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Parental occupational paint exposure and risk of childhood leukemia in the offspring: Findings from the Childhood Leukemia International Consortium

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Abstract

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Purpose—It has been suggested that parental occupational paint exposure around the time of conception or pregnancy increases the risk of childhood leukemia in the offspring.

Methods—We obtained individual level data from 13 case-control studies participating in the Childhood Leukemia International Consortium (CLIC). Occupational data were harmonized to a compatible format. Meta-analyses of study-specific odds ratios (ORs) were undertaken, as well as pooled analyses of individual data using unconditional logistic regression.

Results—Using individual data from fathers of 8,185 cases and 14,210 controls, the pooled OR for paternal exposure around conception and risk of acute lymphoblastic leukaemia (ALL) was 0.93 (95% confidence interval (CI) 0.76, 1.14). Analysis of data from 8,156 ALL case mothers and 14,568 control mothers produced a pooled OR of 0.81 (95% CI 0.39, 1.68) for exposure during pregnancy. For acute myeloid leukaemia (AML), the pooled ORs for paternal and maternal exposure were 0.96 (95% CI 0.65, 1.41) and 1.31 (95% CI 0.38, 4.47) respectively, based on data from 1,231 case and 11,392 control fathers and 1,329 case and 12,141 control mothers. Heterogeneity among the individual studies ranged from low to modest.

Conclusions—Null findings for paternal exposure for both ALL and AML are consistent with previous reports. Despite the large sample size, results for maternal exposure to paints in pregnancy were based on small numbers of exposed. Overall, we found no evidence that parental occupational exposure to paints increases the risk of leukemia in the offspring, but further data on home exposure are needed.

Keywords

paint; parental occupation; leukemia; childhood; pooled analysis; meta-analysis

Introduction

Little is known about the etiology of childhood leukemia and its main sub-types, acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) but it is likely that they are attributable to a mixture of both genetic and environmental factors [1], which may vary by disease sub-type or, in the case of ALL, by immunophenotype. Some of the most common chromosomal translocations seen in ALL [2,3] and AML [4] may be of prenatal origin, suggesting a role for parental exposures. Individual studies rarely have sufficient statistical power to investigate potential risk factors by sub-type, especially for uncommon exposures. To overcome this problem, we pooled data from studies in the Childhood Leukemia International Consortium (CLIC), a multi-national collaboration of case-control studies of childhood leukemia [5]. The focus of these analyses was parental occupational exposures to paints.

It has been suggested that parental occupational paint exposure around the time of conception or pregnancy increases the risk of childhood leukemia in the offspring. Some previous studies have reported that maternal occupational exposure to paints before and during pregnancy increased the risk of ALL [6,7], and AML [8]. This last study also reported an increased risk of AML among children of fathers with ‘Painter’ as his job title, but not using self assessment of exposure [8]. However, other studies have found no association between paternal exposure and ALL [6,7,9–11] or AML [9]. Painting of the

home has also been associated with ALL, with some evidence of a trend of increase in risk with higher levels of exposure [12,13]. A working group of the Monograph program of the International Agency for Cancer (IARC) on the evaluation of carcinogenic risks to humans concluded in 2010 that there was 'limited evidence that paint exposure is related to childhood leukemia', based mainly on reports of maternal exposure [14]. Paint is a generic name for a diverse range of products which can contain a large number of individual chemical compounds such as solvents, resins, binders, extenders and pigments, and some of these individual compounds have been classified as human carcinogens or probable or possible human carcinogens such as ethyl acrylate, titanium dioxide and other pigments [15].

The aim of our analyses was to investigate whether parental occupational paint exposure in the prenatal period increased the risk of ALL or AML in the offspring. We also aimed to investigate whether the relationship varied by immunophenotype of ALL. We used pooled data from 13 studies. While three of these studies have previously published findings specifically in relation to occupational paint exposure [6,10,11], the majority have not.

Methods

For these analyses, we used the 13 CLIC studies that had relevant data available at the time of writing (2012); this included 12 studies with ALL cases and 10 with AML cases, conducted in North America, Europe and Australasia over a 30 year period (Table 1). Original data were requested from each of the 13 participating studies. A summary of study design and participant details, including inclusion criteria, has already been published [5]. All studies were approved by the relevant institutional or regional ethical committees. Cases of childhood leukemia other than ALL or AML were not included in these analyses.

Controls from studies with both ALL and AML cases were included in the analyses of both types of leukemia. Most studies recruited children under the age of 15 years, except the Italian SETIL study that included children up to the age of 10 years and the US Children's Oncology Group (COG)-E14 study of AML that included children up to the age of 18 years.

Original occupational exposure data

The time periods of interest were the year before conception for fathers and during the pregnancy for the mother. However, the studies had data for differing periods around conception or only during pregnancy in some studies (Table 1). In four studies, data for jobs in the time periods were extracted from the provided work history. The French Escale study had paternal exposure data for 'during pregnancy' only, so we used this as a proxy for exposure before conception. The New Zealand study asked mothers about any paint exposures at home or work during pregnancy, without separating out work specifically; thus New Zealand has been left out of the analysis of mother's specific work exposures.

Occupational data were provided in three main formats (Table 1): 1) Nine studies (France: Adele and Escale; Greece: NARECHEM 1993–1994 and 1996–2011; Germany: GCCR; Italy: SETIL; UK: UKCCS; US: NCCLS; COG-E15) provided jobs coded using an occupational coding system, which needed to be assigned paint exposure; 2) Three studies

provided data in which the jobs in the relevant time periods had already been assessed for paint exposure and exposure assigned (Australia, Canada and New Zealand); and 3) One study provided detailed paint questionnaire data which needed to be collated to a single exposure variable (US: COG-E14).

Development of a Job Exposure Matrix (JEM)

A JEM was developed using the assessments from two of the studies from Australia [11]and Quebec, Canada [16], which had used the expert assessment method to assess occupational paint exposure [17]. In this method a full job history is taken, and job specific questionnaires are asked for each job (for example a cabinet maker would be asked the 'Carpenter' questions while a auto spray painter would be asked the 'Panel Beater' questions). The answers to these questions are reviewed on an individual level by experts who determine whether the person was likely to be exposed in that job. For each job title in the International Standard Classifications of Occupation (ISCO) 2008 (08) [18] we determined what proportion of the jobs in the Australian data were assessed as being exposed to paints. All job codes were then assigned to a category relating to the certainty of paint exposure as follows: 1) Job codes where 70% or more people (males and females combined) with the ISCO-08 code had been assessed as exposed to paint ('High likelihood of paint exposure'); 2) Job codes where 25% to < 70% were assessed as exposed ('Moderate likelihood of exposure'); 3) Job codes where 5% to <25% were exposed ('Limited likelihood of exposure'); and 4) Job codes where less than 5% were exposed ('No or minimal likelihood of paint exposure' (Reference Group)). ISCO-08 jobs codes that were rare or not used in the Australian dataset were identified and these were assigned an exposure category by an occupational epidemiologist from within our team (LF). Modifications to the exposure categories were made after doing similar comparisons of expert assessment and job codings [19] from the Canadian study [16]. The final exposure codes in the ICSO-2008 JEM were then assigned to equivalent ISCO88 codes and hence to jobs in the other occupational classification systems using conversion tools (Table 1) [20–24]. In the case of 'many to one' or 'one to many' matches to job codes across systems, a judgment was made of the exposure category that best fitted the original job code description. A full list of the job codes which were categorized as highly likely to be occupationally exposed is shown in Supplementary Table 1.

Harmonisation of occupational data from other studies

Among the three studies where paint exposure had already been assigned, New Zealand had assigned paint exposure simply as exposed or non exposed as derived from more detailed data. In order to pool with the studies for which we used the JEM, we coded exposed subjects as having 'High likelihood of paint exposure'. In the Australian study [11], we coded those with 'probable high or medium exposure' as having 'High likelihood of paint exposure', and 'probable low exposure and possible low/medium/high exposure' as having 'Moderate likelihood of exposure' (Table 1). In the Canadian study [16], we coded those with 'some exposure' as having 'Moderate likelihood of exposure', and those with 'greater exposure' as having 'High likelihood of paint exposure' (Table 1).

The US COG-E14 study had collected detailed data about exposure to spray paints, other paints and lacquers, and total contact time with paints in the air or on the skin or clothing which were categorized into the same four levels of exposure as the JEM, based on standard rules.

Statistical analyses

Two distinct analytic approaches were taken. Firstly, study specific odds ratios (ORs) of ALL and AML and exposure to paints were estimated and included in meta-analyses, in order to explore heterogeneity between studies. Secondly, as the main approach, individual data were pooled in a single dataset and the pooled ORs estimated. Because we did not believe that the 4-category final exposure measure was an accurate measure of dose of occupational exposure, the only ORs presented in the main tables are the ORs between Exposure Category 1 ('High likelihood of paint exposure') to the Reference Category 4 ('No or minimal likelihood of paint exposure') for both the study specific and pooled analyses. While those with other exposure categories were included in the analytical models, a 'trend across categories' was not investigated and results from 'Moderate likelihood of exposure' and 'Limited likelihood of exposure' categories are only shown in Supplementary Table 2. All analyses were done for ALL and AML separately.

Estimation and meta-analyses of study-specific ORs

Unconditional logistic regression (SAS version 9.2, SAS Institute Inc, Cary, NC, USA) was used to estimate study-specific ORs and 95 percent confidence intervals (95% CIs) for occupational paint exposures for mothers during pregnancy and for fathers before conception. All models included child's age and sex and additional study-specific matching variables where applicable. Unconditional logistic regression adjusting for the original matching variables in originally individually-matched studies (all studies except Australia, France: Adele and Escale) was used to increase statistical power by optimizing the number of available cases and controls [25]. By using this method, we were able to include all subjects with complete data, even if their matched pair was missing data. Four of the individual studies had already used this method in their original analyses.[26–29] The following variables were considered *a priori* to be potential confounders or independently competing exposures: birth order, ethnicity, maternal age and education (for maternal analyses); and paternal age and education (for paternal analyses) and were assessed individually for inclusion in the models. Maternal and paternal educations were the only common socio-economic level indicators that were available in all studies. Factors that were independently associated with both the exposure and outcome were retained in the final models. The study-specific ORs were combined in a meta-analysis in Stata version 11.2 (StataCorp LP, College Station Texas, USA, 2009), using the random effects model (to acknowledge the between study heterogeneity [30] relating to issues such as study designs, occupational assessment methods, and changes in paint composition over time). Summary ORs, 95% CIs, I^2 statistics (a measure of the variation across studies that is not due to chance) [31] and forest plots were produced. Studies without any cases or controls in the 'High likelihood of paint exposure' were not included in the meta-analyses (see Supplementary Tables 3 and 4 for details of which studies were included in each of the meta-analyses).

Pooled analyses

Unconditional logistic regression (SAS version 9.2, SAS Institute Inc, Cary, NC, USA) was also used to estimate pooled ORs and 95% CIs for occupational paint exposures in mothers during pregnancy and for fathers before conception. All models included the child's age, sex, and year of birth (grouped into five approximately equal time periods) and a variable denoting the study of origin. The following variables were tested to determine whether they were independently associated with both the exposure and outcome where the data were available: birth order; birth weight; parent's age and education (secondary education not completed, completed secondary education, and tertiary education); and ethnicity (Caucasian, European or White versus the rest) and study-specific matching variables (by allocating all the other studies the same dummy value for each variable). Of these, the following variables were retained: maternal age and education for maternal exposure and the risk of ALL; maternal education for maternal exposure and the risk of AML; and paternal education for all analyses of paternal exposures. Where possible, analyses were stratified by ALL immunophenotypes, by sex and type of occupational assessment. Results were estimated for children aged less than 5 years at diagnosis or older, to explore whether parental exposure before birth was more relevant in younger children. Finally, as there had been changes to the maximum levels of volatile organic compounds allowed in paints in the mid 1990's [32,33], results were also estimated for children born before 1996 and those born later. As children with Down syndrome have higher rates of leukemia than other children, analyses were repeated excluding these children.

The two studies with expert assessment (Australia and Canada), which only had ALL cases had both classed exposure as a two level variable, albeit using different definitions based on likelihood, level, and frequency (for one of them) of exposure. Using these data as a crude indicator of exposure dose, we also investigated a trend relationship.

Sensitivity analyses

We also created two variables to test the sensitivity of the analyses to the choice of the definition of the exposed group by using lower cut-off levels for the 'High likelihood of paint exposure' categories of the JEM for studies which had job codes. For the first sensitivity analyses we combined the first and second categories in the original JEM (that is, all jobs codes where 25% or more people were estimated to be exposed) and for the second, we used a cut off of 35% or more (which mainly included jobs related to construction, seafaring and fishing). Using these exposure category variables, we would have missed less people who were truly exposed to paint, but would have also misclassified more truly unexposed as exposed. For the studies which did not use job codes, we used the same categories as in the original variable.

Results

Data were obtained from a total of 13 studies, 12 studies for 8,835 ALL cases and from 10 studies for 1,357 AML cases (Table 2). There were 15,486 controls from studies with ALL cases and 12,443 from those with AML cases. Maternal and paternal occupational data were available for over 90% of ALL and AML cases and controls (Table 2). These figures reflect

data missing from the original studies; for example, most studies had fewer fathers participating than mothers, and sometimes occupational histories were incomplete. Demographic characteristics of the total sample and the individual studies are shown in Supplementary Table 5.

Meta-analyses of study-specific ORs

While 12 studies with 8185 cases and 14,210 controls were included in the analysis of paternal exposure around conception and risk of ALL, only four studies with 3,306 cases and 4,356 controls were included in the meta-analysis of maternal occupational paint exposure and risk of ALL in the offspring, as the remaining studies had no cases or controls in the High likelihood of paint exposure (Supplementary Table 3). The summary ORs for paternal exposure and the risk of ALL in the offspring were 0.94 (95% CI 0.76, 1.15) (Figure 1) and for maternal exposure 0.79 (95% CI 0.36, 1.71) with little evidence of heterogeneity among the ORs (Figure 2). When individual studies were omitted in turn from the meta-analyses, the summary estimate changed by about 5% and 18% (OR scale) for the paternal and maternal meta-analyses respectively.

Seven studies with 1,160 cases and 9,945 controls were included in the AML paternal meta-analyses (Supplementary Table 4). The summary OR for paternal occupational paint exposure and the risk of AML in the offspring was 1.09 (95% CI 0.73, 1.63) with little or low heterogeneity among the ORs (Figure 1). When individual studies were removed one by one, the summary estimates changed by up to 14%. As only one AML study had any case mothers in the ‘High likelihood of paint exposure’ category, no meta-analysis was performed.

Pooled analyses of individual data

The analyses for ALL included 8,185 case fathers and 14,210 control fathers from 12 studies, and 8,156 case mothers and 14,568 control mothers from 11 studies. The OR for paternal occupational paint exposure and the risk of ALL was 0.93 (95% CI 0.76, 1.14) (Table 3). There was little difference in the OR when the analyses were done by immunophenotype or when stratified by child’s sex, age at diagnosis, year of birth or type of occupational assessment (Table 3), but the estimates lacked precision. When the analyses were restricted to the two studies which used expert assessment with two levels of exposure, no evidence of a trend relationship was found in relation to paternal exposure and the risk of ALL (p trend 0.37, results not otherwise shown). The pooled OR for maternal occupational paint exposure during pregnancy and the risk of ALL was 0.81 (95% CI 0.39, 1.68) (data not otherwise shown). There were only 13 case mothers (0.16%) and 20 control mothers (0.14%) in the ‘High likelihood of paint exposure’ category so the only sub group analysis was the investigation of a trend relationship using the two studies with a two level exposure variable, based on expert assessment. The small numbers in the highest exposure category (6 cases and 10 controls) prevented any meaningful assessment of a trend relationship. The ORs for the two levels of exposure were 0.77 (95% CI 0.27, 2.16) for the highest level and 1.61 (95% CI 1.11, 2.32) for the lower category but one study contributed nearly all the subjects to these analyses.

The analyses for AML included 1,231 case fathers and 11,392 control fathers from ten studies and 1,309 case mothers and 11,859 control mothers from nine studies. The OR for paternal exposure around conception was 0.96 (95% CI 0.65, 1.41), with little difference seen when stratified by sex, age at diagnosis, year of birth or type of occupational assessment (Table 3). The OR for maternal occupational paint exposure during pregnancy and risk of AML was 1.31 (95% CI 0.38, 4.47), with five cases (0.4%), who were all from US COG E-14 and ten control mothers (0.1%) in the 'High likelihood of paint exposure' category (data not otherwise shown). Thus, no sub-group analyses were performed.

When all the analyses for ALL and AML were repeated excluding children with Down syndrome (103 ALL cases and six controls, 89 AML cases and four controls), there was little change in the results and there was also little difference when the analyses were adjusted for the exposure level of the other parent (data not shown).

Influence analyses for paternal exposure were performed by leaving out individual studies in turn and then two studies in turn. Leaving out studies made little difference to the results (data not shown).

When we repeated the analyses using the two sensitivity variables with different definitions of 'High likelihood of paint exposure', the proportion of cases and controls in the estimates were in line with the original findings for both of the sensitivity variables (data not shown). However, the proportion of women in the 'High likelihood of paint exposure' categories remained low for both variables (0.6% and 0.4% of control mothers respectively).

Discussion

We found no evidence of any association between paternal or maternal occupational exposure to paints and ALL or AML in the offspring. Estimates for maternal exposure lacked precision because there were so few women in the high exposure group.

Our null findings in relation to paternal exposure to paint and ALL are similar to previously published literature [7,9]. Not surprisingly, they are also consistent with the published findings of three of the CLIC studies which contributed ~28% of cases to the current pooled analyses [6,10,11], despite the different methods of occupational assessment used in the initial reports [6,10]. The null findings for AML are also similar to those of a large UK study with 2,367 cases which assigned exposure based on job title [9], but not with those of a study from the US which assigned exposure based on job titles, but which included few exposed men (seven cases and one control) [8].

Despite having over 8,000 ALL cases, 1,000 AML cases and 14,000 controls, we had low statistical power to investigate maternal exposure as so few women (< 0.5%) were assigned to the 'High likelihood of paint exposure' category. Because of the format of the original data, we could only investigate likelihood of exposure, not level of exposure. Using the studies with expert assessment, there was an increased risk of ALL following maternal paint exposure at low levels during pregnancy, but as only one of the studies contributed most of the subjects to this analysis, these findings are hard to interpret. The IARC Monograph which concluded that there was 'limited evidence that paint exposure is related to childhood

leukemia' [14], had reviewed the findings of four reports (three of ALL) related to maternal occupational exposure to paints [6–8,34] as well as the findings in relation to home exposures [12,13,35]. The two studies that found an increased risk of ALL with maternal occupational exposure to paints during pregnancy [6,7] were the German study and US COG E-15 that are part of the current CLIC pooled analyses; however, both these original studies used different occupational assessment from those used in the current analyses. Our current analyses using a JEM which identified parents highly likely to have been exposed found much lower prevalence of exposure (combined study total of 0.1% of cases and 0.1% of controls) than in the original studies. The investigators in the German study [6] concluded that their positive finding, based on self assessment, was related to differential bias as a higher proportion of case mothers than control mothers reported exposures that seemed implausible when the job codes were examined. In addition, the German translation of the word 'colorants' which was included in the definition of 'paints' was similar to the translation for hair colorants, so women who were hairdressers reported that they had been exposed [36]. The third ALL study [34] evaluated for the IARC Monograph [14] found an increased risk of ALL with maternal occupational exposure to the broad category of 'chemicals' which, in addition to paints, included petroleum products and other unspecified chemicals, with 4.8% of case and 2.2% of control mothers classified as exposed. Thus the different finding could be related to exposures other than paints.

The only previous study which reported an increased risk with AML [8] also used self-reported paint exposures to assign exposure with 15% of case mothers and 9% of control mothers reporting exposure, thus the concerns about recall bias could also apply.

Recruiting control subjects who are representative of the source population from which the cases are drawn is one of the greatest challenges in case-control studies[37]. Each of the original studies had chosen what was thought to be the most appropriate source and method to recruit such controls in their source population at the time the study was conducted (Table 1). While most had used individually matched controls, others had used frequency matching and the ratio of cases to controls varied. In order to pool the data, we decided to break the original matching, but we adjusted for the main matching factors (age and sex) in the analyses and as well tested the relevance of other individual study matching factors such as geographical region. Breaking the individual matching allowed us to use all available cases and controls with still controlling for possible confounding. This approach had already been used in the analyses of some of the original studies we pooled and shown to keep the validity of the study findings.

The major strength of this current investigation was the large sample size and access to the original data to harmonize exposure assessment and categories. Despite this, the analyses of paternal exposure by sub-type of leukemia lacked statistical power.

Another major strength was that all studies collected information about the jobs held, rather than directly about exposure, a method which, as we have noted above, is more prone to recall bias. The studies that included more probing questions about paint use, asked these in a structured manner only after the job information had been obtained. In addition, paint exposure was assigned blinded to case control status of subjects, whether this was done in

the original study or during the current investigation. However, there were methodological challenges because of the different forms of occupational exposure data provided by different CLIC studies. In order to harmonize the data, a crude measure of exposure was developed. For most studies, we had only job title information coded in different formats. Most of the job titles that we included in the 'High likelihood of paint exposure' category had the words 'paint or 'painter' in the title, thus we can assume they were exposed to paint. However, we may have missed other individuals with high levels of paint exposure who had other job titles. The proportion of controls categorized in the 'High likelihood of paint exposure' was generally lower in studies where exposure was based on job title than in the four studies which assigned exposure using more discriminatory methods. When we lowered the cut off for 'High likelihood of paint exposure', our findings were unchanged, but as we expect to have increased the amount of misclassification in the exposure variable (in particular more false positives), caution is warranted as the increased level of non differential measurement error may have biased these findings towards the null.

Despite these limitations, the estimates obtained for paternal exposure and both ALL and AML using studies that had used coded job titles were similar to the four studies that used other methods of occupational assessment. It is unlikely that all people would have the same level of exposure in all industries and that exposures would have been similar across all the study populations (North America, Europe and Australasia) and over time (30 years). The types of paints used would have varied by industry and the composition of paints would have changed over time. For example, in the mid 1990's, changes to government legislation resulted in a reduction in the volatile organic compounds allowed in paints in many countries such as the United States [32], and United Kingdom [33]. However our findings were similar for fathers of children born before 1996 and those born in or after 1996.

The focus of our study was parental occupational exposure and not exposure in the home. In the home, paint exposure can occur in two ways. Firstly, a person can be exposed by the individual using paint themselves. Secondly, they can also be exposed by spending time in an environment where paint had recently been used, such as living in a freshly painted house. While the level of exposure may be lower, the exposure can extend over a prolonged time period [38]. In addition, it may also be more common as a Danish cohort study reported that 45% of pregnant women were exposed to paint fumes in the home [39].

In conclusion, we found no association between parental occupational exposure to paints and the risk of childhood leukemia, including among disease subgroups for fathers. Our null findings for maternal exposure were based on small numbers, but as there was some evidence of an increased risk with low levels of exposure in one of the studies, further investigations using detailed occupational assessments are needed as are data on home exposures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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COG: The E14 and E15 cohorts of the Children's Oncology Group was identified by CCG (Children's Cancer Group) principle and affiliate member institutions. Further information can be found on the web-site: http://www.curesearch.org/.

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Abbreviations

ALL	acute lymphoblastic leukemia
AML	acute myeloid leukemia
Aus-ALL	Australian Study of Causes of Acute Lymphoblastic Leukaemia in Children
CI	Confidence interval
CLIC	Childhood Leukemia International Consortium
COG	Childhood Oncology Group (Children's Cancer Group)
ESCALE	Epidemiological Study on childhood Cancer and Leukemia
GCCR	German Childhood Cancer Registry
ISCO	International Standard Classification for Occupation
JEM	Job Exposure Matrix
NARECHEM	Nationwide Registration for Childhood Haemotological Malignancies
NCCLS	Northern California Childhood Leukemia Study (USA)
NEC	Not else classified

NZCCS	New Zealand Childhood Cancer Study
OR	Odds ratio
RDD	random digit dialling
SETIL	Italian Multicentric Epidemiological Study on Risk Factors for Childhood Leukaemia and Non-Hodgkin's Lymphoma
UKCCS	United Kingdom Childhood Cancer Study

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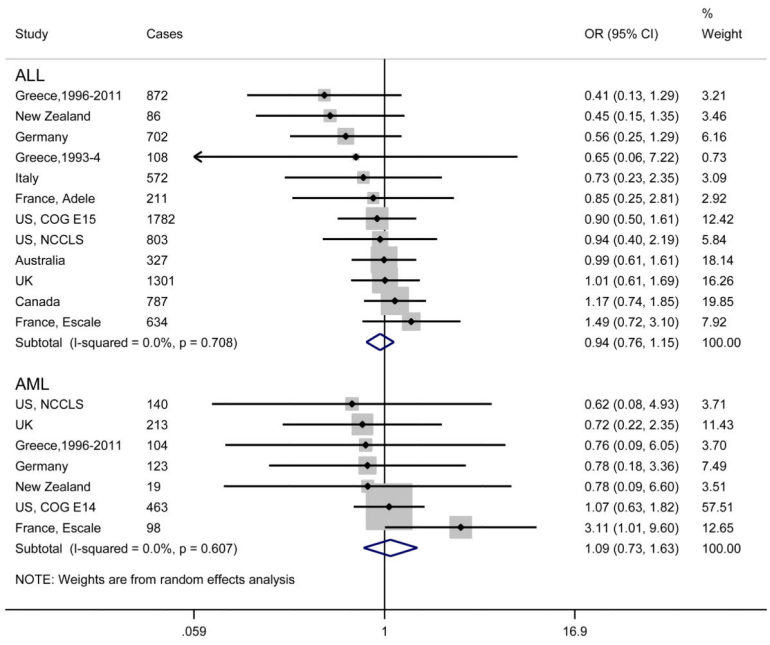

Figure 1.

Forest plot showing individual and summary odds ratios for paternal occupational paint exposure and the risk of ALL and AML in the offspring (comparing ‘Highly likely to be exposed’ group to ‘Unlikely to be exposed’ group (reference), using random effects models.

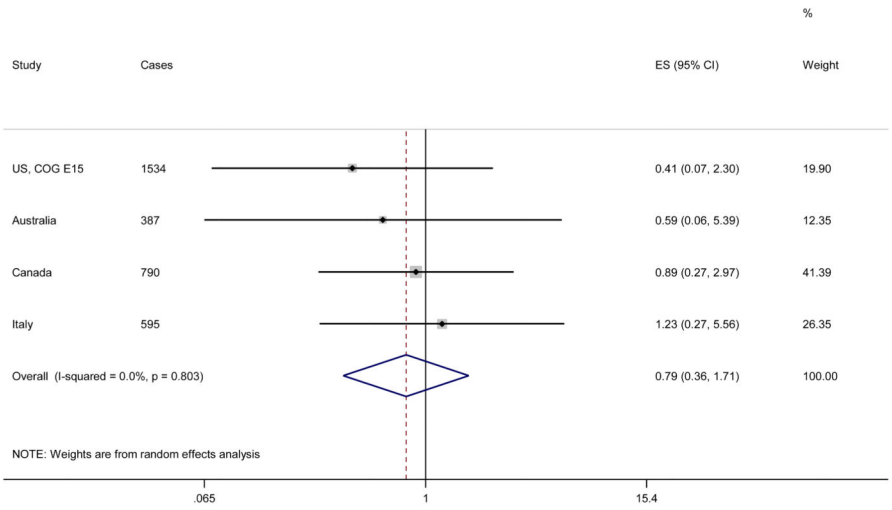

Figure 2.

Forest plot showing individual and summary odds ratios for maternal occupational paint exposure during pregnancy and the risk of ALL in the offspring (comparing ‘Highly likely to be exposed’ group to ‘Unlikely to be exposed’ group (reference), using random effects model.

Table 1

Details of occupational exposure assessment in the 13 studies in the CLIC pooled analyses of parental occupational paint exposure and the risk of leukemia in the offspring

Country, Study (years of case accrual)	Method of occupational assessment	Case			Control			Time period(s) of interest[1],	Scope of assessment	Final exposure variable[2]	Prevalence of 'High likelihood of paint exposure' amongst controls		Source of conversion tool to other Occupational Classifications (where applicable)
		Source	Participation[c]	N[d]	Source & type of matching	Participation[3]	N[4]				Mothers	Fathers	
1. Use of an Occupational Classification System													
France, ADELE (1993–1999)	ISCO 1988	Hospitals	95%	ALL: 240 AML: 36	Hospitals (same as cases) Frequency matched	99%	288	Extracted from work history (start & end year of each job) **1** Main year before conception (defined as the year of the mid point of the year before conception) **2** Main year of pregnancy (defined as the year of the midpoint of the pregnancy)	All jobs held in time periods	4 level 1. 'High likelihood of paint exposure' 2. 'Moderate likelihood of exposure' 3. 'Limited likelihood of exposure' 4 = 'No or minimal likelihood of paint exposure'	0.0	3.0	Correspondence Table ISCO 08 to ISCO 88 [20]
Greece, NARECHEM (1993–1994)	ISCO 1988	Nationwide hospital cancer registry	100%	ALL; 140 AML: 13	Hospital Individual matched	96%	300	**1** One year before birth **2** During pregnancy	All jobs held in time periods	As above	0.0	1.3	Correspondence Table ISCO 08 to ISCO 88 [20]
France ESCALE (2003–2004)	ISCO 1968	Population-based cancer registry (nationwide)	91%	ALL: 648 AML: 101	Population quotas by age, sex, region (nationwide) Frequency matched	71%	1681	**1** During pregnancy[5]	Main job in time period	As above	0.0	1.2	Correspondence Table ISCO 68 to ISCO 88 [21]

Country, Study (years of case accrual)	Method of occupational assessment	Case			Control			Time period(s) of interest[1],	Scope of assessment	Final exposure variable[2]	Prevalence of 'High likelihood of paint exposure' amongst controls		Source of conversion tool to other Occupational Classifications (where applicable)
		Source	Participation[c]	N[d]	Source & type of matching	Participation[3]	N[4]				Mothers	Fathers	
Greece, NARECHEM (1996–2010)	ISCO 1968	Nationwide hospital cancer registry	83%	ALL: 964 AML: 113	Hospital Individual matched	96%	1085	**1** One year before birth **2** During pregnancy	All jobs held in time periods	As above	0.0	1.1	Correspondence Table ISCO 68 to ISCO 88 [21]
Italy, SETIL (1998–2001)	ISCO 1968	Nationwide clinical database	91%	ALL: 601 AML: 32	Population-based National Health Service Registry	70%	1044	Extracted from work history (start & end year of each job) **1** Main year before conception (defined as the year of the mid point of the year before conception) **2** Main year of pregnancy (defined as the year of the midpoint of the pregnancy)	All jobs held in time periods	As above	0.4	1.0	Correspondence Table ISCO 68 to ISCO 88 [21]
Germany, GCCR (1988–1994)	Germany, Bundesgentur fur Abeit Wirtschaftsklasse 1988	Population-based cancer registry (nationwide)	82%	ALL: 751 AML: 130	Population-based registry (community based but complete nationwide coverage) Individual matched	71%	2458	**1** Conception **2** During pregnancy	Main job in time periods	As above	<0.1	1.5	Correspondence Table to ISCO 88 obtained from Federal Statistical Office, Germany [22]
UK, UKCCS (1991–1996)	UK, Standard Occupational Classification 1990	Population-based tailored referral systems	93%	ALL: 1461 AML: 248	GP registries (nationwide) Individual matched	64%	3448	**1** Around conception **2** During pregnancy	All jobs held in time periods	As above	0.0	1.7	Correspondence Table to ISCO 88 obtained from Office for National Statistics, UK [23]

Country, Study (years of case accrual)	Method of occupational assessment	Case			Control			Time period(s) of interest[1],	Scope of assessment	Final exposure variable[2]	Prevalence of 'High likelihood of paint exposure' amongst controls		Source of conversion tool to other Occupational Classifications (where applicable)
		Source	Participation[c]	N[d]	Source & type of matching	Participation[3]	N[4]				Mothers	Fathers	
US, NCCLS (1995–2008)	US, Census Occupational Classification Codes, 1990	Hospitals	86%	ALL: 840 AML: 145	Birth registry (statewide) Individual matched	68%	1226	Extracted from work history (start and end month, year of each job) **1** Year before conception **2** During pregnancy	All jobs held in time periods	As above	0.1	1.2	Correspondence Tables obtained from the National Crosswalk Center [24] between 1990 Census to 2000 Census codes and 2000 Census codes to ISCO 88
US, COG-E15 (1989–1993)	US, Department of Lab or Dictionary of Occupational Titles (4th ed., rev. 1991)	Children's Cancer Group clinical trials	87%	ALL: 1914	RDD Individual matched	70%	1987	Extracted from work history (start and end month, year of each job) **1** Year before conception **2** During pregnancy	All jobs held in time periods	As above	0.2	1.4	Correspondence Tables obtained from the National Crosswalk Center [24] between DOT to 2000 Census codes and 2000 Census codes to ISCO 88
2. Paint exposure already assigned													
Australia, Aus-ALL [11] (2003–2007)	Answers to initial structured questionnaire and follow-up job specific interview reviewed by expert[14]	Hospitals (nationwide)	75%	ALL: 389	RDD Frequency matched	64 % of agreed controls	876	**1** One year before birth	All jobs held in time period	3 level: 1 = medium/ high exposure 2 = low expo sure 4 = not exposed	0.5	7.5	
Canada, Quebec [16] (1980–2000)	Answers to initial structured interview and	Hospitals (province wide)	93%	ALL: 790	Health Insurance file population-	86%	790	**1** Two years before conception	All jobs held in	3 level:	0.8	4.6	

Country, Study (years of case accrual)	Method of occupational assessment	Case			Control			Time period(s) of interest[1],		Scope of assessment	Final exposure variable[2]	Prevalence of 'High likelihood of paint exposure' amongst controls		Source of conversion tool to other Occupational Classifications (where applicable)
		Source	Participation[c]	N[d]	Source & type of matching	Participation[3]	N[4]					Mothers	Fathers	
	follow-up job specific questions reviewed by expert[12,16]				based registry (province-wide.) Individual matched			**2**	During pregnancy	time periods	1 = greater exposure 2= some exposure 4 = not exposed			
New Zealand, NZCCS (1990–1993)	Exposure assignment based on detailed questionnaire and interview about paint exposures in each job	Regis try (nationwide)	92%	ALL: 97 AML: 22	Birth registry (nation wide) Individual matched	69%	303	**1**	Two years before birth (No maternal exposure data available)	All jobs held in time periods	2 level: 1 = exposed 4 = not exposed	NA	11.4	
3. Paint exposure data collected, but exposure not assigned														
US, COG-E14 (1988–1993)	Detailed questionnaire about each type of paint use in each job	Children's Cancer Group clinical trials	76%	AML: 517	RDD Individual matched	72%	610	Extracted from work history (start and end month, year of each job) **1** Year before conception **2** During pregnancy		All jobs held in time periods	4 level: Tertiles of exposure[6] 1 = 'High' 2 = 'Medium' 3 = 'Low' 4 = unexposed	0.8	6.2	

[1] The time periods of interest were 1. Around conception for the father and 2. During pregnancy for the mother.

[2] In the final pooling process, a 4 level variable was used, but levels 2 and or 3 were empty for studies with less than 4 categories.

[3] Participation fractions are based on information available from published studies or obtained directly from study personnel. Definition of the participation fraction may vary across studies.

[4] Occupational histories were available for more than 90% of parents. The numbers of mothers and fathers with occupational histories are in Supplementary Table 5.

[5] In France ESCALE, paternal exposure during pregnancy was used as a proxy for paternal exposure at conception as these data were not available.

[6] Based on tertiles of the total time any paint was in the air the subject or on the skin/clothing during time period among exposed control mothers and fathers.

ISCO: International Standard Classification for Occupation

RDD: random digit dialing

Table 2

Demographic characteristics of participants in the CLIC pooled analyses of parental occupational paint exposure and the risk of leukemia in the offspring

	ALL (12 studies)				AML (10 studies)			
	Case (n= 8835)		Control[1] (n = 15486)		Case (n= 1357)		Control[2] (n= 12443)	
	n	%[3]	n	%[3]	n	%[3]	n	%[3]
Sex								
Boy	4972	*56.3*	8634	*55.8*	713	*52.5*	6928	*55.7*
Girl	3863	*43.7*	6852	*44.2*	644	*47.5*	5515	*44.3*
Age (years)[4]								
0–1	958	*10.8*	2272	*14.7*	376	*27.7*	2000	*16.1*
2–4	4109	*46.5*	6156	*39.8*	259	*19.1*	4610	*37.0*
5–9	2570	*29.1*	4507	*29.1*	313	*23.1*	3526	*28.3*
10–14	1198	*13.6*	2551	*16.5*	342	*25.2*	2231	*17.9*
15–17	0	*0.0*	0	*0.0*	67	*4.9*	76	*0.6*
Year of birth								
1970–1978	294	*3.3*	395	*2.6*	151	*11.1*	289	*2.3*
1979–1987	2555	*28.9*	4318	*27.9*	426	*31.4*	2943	*23.7*
1988–1996	3927	*44.5*	7226	*46.7*	578	*42.6*	6350	*51.0*
1997–2005	1936	*21.9*	3394	*21.9*	175	*12.9*	2710	*21.8*
2006–2011	123	*1.4*	153	*1.0*	27	*2.0*	151	*1.2*
Child has Down Syndrome								
Yes	103	*1.2*	6	*<0.1*	89	*6.6*	4	*<0.1*
No	8730	*98.8*	15479	*100.0*	1267	*93.4*	12438	*100.0*
Missing	2	*0.0*	1	*0.0*	1	*0.1*	1	*0.0*
Maternal education								
Did not finish secondary education	2327	*26.3*	3950	*25.5*	322	*23.7*	3479	*28.0*
Completed secondary education	3859	*43.7*	6619	*42.7*	664	*48.9*	5098	*41.0*
Tertiary education	2588	*29.3*	4756	*30.7*	358	*26.4*	3706	*29.8*
Missing	61	*0.7*	161	*1.0*	13	*1.0*	160	*1.3*
Paternal education								

	ALL (12 studies)				AML (10 studies)			
	Case (n= 8835)		Control[1] (n = 15486)		Case (n= 1357)		Control[2] (n= 12443)	
	n	%[3]	n	%[3]	n	%[3]	n	%[3]
Did not finish secondary education	2420	*27.4*	4266	*27.5*	349	*25.7*	3847	*30.9*
Completed secondary education	3341	*37.8*	5400	*34.9*	559	*41.2*	4095	*32.9*
Tertiary education	2579	*29.2*	4757	*30.7*	348	*25.6*	3708	*29.8*
Missing	495	*5.6*	1063	*6.9*	101	*7.4*	793	*6.4*
Maternal occupational paint exposure data during pregnancy available	8156	*92.3*	14568	*94.1*	1309	*96.5*	11859	*95.3*
Paternal occupational paint exposure data around conception available	8185	*92.6*	14210	*91.8*	1231	*90.7*	11392	*91.6*
Occupational paint exposure data available for both parents	7610	*86.1*	13421	*86.7*	1192	*87.8*	10901	*87.6*

[1]Includes controls from all studies with ALL cases (that is, all studies except US, COG-E14).

[2]Includes controls from all studies with AML cases (that is, all studies except Australia, Aus-ALL, Canada, Quebec and US, COG-E15).

[3]All percentages have been rounded to one decimal place and thus the totals may range from 99.9%–100.1%

[4]Age groups are based on the child's age at the censoring date. For case, this was the date at diagnosis and for controls, it was the date that the study investigators nominated (either the date of recruitment or the date of the questionnaire return).

Table 3

Pooled OR (95% CI) for the association between paternal occupational exposures to paint and the risk of leukaemia in the offspring: Overall and by subgroups

	Paternal exposures around conception		
	Total N Case/Controls	**% in High likelihood of exposure group**	**OR[1,2], (95% CI)**
1. ALL			
Overall	8185/14210	2.0/2.1	0.93 (0.76, 1.14)
Immunophenotype			
B-lineage cases	6457/14210	2.1/2.1	0.93 (0.75, 1.15)
T-lineage cases	826/14210	2.1/1.7	0.80 (0.46,1.39)
Age at diagnosis			
Less than 5 years	4750/7826	2.3/2.1	1.05 (0.81, 1.36)
5 or more years	3435/6384	1.7/2.2	0.78 (0.56, 1.08)
			Interaction *p* value = 0.45
Sex			
Girls	3587/6276	2.0/2.1	0.97 (0.71, 1.31)
Boys	4598/7934	2.0/2.1	0.90 (0.69, 1.18)
			Interaction *p* value = 0.12
Child's birth year			
Before 1996	5961/10385	2.0/2.1	0.88 (0.69, 1.11)
1996 or later	2224/3825	2.0/2.1	1.08 (0.74, 1.57)
			Interaction *p* value =0.74
Type of occupational assessment			
Assessment based on expert assessment[3]	1114/1536	6.2/6.0	1.13 (0.81,1.58)
Assessment based on coded job titles[4]	6935/12384	1.3/1.4	0.87 (0.67,1.14)
			Interaction *p* value =0.29
2. AML			
Overall	1231/11392	3.3/1.9	0.96 (0.65,1.41)
Age at diagnosis			
Less than 5 years	584/6118	3.3/1.8	0.96 (0.54, 1.73)
5 or more years	647/5274	3.4/2.0	0.90 (0.53,1.53)
			Interaction *p* value = 0.68
Sex			
Girls	588/5034	3.1/2.0	0.77 (0.43, 1.37)
Boys	643/6358	3.6/1.8	1.17 (0.69, 1.98)
			Interaction *p* value = 0.43
Child's birth year			
Before 1996	1008/8235	3.8/2.2	0.96 (0.64, 1.44)
1996 or later	223/3157	1.3/1.0	1.21 (0.36, 4.11)
			Interaction *p* value = 0.69
Type of occupational assessment			

	Paternal exposures around conception		
	Total N Case/Controls	**% in High likelihood of exposure group**	**OR[1,2], (95% CI)**
Assessment not based on coded job titles[5]	482/808	6.0/8.0	0.96 (0.58, 1.59)
Assessment based on coded job titles[6]	749/10584	1.6/1.4	0.94 (0.52, 1.72)
			Interaction *p* value = 0.46

[1] OR comparing Group 1 (High likelihood of paint exposure) to reference group 4 (No or minimal likelihood of paint exposure)

[2] Adjusted for age, sex, birth year group, study and paternal education

[3] Australia (Aus-ALL), Canada.

[4] France (ADELE & ESCALE), Greece (NARECHEM 1993–1994 & 1996–2011), Germany (GCCR), Italy (SETIL), UK (UKCCS), US (COG-E15) US, NCCLS. See Table 1 for details of the Occupational coding system.

[5] New Zealand (NZCCS), US (COG (CCG-E14).

[6] France (ADELE & ESCALE), Greece (NARECHEM 1993–1994 & 1996–2011), Germany (GCCR), Italy (SETIL), UK (UKCCS), US (COG-E14) US, NCCLS. See Table 1 for details of the Occupational coding system.

Table 4

Sensitivity analyses using different definitions of 'High likelihood of paint exposure'

	ALL			AML		
	Total N Case/Controls	**% in High likelihood of exposure group**	**OR[1,2], (95% CI)**	**Total N Case/Controls**	**% in High likelihood of exposure group**	**OR[1,2], (95% CI)**
Fathers						
Original exposure[3] variable	8185/14210	2.0/2.1	0.93 (0.76, 1.14)	1231/11392	3.3/1.9	0.96 (0.65,1.41)
Sensitivity 1[4]	8185/14210	7.4/8.2	0.92 (0.82, 1.02)	1231/11392	7.6/8.6	0.92 (0.72, 1.17)
Sensitivity 2[5]	8185/14210	5.7/6.3	0.90 (0.80, 1.02)	1231/11392	6.7/6.7	0.95 (0.73, 1.24)
Mothers						
Original exposure variable[3]	8156/14568	0.16/0.14	0.81 (0.39, 1.68)			Not presented as only 1 study with cases in exposure group
Sensitivity 1[4]	1309/11859	0.8/0.6	0.99 (0.70, 1.41)	1309/11859	0.8/0.6	1.07 (0.52, 2.21)
Sensitivity 2[5]	1309/11859	0.5/0.4	1.00 (0.65, 1.56)	1309/11859	0.5/2.4	0.88 (0.34, 2.30)

[1] OR comparing Group 1 (High likelihood of paint exposure) to reference group 4 (No or minimal likelihood of paint exposure)

[2] Adjusted for age, sex, birth year group, study and education of the relevant parent

[3] 'High likelihood of paint exposure' based on original comparison of expert assessment and job codes where 70% or more people with job code assessed as exposed to paint.

[4] 'High likelihood of paint exposure' based on original comparison of expert assessment and job codes where 25% or more people with job code assessed as exposed to paint.

[5] 'High likelihood of paint exposure' based on original comparison of expert assessment and job codes where 35% or more people with job code assessed as exposed to paint.