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Childhood brain tumours: associations with parental occupational exposure to solvents

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Background: Parental occupational exposures have been associated with childhood brain tumours (CBT), but results are inconsistent. Few studies have studied CBT risk and parental solvent exposure, suggesting a possible association. We examined the association between CBT and parental occupational exposure to solvents in a case–control study.

Methods: Parents of 306 cases and 950 controls completed detailed occupational histories. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated for both maternal and paternal exposure to benzene, other aromatics, aliphatics and chlorinated solvents in key time periods relative to the birth of their child. Adjustments were made for matching variables (child's age, sex and state of residence), best parental education and occupational exposure to diesel exhaust.

Results: An increased risk of CBT was observed with maternal occupational exposures to chlorinated solvents (OR = 8.59, 95% CI 0.94–78.9) any time before birth. Paternal exposure to solvents in the year before conception was associated with an increased CBT risk: OR = 1.55 (95% CI 0.99–2.43). This increased risk appeared to be mainly attributable to exposure to aromatic solvents: OR = 2.72 (95% CI 0.94–7.86) for benzene and OR = 1.76 (95% CI 1.10–2.82) for other aromatics.

Conclusions: Our results indicate that parental occupational exposures to solvents may be related to an increased risk of CBT.

Parental occupational exposures to various chemical agents have been associated with childhood brain tumours (CBTs) in several studies, but results have been inconsistent (Baldwin and Preston-Martin, 2004). Positive associations were reported for a variety of industries and occupations, such as motor vehicle-related occupations, the chemical and petroleum industries, and jobs with frequent exposure to paints (Cordier *et al*, 1997; Colt and Blair, 1998). The suggested causative agents were polycyclic aromatic hydrocarbons and unspecified solvents (Cordier *et al*, 1997; Colt and Blair, 1998). Relatedly, a recent meta-analysis showed a positive correlation between parental occupational exposure to pesticides and CBT (Vinson *et al*, 2011).

Few studies have looked in detail at occupational exposure to solvents. Paternal exposure to chemical solvents (not further specified) was found to be associated with an almost threefold increase of CBT in the 1970s (Peters *et al*, 1981). Cordier *et al* (1997) reported an increased risk for maternal occupational exposure to solvents at high levels, with an odds ratio (OR) of 2.4 (95% confidence interval (CI) 1.2–4.9). High exposure was defined by the authors on page 691 of their paper as being classified in either exposure category: (1) 'job may entail exposure to levels definitely higher than for the general population, but available information does not permit discrimination between exposed and not exposed' if the probability of exposure was more than 2/3; (2) 'job entails exposure to the specific agent at levels clearly higher than the general population'; or (3) 'job entails exposure to the specific agent, and exposure is known to be particular high' (Cordier *et al*, 1997).

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Solvents comprise a wide range of chemicals: benzene, other aromatics (such as toluene or xylene), aliphatics (such as hexane or ethylene) and chlorinated solvents (such as trichloroethylene or perchloroethylene). Exposures occur, among others, in the chemical, printing and petroleum industries, or in jobs that involve degreasing, painting or dry cleaning. In all previous studies on CBT, solvents were assessed as one group, whereas the different chemical types may have different effects.

We conducted an Australian, nation-wide case–control study of CBT (Aus-CBT) collecting parents' full occupational histories (Greenop *et al*, 2013; Peters *et al*, 2013). In previous analyses we have shown that parental occupational exposure to diesel exhaust may increase the risk of CBT; maternal exposure to diesel exhaust any time before birth showed an OR of 1.77 (95% CI 0.96–3.26), whereas paternal exposure around the time of the child's conception showed an OR of 1.39 (95% CI 0.97–1.99) (Peters *et al*, 2013). We also observed increased CBT risks following parental exposure to pest control treatments in the year before the pregnancy (OR 1.54, 95% CI 1.07–2.22) and during the pregnancy (OR 1.52, 95% CI 0.99–2.34) (Greenop *et al*, 2013).

In this paper we examined the association between parental occupational exposure to specific solvent groups and risk of CBT.

MATERIALS AND METHODS

Study population. The Aus-CBT study population has been described in detail (Milne *et al*, 2012). In brief, incident cases (aged 0–14 years, diagnosed between 2005 and 2010) were identified through all 10 paediatric oncology centres in Australia. Approximately three controls, frequency matched by age, sex and state of residence, were recruited for each brain tumour case by random-digit dialling. Controls matched to CBT cases diagnosed in 2005 and 2006 were originally recruited as controls for the Australian childhood acute lymphoblastic leukaemia (Aus-ALL) study (Milne *et al*, 2009). Written informed consent was obtained from all parents and ethics approval was granted by all participating hospitals.

Data collection. Information about residence, lifestyle factors, medical history and occupation was collected from all parents by a mailed questionnaire. For each job held for more than 6 months, subjects were asked the year started and finished, job title, employer, main tasks and hours worked per week. Job-specific modules with more detailed questions about the tasks undertaken were selected for jobs involving potential exposure to agents of interest. In total, 46 different job modules were available. The selected modules were subsequently asked in computer-assisted telephone interviews. Parents were only included in the current analyses when a job history was available, that is, parents who never had a job before the birth of their child or who did not provide a job history were excluded from the analyses of occupational exposures.

Exposure assessment. We assessed parental occupational exposure to solvents qualitatively (i.e. exposed or non-exposed) based on the job characteristics obtained in the telephone interviews. Based on the questions in the job-specific modules, one of the authors (SP) had written rules to assign exposures (yes/no) to solvents. The preliminary rules were discussed with another author (DG) and modified where necessary to finalise the exposure rules. We assessed the following subtypes of solvents: benzene, other aromatics, aliphatics and chlorinated solvents. For the different exposures, different numbers of questions were selected: benzene was based on 16 questions from 14 job modules; other aromatic solvents based on 31 questions from 16 modules; aliphatic solvents based on 30 questions from 16 modules; and chlorinated solvents based on 20 questions from 11 modules (Peters *et al*, 2014). The *a priori* exposure rules were then applied to the information collected in the telephone interviews with the parents. Exposure was assigned blinded to the case–control status.

Exposure variables were created for specific time periods relative to the birth year of the child. These key time periods were exposure at any time before the child's birth year; exposure in the year 2 years before the birth year (capturing 'the year before conception' for fathers only); exposure in the year before the child's birth year (capturing the time during pregnancy for mothers); and exposure in the year after the child's birth year (representing the time of breast feeding – mothers only).

Statistical analyses. ORs and 95% CIs were estimated for maternal and paternal occupational exposures to solvents associated with risk of CBT in their offspring, using unconditional logistic regression models. All models were adjusted for the frequency-matching variables. Models were additionally adjusted for best parental education (as a measure of socio-economic status (SES)) and occupational exposure to diesel exhaust. Other potential confounders that were considered, based on their suggested association with CBTs and potential association with occupational exposure to solvents, were any maternal alcohol use during pregnancy, any maternal smoking during pregnancy, maternal age at child's birth and paternal alcohol use in the year prior to pregnancy. The addition of these variables changed the ORs by $<5\%$, so they were not included in the final models. We have also included occupational exposures to benzene, other aromatics, aliphatics, chlorinated solvents and diesel exhaust in one model (OR2). Analyses were conducted in SAS v.9.3 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Parents of 374 cases consented to participate (65.8% of those invited by their physician). More details of case selection have been published (Peters *et al*, 2013). Full occupational histories were provided by 293 (78.3%) consenting case mothers and 242 (64.7%) consenting case fathers. In all 3624 families of eligible control children were identified, of whom 2255 (62.2%) agreed to participate. To reach our frequency-matching quotas, 1467 of these families were recruited to the study. Full occupational information was provided by 935 control mothers (63.7% of recruited) and 795 fathers (54.2%). Overall, occupational information of at least one of the parents was available for 306 cases and 950 controls. These families were included in the analyses (Table 1).

Maternal exposure to all solvents combined any time before birth of their child suggested an increased risk of CBT, showing an OR of 1.16, but with a wide CI (Table 2). When analyses were specified to type of solvent, the increased risk was most pronounced with maternal occupational exposure to chlorinated solvents (OR 8.79, 95% CI 0.96–80.7) at any time before birth. Overall, few women were exposed to solvents in the year before birth (Table 2) or in the year after birth (data not shown).

Paternal occupational exposure to all solvents combined any time before the child's birth appeared to be associated with CBT risk: OR 1.27 (95% CI 0.90–1.79, Table 3). The OR for paternal exposure in the year before conception was 1.55 (95% CI 0.99–2.43). Risk of CBT seemed to be increased with paternal occupational exposure in the year before conception to benzene (OR 2.66, 95% CI 0.92–7.69), other aromatics (OR 1.75, 95% CI 1.10–2.79) and aliphatics (OR 1.42, 95% CI 0.90–2.24) (Table 3). The OR for exposure to chlorinated solvents was also elevated (2.33), but, being based on very small numbers exposed, the CI was wide.

Exposures to other aromatic solvents and aliphatic solvents were strongly correlated among men ($R_{\text{Pearson}} = 0.90$). When both exposures in the year before conception were included in the

Table 1. Characteristics of Australian childhood brain tumour case–control study (Aus-CBT) participants

	Cases ($n=306$)	Controls ($n=950$)
Sex		
Boy	183 (59.8%)	500 (52.6%)
Girl	123 (40.2%)	450 (47.4%)
Age at case diagnosis or control recruitment (mean years)	7.0	6.2
Year of birth (median)	2001	2001
Case histology		
Low-grade glioma	146 (47.7%)	—
High-grade glioma	27 (8.8%)	—
Embryonal tumour	72 (23.5%)	—
Germ cell tumour	20 (6.5%)	—
Ependymoma	22 (7.2%)	—
Other/unclassified	19 (6.2%)	—
Control type		
Aus-CBT	—	532
Aus-ALL	—	418
State of residence		
NSW/ACT	103 (33.7%)	286 (30.1%)
VIC/TAS	86 (28.1%)	251 (26.4%)
SA/NT	19 (6.2%)	78 (8.2%)
WA	42 (13.7%)	114 (12.0%)
QLD	56 (18.3%)	221 (23.3%)
Parents included in the study		
Mothers	293	935
Fathers	242	795
Best parental education		
Did not complete secondary school	43 (14.1%)	92 (9.7%)
Completed secondary school and/or trade qualification	101 (33.0%)	303 (31.9%)
University/college	162 (52.9%)	555 (58.4%)

Abbreviations: ACT = Australian Capital Territory; Aus-ALL = Australian childhood acute lymphoblastic leukaemia; Aus-CBT = Australian, nation-wide case–control study of CBT; NSW = New South Wales; NT = Northern Territory; SA = South Australia; TAS = Tasmania; VIC = Victoria; WA = Western Australia.

same model and adjusted for diesel exhaust exposure, only exposure to other aromatic solvents (OR 4.24, 95% CI 1.10–16.4) was associated with an increased risk of CBT (the OR for aliphatic solvents was 0.39, 95% CI 0.10–1.49) (data not shown). When all exposures were modelled together, the association between CBT risk and paternal exposure to other aromatics appeared to be strongest (OR2 4.47, 95% CI 1.12–17.8; Table 3).

Excluding the Aus-ALL controls from the analyses revealed similar risk estimates (data not shown). When both parents had occupational exposure to solvents any time before the child's birth, the OR for CBT was 2.04 (95% CI 0.90–4.64, based on 25 exposed controls and 13 exposed cases), compared with the non-exposed case (data not shown).

DISCUSSION

Our results suggest that parental occupational exposure to solvents is associated with an increased risk of CBT. For paternal exposure, this seemed mainly driven by exposure to aromatic solvents in the year before conception. For mothers, a positive association, although based on very small numbers exposed, was observed between CBT risk and exposure to chlorinated solvents any time before the child's birth.

Our overall findings are consistent with previous reports on the association of CBT with parental exposure to solvents. We observed an OR of 1.16 (95% CI 0.71–1.90) for combined solvent exposure any time before birth for mothers. This risk estimate is lower than the OR of 2.4 (95% CI 1.2–4.9) reported by Cordier *et al* (1997) for occupational exposure in the 5-year period before the child's birth. This OR of 2.4 reflected the risk for the highest exposure category. For any exposure, the OR for mothers in their study was 1.3 (95% CI 0.9–2.0) (Cordier *et al*, 1997). However, we additionally adjusted for occupational exposure to diesel exhaust, whereas without this adjustment the OR for maternal exposure would have been 1.32 (95% CI 0.85–2.06; data not shown). For paternal exposure to combined solvents Cordier *et al* did not observe an increased risk, while we found an OR of 1.27 (95% CI 0.90–1.79) any time before birth and an OR of 1.55 (95% CI 0.99–2.43) for exposure in the year before conception. Such an increased risk of CBT associated with paternal exposure to solvents was also found in an earlier study (Peters *et al*, 1981). None of the earlier studies considered the risks by specific type of solvents.

In the model where all solvents and diesel exhaust were mutually adjusted (OR2), the evidence was strongest for an association of CBT with exposure of fathers to aromatic solvents. The association with occupational exposure to diesel exhaust reported previously (Peters *et al*, 2013) attenuated when modelled together with the specific solvent exposures (OR2). When testing for interactions between exposure to diesel exhaust and solvents, we observed a significant interaction ($P=0.049$) for paternal exposure in the year before conception. Stratified analyses of the association between paternal occupational exposure to solvents in the year before conception and the risk of CBT revealed an OR of 1.03 (95% CI 0.54–1.99) among fathers not occupationally exposed to diesel exhaust in that year and an OR of 2.48 (95% CI 1.23–4.98) among fathers who were occupationally exposed to diesel exhaust in the same period (data not shown). No interactions were observed for paternal or maternal exposures any time before birth.

The timing of parental exposure relative to the child's birth can give a clue to the most biologically relevant period of exposure: preconceptional exposure (germ cell effect), perinatal exposure (i.e. intra-uterine or trans-placental) or postnatal exposure (via breast feeding). The detailed job histories obtained from both parents allowed us to assess occupational exposures for the potentially relevant time periods. However, numbers of exposed mothers were generally too low to specify time periods. While we did observe an increased risk for maternal exposure to chlorinated solvents any time before birth, this was based on only three exposed case mothers and four exposed control mothers. None of the mothers was exposed to chlorinated solvents in the year of the pregnancy.

For paternal exposure, the year before conception appeared to have the largest impact as all those ORs were higher than the ORs for any time before birth. This finding suggests a potential effect on sperm cells. Exposure to aromatic solvents such as toluene and xylene showed the strongest relation with CBT in our population. Toluene has been causally linked to DNA damage in the sperm of rats (Nakai *et al*, 2003), which could potentially lead to carcinogenic effects in the offspring.

The use of organic solvents in Australia and many other developed economies is widespread, including in paints and lacquers, dry cleaning, printing and degreasing. It is recommended that exposures be kept as low as workable and many solvents have occupational exposure standards (e.g. for toluene the 8-h TWA is 50 p.p.m. and the short-term exposure limit is

Table 2. Maternal occupational exposure in different time periods relative to the birth of their child

	Exposure time period	Cases/controls	OR	95% CI
All solvents combined				
Any time before birth	Non-exposed	262/856	1.00	ref.
	Exposed	31/79	1.16	0.71–1.90
In the year before birth	Non-exposed	287/918	1.00	ref.
	Exposed	6/17	1.19	0.42–3.35
Benzene				
Any time before birth	Non-exposed	280/899	1.00	ref.
	Exposed	13/36	0.94	0.45–1.97
In the year before birth	Non-exposed	291/931	1.00	ref.
	Exposed	2/4	2.36	0.22–25.7
Other aromatics				
Any time before birth	Non-exposed	279/887	1.00	ref.
	Exposed	14/48	0.66	0.31–1.38
In the year before birth	Non-exposed	289/926	1.00	ref.
	Exposed	4/9	1.51	0.37–6.16
Aliphatics				
Any time before birth	Non-exposed	267/876	1.00	ref.
	Exposed	26/59	1.29	0.74–2.27
In the year before birth	Non-exposed	288/921	1.00	ref.
	Exposed	5/14	1.20	0.38–3.81
Chlorinated				
Any time before birth	Non-exposed	289/932	1.00	ref.
	Exposed	3/4	8.79	0.96–80.7
In the year before birth	Non-exposed	293/935	—	—
	Exposed	0/0	—	—

Abbreviations: CI = confidence interval; OR = odds ratio. All models are adjusted for frequency-matching variables (child's sex, age at diagnosis, and state of residence), best parental education and occupational exposure to diesel exhaust.

150 p.p.m. in Australia) (National Occupational Health and Safety Commission, 1990). The median birth year of the children in the current study was 2001 (range 1990–2010), so the relevant paternal exposures in the years before conception will largely have been below this limit. The current use of halogenated solvents should be lower than in previous decades because Australia ratified the Montreal protocol and committed to phasing out the industrial use of particular solvents (e.g. carbon tetrachloride and methyl chloroform) by the end of 1995 and specific uses (e.g. methyl bromide in horticulture) by the end of 2005 (Montreal Protocol, 1987). The Australian government committed to a 90% reduction in the use of hydrochlorofluorocarbons by 2015 and complete phasing out by 2020 (Montreal Protocol, 1987).

Control families were recruited by national random-digit dialling. Approximately 90% of Australian households had a landline telephone connection during the recruitment period (Dal Grande and Taylor, 2010), so families contacted were likely to be representative of the wider population. The participation rates in our study were relatively low, however, among both the cases and the controls. Subjects of highest SES are more likely to participate in a study than subjects of lower SES when recruitment is done via random-digit dialling (Bailey *et al*, 2010). Previous analyses have shown that the control families used in our study were of higher SES than the general population (Mazloum *et al*, 2012). We aimed to minimise selection bias by adjusting for SES by means of the highest level of education completed by one of the parents. Adjustment for parental education resulted in slightly lower risk estimates overall, both for paternal and for maternal occupational exposure to solvents, when compared to models not adjusted for education.

Recall bias may have influenced the results, as case parents may reflect on and recall past exposures more than control parents, thus biasing the risk estimates upwards (Schuz *et al*, 2003). This bias would be particularly likely when questions are asked about specific, known-toxic exposures. We did not ask direct questions about exposure, rather we sought information on jobs and tasks and assigned specific exposures using pre-defined rules (Peters *et al*, 2014). We cannot rule out, however, greater reporting of jobs or tasks based on case parents' perceptions of hazards that might be associated with them. ORs may be strongly affected by small changes in the probability of false-positive exposure classifications (i.e. being classified as being exposed when truly non-exposed) when studying low prevalence exposures (Jurek *et al*, 2008).

When comparing the rule-based exposure assessment method with the more conventional case-by-case expert assessment, it appeared that the assessment of exposure to solvents showed less agreement than pesticides and diesel exhaust, although agreement was still moderate to good for solvents (Peters *et al*, 2014). Chlorinated solvents showed the lowest agreement ($\kappa = 0.26$ for men and $\kappa = 0.46$ for women on a job level), indicating that these solvents are particularly difficult to assess. It is likely that exposure misclassification will have occurred, but without a gold standard we can neither define the specificity of the method nor state whether we under- or overestimated the true exposures.

Exposure misclassification may result in spurious risk estimates; it may therefore be worthwhile applying a more detailed exposure

Table 3. Paternal occupational exposure in different time periods relative to the birth of their child

	Exposure time period	Cases/controls	OR	95% CI	OR2	95% CI
All solvents combined						
Any time before birth	Non-exposed	154/555	1.00	ref.		
	Exposed	88/240	1.27	0.90–1.79		
In the year before conception	Non-exposed	199/703	1.00	ref.		
	Exposed	43/92	1.55	0.99–2.43		
Benzene						
Any time before birth	Non-exposed	220/716	1.00	ref.	1.00	ref.
	Exposed	22/79	0.82	0.48–1.37	0.65	0.37–1.16
In the year before conception	Non-exposed	235/787	1.00	ref.	1.00	ref.
	Exposed	7/8	2.66	0.92–7.69	2.07	0.68–6.35
Other aromatics						
Any time before birth	Non-exposed	163/584	1.00	ref.	1.00	ref.
	Exposed	79/211	1.27	0.90–1.81	1.43	0.68–3.00
In the year before conception	Non-exposed	202/717	1.00	ref.	1.00	ref.
	Exposed	40/78	1.75	1.10–2.79	4.47	1.12–17.8
Aliphatics						
Any time before birth	Non-exposed	157/563	1.00	ref.	1.00	ref.
	Exposed	85/232	1.25	0.88–1.78	0.98	0.47–2.06
In the year before conception	Non-exposed	202/704	1.00	ref.	1.00	ref.
	Exposed	40/91	1.42	0.90–2.24	0.32	0.08–1.29
Chlorinated						
Any time before birth	Non-exposed	232/775	1.00	ref.	1.00	ref.
	Exposed	10/20	1.76	0.80–3.85	1.59	0.70–3.58
In the year before conception	Non-exposed	239/791	1.00	ref.	1.00	ref.
	Exposed	3/4	2.33	0.50–10.9	2.83	0.55–14.5
Diesel exhaust						
Any time before birth	Non-exposed	144/506			1.00	ref.
	Exposed	98/289			1.08	0.77–1.52
In the year before conception	Non-exposed	191/656			1.00	ref.
	Exposed	51/139			1.09	0.72–1.66

Abbreviations: CI = confidence interval; OR = odds ratio. Models are adjusted for frequency-matching variables (child's sex, age at diagnosis and state of residence), best parental education and occupational exposure to diesel exhaust; OR2 models include occupational exposure to benzene, other aromatics, aliphatics, chlorinated solvents and diesel exhaust, as well as the matching variables and best parental education.

assessment method taking into account exposure levels. In the previous Aus-ALL study, levels of exposure have been studied by applying case-by-case expert assessment (Reid *et al*, 2011). The same approach could be applied to the Aus-CBT study population, focusing on the specific exposures that appeared to be associated with an increased CBT risk. Additionally, larger study populations may be beneficial when studying a rare disease like CBT in more detail. Pooled analyses of CBT case–control studies where full job histories have been collected may improve our understanding of the effect of occupational exposures on the risk of CBT and its subtypes.

Our results suggest that parental occupational exposures to solvents may be related to CBT. In particular, paternal exposure to aromatic solvents and maternal exposure to chlorinated solvents appeared to be associated with an increased risk of CBT in their offspring.

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