethane, and toluene than controls. However, controls tended to have greater cumulative exposure levels to benzene, chlorinated hydrocarbons, other organics, and trichloroethylene than cases. Solvent exposure was also generally greater among male compared with female participants.

Joint solvent exposure was quite frequent (Table 3). Among ever exposed to aliphatic and alicyclic hydrocarbons, two of the more common exposures, 80.2% were also exposed to aromatic hydrocarbons, 64.5% to other organics, and 76.1% to toluene. Among those ever exposed to other organics, 96.2% were also exposed to aliphatic and alicyclic hydrocarbons, 97.7% to aromatic hydrocarbons, and 91.7% to toluene. Among those ever exposed to toluene, 82% were also exposed to aliphatic and alicyclic hydrocarbons, 100% to aromatic hydrocarbons, and 66.1% to other organics. However, among those ever exposed to more prevalent aromatic hydrocarbons, $<40\%$ were also ever exposed to another solvent.

Table 4 provides ORs and 95% CIs for associations between ever/never exposure to any solvent or to specific solvents/solvent groups and glioma risk. There was no association between ever exposure to any solvent and glioma risk overall (OR = 0.91, 95% CI 0.74–1.11). ORs for specific solvents/solvent groups were also <1 ranging from 0.23 for trichloroethylene to 0.97 for other organics, and for benzene, there was a statistically significantly reduced association (OR = 0.55, 95% CI 0.31–0.97). Results were also similar for men and women separately. There was no significant trend for any specific solvent/solvent group according to categories of quartiles of cumulative exposure (Table 5) or years of exposure overall or according to different time windows of exposure 5–14, 15–24, or 25+ years in the past (not shown).

Results for ever/never exposure were similar with adjustment for other potential confounding variables (above) as well as in sensitivity analysis, excluding proxy respondents (5.02%), participants >69 years of age (5.59%), participants with a personal history of neurofibromatosis and/or tuberous sclerosis (0.25%), or participants with a poor quality interview (31.22%). Results were also similar using different lag periods or probabilities of exposure (not shown).

There was also no association between ever exposure to any solvent or to specific solvents/solvent groups for either high- or low-grade glioma (Table 6). There was no evidence for effect modification of results overall by sex, age group, education, age at first exposure, cigarette smoking status, or country (*P* values for interaction >0.05).

DISCUSSION

We have investigated glioma and occupational solvent exposure within a collaborative project, including case–control studies from seven countries, the INTEROCC project. Our results did not suggest an association between glioma and occupational exposure to any solvent or specific solvents/subgroups. Analysis by grade of glioma also did not suggest any association. The results were consistent across all solvents/subgroups and with both ever/never and cumulative metrics of exposure. Our results therefore do not suggest that occupational exposure to solvents may increase the risk of glioma.

Results of previous studies of occupational solvent exposure and brain tumour risk are mixed and limited. Early large-scale US death certificate-based studies using JEMs reported some positive associations with mortality from cancer of the central nervous system among women, though there was no clear trend according to probability or intensity of exposure (Cocco *et al*, 1998, 1999). Other studies based on death certificates and interviews with next-of-kin participants for complete occupational history, including ~300 case and control participants, reported some evidence for positive associations with astrocytic brain tumours among men (Thomas *et al*, 1987; Heinemann *et al*, 1994). However, in one study there was no increase in risk among men in the highest exposure category, though there were few participants (Thomas *et al*, 1987). In the other study, there were positive associations, particularly with methylene chloride exposure, according to increasing probability and intensity of exposure but not level of cumulative exposure (Heinemann *et al*, 1994).

In one early case–control study of self-reported exposure including 192 glioma cases and 192 controls, there was a positive OR among men, but not among women, with a history of exposure to solvents, degreasers, or cleaning agents (OR=2.6, 95% CI 1.3–5.2) (Rodvall *et al*, 1996). However, in a pooled analysis of data from six countries including the previous study, there was no association between self-reported exposure to solvents and cleaning agents and glioma risk among men (OR=0.85, 95% CI 0.64–1.12) or women (OR=0.92, 95% CI 0.59–1.43) (Schlehofer *et al*, 2005). In a large-scale Swedish census-based record linkage study, though there was no association between occupational solvent exposure assessed using a JEM and glioma risk among those with either possible or probable exposure overall (Navas-Acien *et al*, 2002a), there was some evidence for a positive association among those with a concurrent moderate-to-high ELF exposure (Navas-Acien *et al*, 2002b). Interactions between occupational chemical exposure and ELF in INTEROCC are examined elsewhere (Turner *et al*, 2017). There was no evidence for interactions between occupational ELF and chemical exposures for glioma risk observed (Turner *et al*, 2017).

More recently, results from the Upper Midwest Health Study including 798 glioma cases and 1175 population controls reported no positive association with any exposure or levels of cumulative exposure to six chlorinated solvents with exposure estimated based on occupation and industry information collected during participant interviews combined with bibliographic databases of published exposure levels (Ruder *et al*, 2013). There was also no association between occupational exposure to six chlorinated solvents and glioma risk in a hospital-

Table 3. Joint exposure to solvents in INTEROCC, 2000–2004[a,b]

	Aliphatic and alicyclic hydrocarbons	Aromatic hydrocarbons	Benzene	Chlorinated hydrocarbons	Gasoline	Methylene chloride	Other organics	Perchloroethylene	1,1,1-Trichloroethane	Toluene	Trichloroethylene
n	197	503	82	16	29	0	132	0	4	183	12
Aliphatic and alicyclic hydrocarbons	—	31.4	45.1	37.5	100	0	96.2	0	0	82.0	50.0
Aromatic hydrocarbons	80.2	—	98.8	81.3	100	0	97.7	0	50.0	100	100
Benzene	18.8	16.1	—	75.0	100	0	7.6	0	25.0	28.4	100
Chlorinated hydrocarbons	3.0	2.6	14.6	—	0	0	4.5	0	100	3.3	100
Gasoline	14.7	5.8	35.4	0	—	0	0	0	0	15.8	0
Methylene chloride	0	0	0	0	0	—	0	0	0	0	0
Other organics	64.5	25.6	12.2	37.5	0	0	—	0	0	66.1	50.0
Perchloroethylene	0	0	0	0	0	0	0	—	0	0	0
1,1,1-Trichloroethane	0	0.4	1.2	25.0	0	0	0	0	—	0	8.3
Toluene	76.1	36.4	63.4	37.5	100	0	91.7	0	0	—	50.0
Trichloroethylene	3.0	2.4	14.6	75.0	0	0	4.5	0	25.0	3.3	—

[a]Values of cells in each column represent the percentage of participants with exposure to solvent A co-exposed to solvent B.
[b]For cases and controls combined.

Table 4. ORs (95% CIs)[a] for risk of glioma associated with ever/never occupational solvent exposure with at least 1 year exposure and lagged for 5 years, $P \geqslant 25\%$

	All					Men					Women				
Agent	**Cases**	**Controls**	**OR**	**95% CI**		**Cases**	**Controls**	**OR**	**95% CI**		**Cases**	**Controls**	**OR**	**95% CI**	
None (Ref.)	1663	4614	1.00	—	—	937	1853	1.00	—	—	726	2761	1.00	—	—
Any solvent	177	381	0.91	0.74	1.11	164	318	0.95	0.77	1.18	13	63	0.66	0.36	1.23
Aliphatic and alicyclic hydrocarbons	58	136	0.87	0.63	1.21	52	100	0.97	0.68	1.38	6	36	0.54	0.22	1.30
Aromatic hydrocarbons	152	344	0.86	0.69	1.06	144	299	0.90	0.72	1.12	8	45	0.56	0.26	1.20
Benzene	16	65	0.55	0.31	0.97	14	41	0.66	0.35	1.24	2	24	0.27	0.06	1.19
Chlorinated hydrocarbons	3	13	0.57	0.16	2.07	3	8	0.78	0.20	3.03	0	5	—	—	—
Gasoline	4	25	0.36	0.12	1.05	3	13	0.44	0.12	1.62	1	12	0.24	0.03	1.84
Other organics	43	87	0.97	0.66	1.43	39	75	0.98	0.65	1.47	4	12	1.05	0.32	3.39
Toluene	55	125	0.90	0.64	1.26	49	100	0.94	0.65	1.35	6	25	0.74	0.30	1.84

Abbreviations: CI = confidence interval; OR = odds ratio.
[a]ORs computed using conditional logistic regression stratified by age, sex, and country–region and adjusted for education. Some participants are excluded from analysis as some strata are dropped owing to the absence of within-group variance.

based case–control study in three US hospitals (*n* glioma cases = 489, *n* meningioma cases = 179, *n* controls = 799) based on self-reported job-specific module data and industrial hygienist-assessed exposure based on literature review. However, the authors found a positive, though imprecise, OR with higher weekly average exposure to carbon tetrachloride among exposed subjects only (OR = 7.1, 95% CI 1.1–45.2) (Neta *et al*, 2012). This study had excellent exposure assessment but was limited by its relatively small numbers.

The main strength of the current study is the large sample size for a population-based case–control study. With 2000 cases and over 5000 controls, INTEROCC is the largest glioma study of its type with all cases either confirmed histologically or using unequivocal image diagnosis capturing complete occupation history information on participants. We also used the INTEROCC-JEM, developed and refined from the well-known FINJEM, with additional exposure estimates and expert input (van Tongeren *et al*, 2013) and assigned estimates of exposure to 11 specific solvents or groups of solvents, contributing to the sparse literature on specific solvent types with detailed data on duration and cumulative levels of exposure in multiple time windows.

We found a relatively low prevalence of exposure to the solvents investigated, ranging from 7.6 to 9.6% of subjects with exposure to 'any' solvent, as well as a low percentage of participants with high levels of exposure. The recent case–control study of Neta *et al* (2012) reported exposure prevalence to chlorinated solvents to be ~15%. This could suggest that the INTEROCC-JEM is more specific with exposures defined at a cutoff $P \geqslant 25\%$, although it could also be due to differences in the substances covered in the study by Neta *et al* (2012) and our current study. Three of the chlorinated solvents (trichloroethylene; 1,1,1-trichloroethane; and perchloroethylene) examined in Neta *et al* (2012) were also examined in INTEROCC, while the other three (dichloromethane, chloroform, and carbon tetrachloride) were not individually covered in the INTEROCC study but were covered by the category of chlorinated hydrocarbons. The proportion of ever solvent exposure in INTEROCC increased to 15.0–16.9% of controls and cases, respectively, with a cutoff $P \geqslant 5\%$. However, the use of this cutoff point resulted in very similar exposure–response associations with glioma to those with $P \geqslant 25\%$. Exposure assessment in Neta *et al* (2012) was conducted using job specific modules, an exposure assessment methodology considered superior to the JEM (Stewart *et al*, 1996). It has been previously observed that prevalence of many hazards are higher in studies that use this expert assessment method compared with JEMs (Benke *et al*, 2001; Lavoué *et al*, 2012). For example, in the case of farmers, solvent exposure will be attributed if respondents reported activities such as painting or degreasing as there may be exposure to aromatic hydrocarbons, aliphatic and alicyclic hydrocarbons, chlorinated hydrocarbons, trichloroethylene, or other organics. However, the occupation of farmer is not considered as having solvent exposure in the INTEROCC-JEM, due to the low prevalence of exposure among farmers. JEMs cannot reproduce this degree of sensitivity to such variability within occupation codes. JEMs also suffer from varying degrees of non-differential misclassification, and past validation studies indicate that this can result in biased ORs both towards and away from the null (Benke *et al*, 2001; Burstyn *et al*, 2012). Further, JEMs are typically considered geographically biased (Benke *et al*, 2001). As the INTEROCC-JEM has been applied to data from seven countries in this study, it is likely that some degree of misclassification has been introduced owing to geography. However, there were extensive efforts made to limit this bias in the current study, as described previously (Lavoué *et al*, 2012; van Tongeren *et al*, 2013), and there was no evidence for significant effect modification by country. In other analyses in INTEROCC, there were positive associations observed between occupational iron and oil mist exposure and meningioma risk where there was a similar low prevalence of exposure (Sadetzki *et al*, 2016).

Other potential limitations of this study include low participation rates, particularly among controls, and potential related participation biases, though cases and controls were similar in terms of key demographic factors, with the exception of gender distribution, including age, educational attainment, and socio-economic position, and such factors were adjusted for in analysis. Results excluding proxy respondents or participants with a poorer quality interview were, however, similar and ORs according to tumour grade tended to be lower among participants with a low-grade rather than a high-grade glioma, suggesting that there may be some other study factor resulting in the consistently reduced ORs here. The results' tables had small numbers in some strata and this would cause instability in the ORs particularly when numbers of cases and controls are <5 in a cell. Furthermore, it is difficult to interpret findings for a specific exposure in the context of mixed exposures.

In summary, the results of the present study and other recent case–control studies provide no clear indication that occupational

Table 5. ORs (95% CIs)[a] for risk of glioma associated with quartiles of lifetime cumulative occupational solvent exposure with at least 1 year exposure and lagged for 5 years, $P \geqslant 25\%$

	All						Men						Women					
Agent[b]	Cases	Controls	OR	95% CI		P-trend	Cases	Controls	OR	95% CI		P-trend	Cases	Controls	OR	95% CI		P-trend
Aliphatic and alicyclic hydrocarbons																		
Never exposed	1663	4614	1.00	—	—		937	1853	1.00	—	—		726	2761	1.00	—	—	
0–729.2	6	35	0.36	0.15	0.88		5	18	0.52	0.19	1.45		1	17	0.15	0.02	1.15	
729.2–4067	22	34	1.46	0.83	2.57		18	22	1.56	0.82	2.98		4	12	1.23	0.38	4.01	
4067–10451.3	14	34	0.85	0.45	1.62		13	28	0.87	0.44	1.72		1	6	0.75	0.09	6.42	
10451.3 +	16	33	0.86	0.46	1.61	0.63	16	35	0.89	0.48	1.66	0.85	0	1	0.00	0.00	0.00	0.41
Aromatic hydrocarbons																		
Never exposed	1663	4614	1.00	—	—		937	1853	1.00	—	—		726	2761	1.00	—	—	
0–1815.4	32	87	0.71	0.47	1.09		28	65	0.77	0.48	1.23		4	22	0.49	0.17	1.47	
1815.4–5231.1	37	86	0.80	0.53	1.20		36	75	0.84	0.55	1.28		1	11	0.38	0.05	3.06	
5231.1–14300	44	86	1.03	0.70	1.51		41	80	1.01	0.68	1.50		3	6	1.65	0.40	6.83	
14300 +	39	85	0.90	0.60	1.34	0.39	39	79	0.96	0.64	1.44	0.60	0	6	0.00	0.00	0.00	0.22
Benzene																		
Never exposed	1663	4614	1.00	—	—	0.09	937	1853	1.00	—	—	0.24	726	2761	1.00	—	—	0.18
0–25.9	0	18	0.00	0.00	0.00		0	8	0.00	0.00	0.00		0	10	0.00	0.00	0.00	
25.9–120	6	15	0.83	0.31	2.24		5	10	0.88	0.29	2.67		1	5	0.72	0.08	6.76	
120–980	9	16	1.32	0.57	3.06		8	10	1.76	0.67	4.58		1	6	0.50	0.06	4.24	
980 +	1	16	0.13	0.02	0.97		1	13	0.14	0.02	1.08		0	3	0.00	0.00	—	
Other organics																		
Never exposed	1663	4614	1.00	—	—		937	1853	1.00	—	—		726	2761	1.00	—	—	
0–1000	8	23	0.67	0.29	1.52		6	17	0.63	0.24	1.63		2	6	0.83	0.16	4.30	
1000–2921.3	16	21	1.29	0.65	2.54		15	19	1.27	0.63	2.57		1	2	1.91	0.14	27.04	
2921.3–8707.5	16	21	1.80	0.92	3.53		15	18	1.86	0.92	3.77		1	3	1.47	0.15	14.49	
8707.5 +	3	22	0.28	0.08	0.93	0.75	3	21	0.29	0.08	0.97	0.77	0	1	0.00	0.00	0.00	0.90
Toluene																		
Never exposed	1663	4614	1.00	—	—		937	1853	1.00	—	—		726	2761	1.00	—	—	
0–964.6	8	32	0.51	0.23	1.12		6	17	0.62	0.23	1.62		2	15	0.34	0.08	1.52	
964.6–4100	15	30	1.11	0.58	2.12		14	23	1.26	0.63	2.51		1	7	0.47	0.06	4.04	
4100–14275	21	32	1.33	0.75	2.38		18	30	1.14	0.62	2.10		3	2	6.67	1.10	40.61	
14275 +	11	31	0.68	0.33	1.37	0.72	11	30	0.69	0.34	1.42	0.36	0	1	0.00	1.00	0.00	0.74

Abbreviations: CI = confidence interval; OR = odds ratio.
[a]ORs computed using conditional logistic regression stratified by age, sex, and country–region and adjusted for education for agents with ⩾10 exposed participants overall. Some participants are excluded from analysis as some strata are dropped owing to the absence of within-group variance.
[b]Metric is prevalence × level (in p.p.m.) × duration (years).

solvent exposure is associated with an increased glioma risk. Future cohort studies may provide additional information to the current findings.

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Table 6. ORs (95% CIs)[a] for risk of glioma by grade associated with ever/never occupational solvent exposure with at least 1 year exposure and lagged for 5 years, $P \geqslant 25\%$

	High grade					Low grade				
Agent	**Cases**	**Controls**	**OR**	**95% CI**		**Cases**	**Controls**	**OR**	**95% CI**	
None (Ref.)	1140	4473	1.00	—	—	502	3872	1.00	—	—
Any solvent	127	376	0.94	0.75	1.18	50	321	0.85	0.61	1.20
Aliphatic and alicyclic hydrocarbons	44	132	0.97	0.67	1.39	14	114	0.68	0.38	1.22
Aromatic hydrocarbons	115	340	0.93	0.74	1.18	37	289	0.68	0.47	1.00
Benzene	15	65	0.69	0.39	1.24	1	54	0.14	0.02	1.04
Chlorinated hydrocarbons	2	13	0.53	0.12	2.40	1	9	0.70	0.08	6.51
Other organics	33	84	1.08	0.70	1.65	10	73	0.74	0.37	1.48
Toluene	43	123	0.99	0.68	1.43	12	107	0.66	0.35	1.25

Abbreviations: CI = confidence interval; OR = odds ratio.
[a]ORs computed using conditional logistic regression stratified by age, sex, and country–region and adjusted for education. Some participants are excluded from analysis as some strata are dropped owing to the absence of within-group variance.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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