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Interactions between occupational exposure to extremely low frequency magnetic fields and chemicals for brain tumor risk in the INTEROCC study

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COMPETING INTERESTS

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Abstract

Objectives: In absence of clear evidence regarding possible effects of occupational chemical exposures brain tumor etiology, it is worthwhile to explore the hypothesis that such exposures might act on brain tumor risk in interaction with occupational exposure to extremely low frequency magnetic fields (ELF).

Methods: INTEROCC is a seven-country (Australia, Canada, France, Germany, Israel, New Zealand, United Kingdom) population-based case-control study, based on the larger INTERPHONE study. Incident cases of primary glioma and meningioma were ascertained from 2000 to 2004. Job titles were coded into standard international occupational classifications and estimates of ELF and chemical exposures assigned based on job-exposure matrices. Dichotomous indicators of cumulative ELF (≥50th vs <50th percentile, 1–4 year time window) and chemical exposures (ever vs never, 5-year lag) were created. Interaction was assessed on both the additive and multiplicative scales.

Results: A total of 1,939 glioma cases, 1,822 meningioma cases, and 5,404 controls were included in the analysis, using conditional logistic regression. There was no clear evidence for interactions between ELF and any of the chemical exposures assessed for either glioma or meningioma risk. For glioma, subjects in the low ELF/metal exposed group had a lower risk than would be predicted from marginal effects. Results were similar according to different exposure time windows, cut points of exposure, or in exposed-only analyses.

Conclusions: There was no clear evidence for interactions between occupational ELF and chemical exposures in relation to glioma or meningioma risk observed. Further research with more refined estimates of occupational exposures is recommended.

Keywords

glioma; meningioma; occupation

INTRODUCTION

There are few well-established risk factors for brain tumors beyond ionizing radiation exposure.[1, 2] Studies investigating other environmental and occupational risk factors have generally reported inconsistent findings. Some studies reported positive associations of various occupations or industries including farming,[3] satellite or aerospace electromechanical manufacturing,[4, 5] pulp and paper production,[6] engineering/architecture,[7] nursing,[8] textile industry maintenance,[9] and food production or processing;[7, 10, 11] some studies suggest that automotive body painters, designers and decorators, managers, military occupations, production managers, teachers, computer programmers, inspectors, and physicians may also be at increased risk of developing brain tumors.[10, 12]

There are also studies reporting associations with specific occupational exposure to metals,[11, 13–15] metalworking fluids,[16] pesticides,[17–19] asphalt,[20] formaldehyde,[21] vinyl chloride,[22] petroleum products, oil mist, and aromatic and aliphatic hydrocarbons.[13, 14] However, the overall strength of evidence supporting these associations is limited due to inconsistent findings across studies, small numbers of study subjects, uncertainties in occupational exposure assessment, and a lack of knowledge on possible interactions between occupational exposures.

Potential health risks associated with occupational exposure to extremely low frequency magnetic fields (ELF) have also been investigated. A 2008 meta-analysis reported a significant positive association between occupational ELF exposure and brain tumor risk (relative risk (RR) = 1.14, 95% confidence interval (CI) 1.07–1.22), although there was little evidence for an exposure-response relationship.[23] Studies published since that time have reported conflicting findings. A U.S. study based on a job-exposure matrix (JEM) supplemented with job modules reported no association between occupational ELF and either glioma or meningioma risk.[24] A French study reported a significant positive, though imprecise association between occupational ELF, as assessed using expert judgment, and meningioma risk (odds ratio (OR) = 3.02, 95% CI 1.10–8.25).[25] Recent cohort studies in the Netherlands and the U.K. also reported no evidence for associations of occupational ELF and brain tumour risk.[26, 27]

Few studies examined occupational ELF in different exposure time windows (ETW). In the international INTEROCC study, a large-scale population-based case-control study including data on nearly 2,000 cases of both glioma and meningioma, based on the larger INTERPHONE study, we recently reported no association between lifetime cumulative ELF exposure and glioma or meningioma risk, although positive associations with ELF were noted in the most recent ETW, 1–4 years prior to the diagnosis/reference date (OR ≥ 90th percentile vs < 25th percentile for glioma = 1.67, 95% CI 1.36–2.07; for meningioma = 1.23, 95% CI 0.97–1.57) possibly suggesting an etiologic role of ELF in brain tumor promotion or progression.[28] Although there was no clear evidence for associations between occupational exposure to either combustion products, dusts, and other chemical agents [29] or solvents [30] and either glioma or meningioma risk in INTEROCC, we recently observed evidence for positive associations between occupational metal exposures, particularly iron exposure in women, as well as oil mist exposure overall, and meningioma risk.[31, McElvenny et al., personal communication, 2017]

There may also be interactions among occupational exposures for brain tumors, but the epidemiological literature on possible interactions is sparse. In a Swedish population-based study in which all males recorded as employed in the 1970 census (~1.5 million) were followed for 19 years through linkage with the cancer registry (2,029 brain tumors), Navas-Acien et al.[32] observed a positive association between ELF and glioma risk only with a concomitant chemical exposure. Similarly, solvent, lead, and pesticide exposure were associated with glioma only with moderate to high ELF exposure (> 0.13 μT work day average exposure). No clear interactions were observed between occupational ELF and chemical exposures for meningioma, though there were few cases in some exposure groups.

The purpose of this analysis is to examine possible interactions between occupational exposures for brain tumors, more specifically, between occupational ELF and metals, solvents, and other chemicals in the INTEROCC study. INTEROCC presents a unique opportunity to examine such interactions within the context of a large, well established study, with detailed occupational history data collected for study participants.

METHODS

Study Population

INTEROCC is a seven-country (Australia, Canada, France, Germany, Israel, New Zealand, United Kingdom) population-based case-control study based on data that was collected for the larger INTERPHONE study of potential cancer risk associated with cellular telephone use.[33] Incident cases of primary glioma and meningioma were recruited from treatment centers in major population areas from the year 2000 to 2004 with completeness of case ascertainment assessed through secondary sources. Cases were between 30 to 59 years of age, although an extended age range was included in Germany (30 to 69 years), Israel (18+ years), and the UK (18 to 69 years). All cases were confirmed histologically or by unequivocal diagnostic imaging. Population controls were selected through different recruitment procedures in different countries (mainly from population registries and electoral lists, as well as from general practitioner patient lists in the UK, and random digit dialing in Ottawa). One control was randomly selected (2 in Germany) for each case of glioma and meningioma in each study centre and was frequency- or individually-matched to cases by sex and year of birth (5-year age categories). To maximize statistical power, all eligible glioma and meningioma controls recruited as part of INTERPHONE were included here.[34] A total of 3,978 cases (2,054 glioma cases and 1,924 meningioma cases) and 5,601 controls were interviewed from 5,399 eligible cases (3,017 glioma cases and 2,382 meningioma cases) and 11,112 controls. Participation rates were 68% (ranging from 56–86% across INTEROCC study countries) for glioma cases, 81% (62–90%) for meningioma cases, and 50% (31–74%) for controls. The control reference date for INTEROCC was set as the date of interview minus the median difference between case diagnosis and interview by country.

Ethics approval was obtained from local research ethics boards, as well as from the Ethical Review Board of IARC (Lyon) for INTERPHONE and the Municipal Institute for Medical Investigation (IMIM) Barcelona for INTERPHONE and INTEROCC. Participants were asked to provide written informed consent prior to being interviewed.

Data Collection

Computer-assisted personal interviews were conducted with study participants by trained interviewers. Proxy respondents, mainly for glioma cases (19% overall, ranging from 8–46% across INTEROCC study countries), were used when necessary. The interview captured data on demographic, family, medical, and other personal characteristics, including an occupational calendar for all jobs held for six month or longer. Detailed occupational data included job title, company name and description, and start and end year for all jobs held.

Occupational ELF and Chemical Exposure Assessment

Following exclusion of a small number of jobs due to invalid start/stop dates (n=622), a total of 35,240 jobs were retained for analysis. Job titles were coded into standard occupational and industrial classification systems (International Standard Classification of Occupations 1968 (ISCO68) (n=1,142 3- or 5-digit codes), 1988 (ISCO88) (n=413 4-digit codes), and the International Standard Industrial Classification 1971 (ISIC71) (n=211 4-digit codes). The number of jobs held by cases and controls was similar, with a mean (SD) of 3.9 (2.6) jobs held by glioma cases, 3.6 (2.6) by meningioma cases, and 3.8 (2.5) by controls. A small number of cases (n=103, 5.0% glioma cases and n=95, 4.9% meningioma cases) and controls (n=122, 2.2%) were excluded as reporting never having been employed.

Estimates of mean workday ELF exposure were assigned to each job based on an updated measurement-based JEM linked primarily to ISCO88 codes, but also to more specific ISCO68 codes for electrical jobs where possible.[28, 35, 36] Included studies in the JEM used personal monitors with bandwidths from 3 to 1000 Hz to measure the full-shift time-weighted average (TWA) ELF exposures to the magnetic flux density in μT. Estimates of geometric mean (GM) ELF exposure were used and available from the JEM for the majority of jobs (92%)[28, 37]. For the remaining jobs, ELF exposures were assigned based on those from similar codes (5%), expert judgment (3%), or study centre specific control mean values for unknown occupations (0.3%).

Occupational exposure to 29 different metals, solvents, or other chemical agents selected *a priori* were assigned to each job based on a modified version of the Finnish job-exposure matrix (FINJEM), covering the time period 1945–2003.[38] A crosswalk was developed between the FINJEM and ISCO68 coding systems. Updates to the FINJEM included dividing the 1960–1984 time period in two periods (1960–1973 and 1974–1984); modifying some entries to enhance their consistency and specificity, as well as generalizability to different study countries; and updating entries for benzo(a)pyrene and polycyclic aromatic hydrocarbons to include occupational exposure to environmental tobacco smoke.[38, 39] Estimates of the proportion of exposed workers (P) and arithmetic mean exposure level (L) were assigned to each job. When P was $< 5\%$, the level in FINJEM was set to zero. Ever exposure was defined as a probability of exposure $\geq 25\%$ for at least one year, with a five year lag. Where $5\% \leq P < 25\%$, individuals were considered of “uncertain” exposure status and were excluded here, as were jobs held for < 1 year. Indicators of lifetime cumulative exposure were constructed based on the sum over all jobs of the products P x L x job duration.

Statistical Analysis

Conditional logistic regression models were used to obtain adjusted ORs and 95% CIs for glioma or meningioma risk according to dichotomous categories of occupational ELF (≥50th percentile (0.46 μT-years) vs <50th percentile of the control exposure distribution) and chemical exposures (ever vs never) in all seven countries combined relative to a common reference category of low ELF/never chemical exposure. For analysis of any metal or individual metals, the reference category comprised participants with no exposure to any metal, similarly the reference category for individual solvents was participants with no exposure to any solvent.[30, 31] Models were stratified by country-region, sex, and five-year age groups, and adjusted for level of education. The main analysis focused on interactions between cumulative occupational ELF in the 1–4 year ETW, since we were interested in assessing potential promotion or progression effects of ELF, and the strongest independent effects of ELF were observed with this metric in this time window in previous work.[28] Occupational chemical exposures were considered with a 5-year lag, also as in previous work.[29–31] Sensitivity analyses were conducted according to level of ELF exposure (≥75th percentile vs <25th percentile of the control exposure distribution), to examine a greater exposure contrast, as well as among exposed subjects only (using the cutpoint of the 50th percentile of the cumulative control exposure distribution for each chemical), to address potential differences by employment/exposure status in chemically exposed vs never exposed, and by level of chemical exposure.

Interaction was assessed on both the additive and multiplicative scales under the assumption that no bias was present.[40] On the additive scale, estimates of the relative excess risk due to interaction (RERI) and associated 95% CIs were calculated where appropriate.[41] On the multiplicative scale, product terms were entered into conditional logistic regression models and their significance assessed according to the likelihood ratio test. All statistical tests were two-sided. Analyses were conducted using SAS version 9.3.[42]

RESULTS

A total of 1,939 glioma cases, 1,822 meningioma cases, and 5,404 controls were retained for analysis following exclusion of participants with no occupational history or missing data on covariates of interest. Whereas glioma cases were predominantly male (62.0%), the majority of meningioma cases were female (72.5%) (Table 1). The mean (SD) age of participants was 51.0 (12.3) years for glioma cases, 54.7 (11.6) years for meningioma cases, and 51.8 (11.3) years for controls. A minority of glioma (47.7%) and meningioma cases (40.9%) and controls (46.4%), had a greater than high school level of education compared to a high school education or less. The United Kingdom and Israel contributed 50.5% of glioma cases; Israel and Germany 57.1% of meningioma cases.

A listing of the most frequent jobs held among participants classified into categories of cumulative ELF exposure in the 1–4 year time window and any metal exposure (5-year lag) is presented in Table 2. The most frequent jobs among participants with low (<50th percentile) cumulative ELF and no metal exposure were secretaries, secondary education teaching professionals, and shop salespersons and demonstrators. In contrast, the most frequent jobs among participants with high (≥50th percentile) cumulative ELF and any metal exposure were machine-tool setters and setter-operators, motor vehicle mechanics and fitters, and plumbers and pipe fitters. Supplementary Table S1 provides the most frequent jobs for categories of ELF and solvent exposure.

Results examining possible interactions between occupational ELF and chemical exposures are presented separately for glioma and meningioma in a series of tables grouped according to those concerning metals and others for results concerning solvents and other chemical agents. While most tables present results relative to a common reference category of low ELF/never chemical exposure, others present results relative to low ELF/low chemical exposure. The later are referred to as “exposed only analysis”.

The prevalence of any metal exposure was 17% overall and 11% for both any metal and high ELF (≥50th percentile) exposure in analysis of glioma (Table 3). The OR (95% CI) for high ELF exposure compared to low ELF exposure in the 1–4 year ETW prior to the index date with no metal exposure was 1.31 (95% CI 1.14–1.51). The OR for any vs never metal exposure (5-year lag) in the low ELF exposure group was significantly reduced (OR = 0.71, 95% CI 0.54–0.95). The OR for both high ELF and any metal exposure was 1.29 (95% CI 1.05–1.59), similar to the OR for ELF alone. Although there was a positive interaction on the multiplicative scale of borderline significance ($p = 0.06$), its direction was driven by the significantly reduced OR in the low ELF/metal exposed group. Similar results were observed across individual metal exposures, or exposure to welding fumes, with positive, and in some cases significant, multiplicative interactions driven by reduced ORs in the low ELF/metal exposed group.

The prevalence of any solvent exposure was 9% overall and 6% for both any solvent and high ELF exposure (Supplementary Table S2). There was an OR of 1.36 (95% CI 1.19–1.56) for high ELF exposure in the 1–4 year ETW with no solvent exposure, an OR of 0.73 (95% CI 0.50–1.06) for any solvent exposure with low ELF, and a combined OR of 1.31 (95% CI 1.00–1.71) for both exposures, again similar to the OR for ELF alone, compared to the low ELF/no solvent exposure reference group. There was no significant interaction observed on the multiplicative scale ($p = 0.22$). Results were generally similar for specific solvents.

For other exposures, there were significant positive interactions observed for asbestos, benzo(a)pyrene, and polycyclic aromatic hydrocarbons on the multiplicative scale ($p < 0.05$), though they were driven - as for metals - by significantly reduced ORs in the chemical exposed groups among those with low ELF; for both benzo(a)pyrene and polycyclic aromatic hydrocarbons, a large number of participants were also considered of “uncertain” exposure status ($5\% \leq P < 25\%$) and were excluded from analysis [38], and ORs in all exposure categories were < 1 (Supplementary Table S2). There was no clear evidence of interaction with other specific chemicals with the OR in the high ELF/chemical exposed group generally ≤ expected. There was no clear evidence for interaction on the additive scale between ELF and any of the chemical agents assessed for glioma.

For meningioma, the prevalence of any metal exposure was 14% overall and 9% for both any metal and high ELF exposure (Table 4). There was a small positive association between high ELF exposure in the 1–4 year ETW of OR = 1.15 (95% CI 1.00–1.33). The OR for any metal exposure in the low ELF group was close to null of OR = 0.96 (95% CI 0.67–1.38). The OR among those with both high ELF and any metal exposure was significantly elevated (OR = 1.46, 95% CI 1.11–1.91) and there was a positive, though non-significant interaction (multiplicative scale) ($p = 0.21$). Results for individual metals were generally similar, with slightly increased ORs among those with both high ELF and metal exposure, though there were also reduced, but non-significant, ORs for lead and welding fume exposure in the low ELF group.

For solvents, the prevalence of any solvent exposure was low (7% overall and 4% for both any solvent and high ELF exposure) (Supplementary Table S3). There was an OR of 1.19 (95% CI 1.03–1.37) for high ELF exposure in the 1–4 year ETW, an OR of 0.91 (95% CI 0.57–1.46) for any solvent exposure, driven by the reduced OR for ever aromatic hydrocarbon exposure, and a combined OR of 1.40 (95% CI 0.98–2.00) for both exposures, compared to the low ELF/no solvent exposure reference group (p interaction multiplicative scale = 0.38). For specific solvents, there were some positive ORs for aliphatic and alicyclic hydrocarbons, other organic solvents, and toluene exposure in the low ELF group, though ORs in the high ELF and chemical exposed groups were not greater than expected.

There were also significant positive multiplicative interactions with benzo(a)pyrene and polycyclic aromatic hydrocarbons ($p < 0.007$) for meningioma, with reduced ORs in both the ELF and chemical exposure groups alone, and a small positive OR among those with both exposures, though again this was in a reduced analytic subgroup, with a large number of participants excluded from analysis due to “uncertain” exposure (Supplementary Table S3). For other specific exposures, there was no clear evidence for interaction (multiplicative scale). There was also no clear evidence for interaction on the additive scale between ELF and any of the chemical agents assessed for meningioma.

In sensitivity analysis according to the 75th (0.58 μT-years) and 25th (0.34 μT-years) percentile of ELF, though ORs in the high ELF group were increased (OR high ELF/never metal exposure for glioma = 1.59, 95% CI 1.30–1.96; meningioma = 1.24, 95% CI 1.00–1.55 for example), the general pattern in results was similar to the main analysis (not shown), and the available sample size was substantially reduced. Results excluding proxy respondents or participants who were judged by the interviewer to be uninterested in the interview were also similar.

When examining categories of high vs low chemical exposure (i.e., exposed only analysis), ORs in the low ELF/high metal exposure group for glioma and meningioma were generally >1, in contrast to the reduced ORs observed in the main analysis, though they were imprecise (Supplementary Table S4 and S5). There was no clear evidence of interaction for either glioma or meningioma in exposed only analysis for most chemical agents (Supplementary Tables S4–S7). There was a significant negative interaction (p multiplicative scale = 0.04) with high iron for meningioma, with the OR in the joint exposure group lower than the product of the individual effects.

In sensitivity analyses according to different ETWs, there was also no clear evidence for interaction for either glioma or meningioma upon examination of ELF in the 5–9 year ETW, and ORs for high ELF were weak/null (OR high ELF/never metal exposure for glioma = 1.07, 95% CI 0.94–1.23; meningioma = 0.98, 95% CI 0.85–1.13 for example) (not shown). There was also no evidence for interaction when examining both ELF and chemical exposures overall (1-year lag for both), though the reduced ORs for any metal exposure were no longer apparent in the low ELF group (OR = 1.00, 95% CI 0.75–1.34 glioma; OR = 1.32, 95% CI 0.92–1.89 meningioma), and for meningioma were significantly elevated for iron (OR = 1.65 95% CI 1.03–2.63) and nickel (OR = 1.70 95% CI 1.03–2.78) specifically (not shown). ORs for ELF were ~ 1.0. We further examined potential interactions between a distal ELF exposure (10+ years) followed by a more recent chemical exposure (<10 years), and again, there was no clear evidence for interactions observed (not shown).

In analyses of potential interactions for meningioma risk among women only, ORs for ELF in the 1–4 year ETW, any metal exposure (5-year lag), and the combined effect were 1.21 (95% CI 1.02–1.43), 0.93 (95% CI 0.50–1.74), and 1.86 (95% CI 1.09–3.15) respectively with a multiplicative interaction term of 1.65 (95% CI 0.73–3.72) ($p = 0.23$). However, there were insufficient numbers of exposed women to examine potential interactions with individual metals.

DISCUSSION

Overall, there was no clear evidence for interactions between occupational ELF and any of the chemical exposures examined, including metals, solvents, dusts, and other chemical agents for either glioma or meningioma risk. For glioma, there was a positive significant interaction on the multiplicative scale between ELF and any metal exposure, as well as with exposure to specific metals, though its direction was driven by a reduced OR in the low ELF/metal exposed group.

To our knowledge, there has been only one previous epidemiological study examining interactions between ELF and chemical exposures for brain tumors. In a 19 year follow-up based on Swedish registry data, Navas-Acien et al.[32] observed a positive association between ELF and glioma in men with a simultaneous chemical exposure. However, results were based on occupation at the beginning of the study period (in the year 1970) and changes in occupation over time were not assessed. In contrast, in the current study, detailed occupational histories were obtained for study participants throughout their working lifetimes (beginning at age 14 years), allowing us to examine both ELF and chemical exposures in specific time windows of interest.

The main analysis of the current study was based on dichotomized categories of ELF exposure in the 1–4 year ETW (according to the 50th percentile), since ELF is suspected of playing a role in brain tumor promotion or progression, and chemical exposures with a 5-year lag (never vs. any exposure).[28] However, we also considered alternate ETWs for both ELF (1-year lag, 5–9 year ETW, and 10-year lag) and chemical exposures (1-year lag, 1–9 year ETW) in sensitivity analyses. It is unclear whether the reduced ORs observed for chemicals in the low ELF group in the 1–4 year ETW, particularly for glioma and metals, were due to chance or some sort of bias. The reduced ORs were generally attenuated using alternate ETWs, further, in analysis overall (1-year lag), significant positive associations were observed for some metals for meningioma.[31] There were also multiple tests performed, raising the possibility of a false significant finding. In exposed only analysis, ORs in the low ELF/high metal group were also not reduced as in the main analysis. There were however, few subjects in some exposure groups, or in some cases inadequate numbers of exposed participants to consider level of chemical exposure. Results were also similar using alternate cut-points for ELF (according to the 25th and 75th percentiles). The previous study by Navas-Acien et al.[32] was unable to consider level of occupational chemical exposure due to small numbers of subjects.

There was also no clear evidence of interactions for meningioma risk in sensitivity analysis including women only, and an insufficient number of women exposed to individual metals to permit further analysis by gender. Navas-Acien et al.[32] included only men in their study.

Other potential limitations include disentangling the effects of individual chemical exposures due to their correlated nature [30, 31] and misclassification of occupational exposures based on the use of JEMs. However, such misclassification is likely non-differential, in terms of case/control status, and likely leads to attenuated risk estimates. There is also Berkson bias due to group-based exposure estimates. There may also be differences in occupational exposures across study countries and time periods. The ELF JEM used here was recently updated [28, 36] as was the chemical FINJEM modified for use in INTEROCC.[38] The use of more refined exposure assessment approaches including expert assessment and more detailed job-specific information may be useful to better detect interactions.[43] Ongoing work as part of INTEROCC on the application of source-based, rather than job-based, exposure matrices for occupational electromagnetic field exposure may be useful in this regard.[44, 45] Finally, participation rates were low, ranging from 68–81% in cases to 50% in controls. Though participation may be related with socioeconomic and employment status,[46] level of educational attainment and occupational prestige (based on the standard international occupational prestige scale (SIOPS)) were generally similar across groups of interviewed participants here.[28] The somewhat lower participation rate for glioma as compared with meningioma cases was expected due to the severity of disease and poorer prognosis.

Results of this study provide no clear evidence for interactions between ELF and chemical exposures from an epidemiologic perspective. Results of experimental studies examining potential co-carcinogenic effects of ELF with other chemical and physical agents are reviewed elsewhere.[47–49] The Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) concluded that results from the limited number of experimental studies of co-exposure, both *in vivo* and *in vitro*, are inconsistent and difficult to compare due to a range of divergent protocols used.[48]

In conclusion, this large-scale population-based study provides no clear evidence for interactions between occupational ELF and chemical exposures in relation to glioma or meningioma risk. Further research with more refined estimates of occupational exposures is recommended. Additionally, only potential interactions with occupational ELF were examined here. It may also be worthwhile to examine interactions with other electromagnetic frequency bands including occupational exposure to radiofrequency fields (RF). The recent International Agency for Research on Cancer monograph on the carcinogenicity of RF noted increased cancer risk in experimental animals in four of six included co-carcinogenicity studies, although there were questions in some studies regarding the experimental model used, the study design, and in reporting.[50] Future examination of interactions between different types of electromagnetic frequency fields, including RF, intermediate frequency, and ELF may also be useful.[48]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What this paper adds

- There are few well-established risk factors for brain tumors. Occupational chemical exposures may act on brain tumor risk in interaction with extremely low frequency magnetic fields (ELF) however, the epidemiological literature is sparse.
- Occupational exposure to 29 different chemical agents and ELF were assigned to the lifetime occupational histories of participants in the 7-country INTEROCC study based on job exposure matrices.
- Results revealed no clear evidence for interactions between occupational ELF and various metals, solvents, or other chemical agents in either glioma or meningioma risk.
- Further research with more refined estimates of occupational chemical and electromagnetic field exposures is recommended.

Table 1.

Characteristics of Case and Control Participants at Enrollment INTEROCC Study, 2000–2004, Australia, Canada, France, Germany, Israel, New Zealand, and United Kingdom.

Characteristic	Glioma Cases (n=1,939)	Meningioma Cases (n=1,822)	Controls[a] (n=5,404)
	Mean (SD) or %	Mean (SD) or %	Mean (SD) or %
Mean (SD) age at reference date	51.0 (12.3)	54.7 (11.6)	51.8 (11.3)
Sex			
Male	62.0	27.5	45.2
Female	38.0	72.5	54.8
Education			
High school or less	52.4	59.1	53.6
Greater than high school	47.7	40.9	46.4
Country			
Australia	14.2	13.9	12.3
Canada	8.6	5.1	11.6
France	4.8	7.6	8.5
Germany	18.6	20.3	27.5
Israel	20.5	36.8	17.3
New Zealand	3.4	2.7	2.7
United Kingdom	30.0	13.5	20.1

[a] Glioma and meningioma controls combined.

Table 2.

Most Frequent Jobs Among Participants in Categories of Cumulative Occupational ELF Exposure in the 1–4 Year Exposure Time Window and Metal Exposure (5-year lag), INTEROCC study, 2000–2004, Australia, Canada, France, Germany, Israel, New Zealand, and United Kingdom.

ISCO88	Job Title	Frequency (n)
Low ELF - Never Metal		
4115	Secretaries	341
2320	Secondary education teaching professionals	182
5220	Shop salespersons and demonstrators	151
5131	Child-care workers	118
2411	Accountants	111
High ELF – Never Metal		
4190	Other office clerks	236
5220	Shop salespersons and demonstrators	226
9132	Helpers and cleaners in offices, hotels and other establishments	127
3415	Technical and commercial sales representatives	119
2230	Nursing and midwifery professionals	117
Low ELF - Any Metal		
8324	Heavy-truck and lorry drivers	34
7223	Machine-tool setters and setter-operators	29
1222	Production and operations department managers in manufacturing	21
5169	Protective services workers not elsewhere classified	15
5220	Shop salespersons and demonstrators	15
High ELF – Any Metal		
7233	Machine-tool setters and setter-operators	83
7231	Motor vehicle mechanics and fitters	59
7136	Plumbers and pipe fitters	43
7212	Welders and flamecutters	40
7222	Tool-makers and related workers	27

Note: out of a total number of 9,681 jobs.

Table 3.

Adjusted ORs (95% CIs) for Glioma in Relation to Categorical Indicators of Cumulative Occupational ELF (1–4 Year Exposure Time Window) and Any Metal (5-year lag) Exposure, INTEROCC study, 2000–2004, Australia, Canada, France, Germany, Israel, New Zealand, and United Kingdom[a].

Metal Exposure	**Low ELF (<50th percentile)**		**High ELF (≥50th percentile)**		**High vs. Low ELF in stratum of metal**	**Interaction Term (multiplicative)[b]**
	Cases/ Controls	**OR (95% CI)**	**Cases/ Controls**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Never metal	557/1791	1.00 (ref)	672/1687	1.31 (1.14–1.51)	1.33 (1.16–1.53)	1.38 (0.98–1.94)
Ever metal	77/242	0.71 (0.54–0.95)	229/401	1.29 (1.05–1.59)	1.50 (1.07–2.10)	
Ever vs. Never metal in stratum of ELF		0.71 (0.53–0.96)		0.99 (0.80–1.23)		
Never cadmium	557/1788	1.00 (ref)	672/1682	1.32 (1.15–1.52)	1.33 (1.16–1.53)	1.62 (0.65–3.99)
Ever cadmium	10/29	0.71 (0.34–1.50)	26/42	1.51 (0.90–2.55)	1.69 (0.46–6.20)	
Ever vs. Never cadmium in stratum of ELF		0.66 (0.29–1.48)		1.17 (0.68–2.01)		
Never chromium	557/1791	1.00 (ref)	672/1687	1.32 (1.15–1.52)	1.33 (1.16–1.53)	1.37 (0.87–2.16)
Ever chromium	40/107	0.77 (0.52–1.15)	132/209	1.40 (1.08–1.82)	1.61 (0.97–2.67)	
Ever vs. Never chromium in stratum of ELF		0.76 (0.50–1.14)		1.05 (0.80–1.37)		
Never iron	557/1791	1.00 (ref)	672/1687	1.32 (1.15–1.51)	1.33 (1.16–1.53)	1.47 (0.99–2.17)
Ever iron	55/169	0.68 (0.48–0.95)	171/286	1.31 (1.04–1.66)	1.70 (1.15–2.53)	
Ever vs. Never iron in stratum of ELF		0.67 (0.47–0.95)		0.99 (0.78–1.27)		
Never lead	557/1791	1.00 (ref)	672/1687	1.32 (1.15–1.52)	1.33 (1.16–1.53)	1.69 (1.05–2.74)
Ever lead	32/122	0.56 (0.37–0.85)	114/216	1.25 (0.96–1.64)	1.70 (1.00–2.86)	
Ever vs. Never lead in stratum of ELF		0.53 (0.35–0.82)		0.95 (0.72–1.25)		
Never nickel	557/1791	1.00 (ref)	672/1687	1.32 (1.15–1.51)	1.33 (1.16–1.53)	1.48 (0.98–2.23)
Ever nickel	50/146	0.71 (0.50–1.02)	152/235	1.39 (1.09–1.78)	1.53 (0.99–2.34)	
Ever vs. Never nickel in stratum of ELF		0.72 (0.50–1.05)		1.04 (0.81–1.35)		

Metal Exposure	Low ELF (<50th percentile)		High ELF (≥50th percentile)		High vs. Low ELF in stratum of metal	Interaction Term (multiplicative)[b]
	Cases/ Controls	OR (95% CI)	Cases/ Controls	OR (95% CI)	OR (95% CI)	OR (95% CI)
Never welding fumes	557/1791	1.00 (ref)	672/1687	1.32 (1.15–1.52)	1.33 (1.16–1.53)	1.81 (1.13–2.90)
Ever welding fumes	33/118	0.57 (0.38–0.87)	137/221	1.38 (1.06–1.78)	2.04 (1.24–3.35)	
Ever vs. Never welding fumes in stratum of ELF		0.55 (0.36–0.85)		1.04 (0.79–1.36)		

[a] Conditional logistic regression models were stratified by country-region, sex, and five-year age groups, and adjusted for level of education. The 50th percentile of ELF among the control distribution was 0.46 μT-years.

[b] *p* values for interaction (multiplicative scale) were as follows: metal (0.06), cadmium (0.30), chromium (0.18), iron (0.05), lead (0.03), nickel (0.06), welding fumes (0.01).

Table 4.

Adjusted ORs (95% CIs) for Meningioma in Relation to Categorical Indicators of Cumulative Occupational ELF (1–4 Year Exposure Time Window) and Any Metal (5-year lag) Exposure, INTEROCC study, 2000–2004, Australia, Canada, France, Germany, Israel, New Zealand, and United Kingdom[a].

Metal Exposure	**Low ELF (<50th percentile)**		**High ELF (≥50th percentile)**		**High vs. Low ELF in stratum of metal**	**Interaction Term (multiplicative)[b]**
	Cases/ Controls	**OR (95% CI)**	**Cases/ Controls**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Never metal	542/1728	1.00 (ref)	563/1627	1.15 (1.00–1.33)	1.18 (1.02–1.37)	1.32 (0.86–2.03)
Ever metal	45/214	0.96 (0.67–1.38)	109/366	1.46 (1.11–1.91)	1.32 (0.81–2.15)	
Ever vs. Never metal in stratum of ELF		0.85 (0.58–1.24)		1.37 (1.03–1.81)		
Never cadmium	-	-	-	-	-	-
Ever cadmium	-	-	-	-	-	
Ever vs. Never cadmium in stratum of ELF		-		-		
Never chromium	542/1689	1.00 (ref)	563/1579	1.17 (1.01–1.35)	1.18 (1.02–1.37)	0.89 (0.48–1.65)
Ever chromium	21/95	1.26 (0.75–2.13)	47/181	1.31 (0.91–1.91)	1.22 (0.56–2.64)	
Ever vs. Never chromium in stratum of ELF		1.16 (0.67–2.03)		1.26 (0.84–1.87)		
Never iron	542/1703	1.00 (ref)	563/1590	1.16 (1.01–1.35)	1.18 (1.02–1.37)	1.26 (0.75–2.13)
Ever iron	28/152	0.96 (0.61–1.50)	69/255	1.41 (1.02–1.94)	1.29 (0.72–2.29)	
Ever vs. Never iron in stratum of ELF		0.84 (0.53–1.35)		1.32 (0.93–1.85)		
Never lead	542/1700	1.00 (ref)	563/1605	1.17 (1.01–1.35)	1.18 (1.02–1.37)	1.42 (0.76–2.65)
Ever lead	19/103	0.78 (0.46–1.33)	50/192	1.30 (0.91–1.85)	1.86 (0.79–4.38)	
Ever vs. Never lead in stratum of ELF		0.69 (0.40–1.19)		1.18 (0.82–1.72)		
Never nickel	542/1695	1.00 (ref)	563/1583	1.16 (1.01–1.35)	1.18 (1.02–1.37)	1.10 (0.63–1.91)
Ever nickel	26/130	1.05 (0.66–1.68)	55/209	1.34 (0.95–1.90)	1.49 (0.78–2.84)	
Ever vs. Never nickel in stratum of ELF		0.95 (0.58–1.55)		1.26 (0.87–1.83)		

Metal Exposure	**Low ELF (<50th percentile)**		**High ELF (≥50th percentile)**		**High vs. Low ELF in stratum of metal**	**Interaction Term (multiplicative)**[b]
	Cases/ Controls	**OR (95% CI)**	**Cases/ Controls**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Never welding fumes	542/1699	1.00 (ref)	563/1590	1.17 (1.01–1.35)	1.18 (1.02–1.37)	1.55 (0.82–2.92)
Ever welding fumes	17/106	0.81 (0.47–1.42)	52/192	1.46 (1.02–2.10)	1.47 (0.73–2.99)	
Ever vs. Never welding fumes in stratum of ELF		0.69 (0.39–1.23)		1.35 (0.92–1.99)		

[a] Conditional logistic regression models were stratified by country-region, sex, and five-year age groups, and adjusted for level of education. The 50th percentile of ELF among the control distribution was 0.46 μT-years.

[b] *p* values for interaction (multiplicative scale) were as follows: metal (0.21), chromium (0.71), iron (0.38), lead (0.27), nickel (0.75), welding fumes (0.18).