Open access • Journal Article • DOI:10.1136/OEMED-2012-100951

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Published on: 01 Sep 2013 - Occupational and Environmental Medicine (Occup Environ Med)

Topics: Paternal Exposure

OEM Online First, published on June 1, 2013 as 10.1136/oemed-2012-100951

ORIGINAL ARTICLE

Risk of childhood leukaemia and non-Hodgkin's lymphoma after parental occupational exposure to solvents and other agents: the SETIL Study

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Received 25 May 2012
Revised 15 April 2013
Accepted 30 April 2013

ABSTRACT

Aim In the context of the Italian Multicentric Epidemiological Study on Risk Factors for Childhood Leukaemia and Non-Hodgkin's Lymphoma (SETIL), the risk of childhood cancer was investigated in relation to parental occupational exposures.

Methods All cases of childhood leukaemia and non-Hodgkin's lymphoma (NHL) in children aged 0–10 years were identified. Controls were chosen at random from the local population in each region. Parents were interviewed using a structured questionnaire. The collected data were blindly reviewed by expert industrial hygienists in order to estimate exposure to a list of agents. Statistical analyses were performed for each agent using unconditional multivariable logistic regression models, taking into account timing of exposure.

Results 683 cases of acute childhood leukaemia, 97 cases of NHL and 1044 controls were identified. Increased risk of childhood leukaemia was found for maternal exposure to aliphatic (OR 4.3) or aromatic hydrocarbons (OR 3.8) in the preconception period, and for paternal exposure to diesel exhaust (OR 1.4), lead exposure (OR 1.4) and mineral oils (OR 1.7). Risk of NHL appeared to be related to paternal exposure to oxygenated solvents (OR 2.5) and petrol exhaust (OR 2.2).

Conclusions We found increased risk for childhood leukaemia associated with maternal occupational exposure to aromatic and aliphatic hydrocarbons, particularly in the preconception period; increased risks were also observed for paternal exposure to diesel exhaust fumes, mineral oils and lead. The risk of NHL appeared to be related to paternal exposure to oxygenated solvent and petrol exhausts.

What this paper adds

- Occupational parental exposure might be related to childhood cancer; paternal occupational exposures have received more attention than maternal exposures.
- SETIL is a large epidemiological case–control study which provides an opportunity to investigate the risk of childhood cancers in relation to parental occupational exposure using one of the best methods to define exposure in the context of case–control studies.
- Results indicate increased childhood leukaemia risk with maternal exposure to occupational aliphatic and aromatic hydrocarbons and paternal exposure to diesel exhaust, lead and mineral oil.
- Maternal exposure to toluene, xylene and benzene was also associated with increasing risk, while paternal petrol exhaust exposure was associated with NHL.
- There is widespread exposure to solvents and exhausts, which are prevalent in many human activities and also in the general environment, so the present results are important from a public health point of view.

INTRODUCTION

The aetiology of childhood neoplasms is poorly understood. Indeed, for childhood leukaemia, the most common childhood cancer, the only established risk factor is prenatal or childhood exposure to ionising radiation. Several possible risk factors have been investigated, such as the power frequency and radiofrequency of electromagnetic fields, pesticide exposure, infectious agents, immunisation and related factors, and parental occupational exposure.[1 2]

Epidemiological studies have shown a possible increasing risk of childhood cancer associated with parental occupational exposure to a variety of agents, suggesting that parental workplace exposure to hazardous chemicals is a potentially important risk factor.[1]

Fabia and Thuy[3] first reported that paternal occupations involving hydrocarbon exposure were associated with an increasing risk of childhood cancer, particularly leukaemia. Subsequently, other studies

To cite: Miligi L, Benvenuti A, Mattioli S, *et al*. *Occup Environ Med* Published Online First: [*please include* Day Month Year] doi:10.1136/oemed-2012-100951

reported an association between childhood leukaemia and paternal exposure to solvents, paints, pigments, plastic materials and inhaled particulate hydrocarbons[4–9] and maternal exposure to solvents, paints and thinners, [7 10 11] but these results have not always been corroborated.[12 13]

The lack of consistent evidence may be due to different study designs, lack of power to detect associations, the quality of exposure assessment and ill defined timing of exposure. The more recent studies are designed to improve these limitations particularly as regards defining exposures.[9–11]

Studies on parental occupational exposure require a clear definition of the time windows of exposure. Occupational parental exposure could contribute to the risk of childhood cancer through different mechanisms including damage to germ cells in the preconception period, to the embryo or the fetus during pregnancy through transplacental transmission, and directly to the child during the postnatal period through breast milk contamination or environmental contamination carried home by parents from the workplace.

In the context of the Italian multicentre, population based, case–control study on risk factors for childhood leukaemia and NHL, the risk of these cancers in relation to parental occupational exposures was investigated and the results for childhood leukaemia and NHL are presented here.

METHODS

The SETIL study is an Italian epidemiological multicentre, population based, case–control study on risk factors for childhood cancers.

Case and control recruitment

All newly diagnosed cases of leukaemia and NHL which occurred in children aged 0–10 years during the period 1998–2001 were identified. Cases were recruited in the paediatric oncology centres associated with the Association of Paediatric Haematology and Oncology (AIEOP), the Italian network of childhood cancer centres. All cases of paediatric neoplasms in children aged 0–14 are recorded when the child is first admitted to any AIEOP unit as either an inpatient or an outpatient. Data are collected using a common registration form which includes the patient's personal identification data, in addition to diagnosis and treatment information. Each new patient is registered by means of electronic case report forms in the AIEOP 'Mod.1.01 Registry' database hosted on the AIEOP website (www.aieop.org) and maintained in collaboration with the Inter-university Computing Centre (CINECA) in Bologna. A list of children eligible for the study was provided monthly on the AIEOP database by each regional research unit. It was estimated that over 95% of Italian children affected by one of the diseases considered for the SETIL study were treated in one of the centres connected to the AIEOP network during the study period.[14]

Controls were chosen at random from the local population in each region, using the national health service records. Two controls were randomly sampled for each childhood leukaemia case, matched for gender, date of birth, and area of residence. The resulting set of controls was also used as a pool in the side study on NHL.

Data collection and exposure assessment

Study subjects' parents were interviewed by trained interviewers using a structured questionnaire. The items included were: parental educational level, personal medical history, exposure to chemical substances at home and in the environment, maternal and child's exposure to electrical appliances in the home, school attendance, and child's lifelong and maternal (during pregnancy) residential history.

Regarding occupational history, information was collected at two levels: (a) the first was based on the standardised collection of a complete work history; and (b) the second consisted of the collection of more specific and detailed information on each job through the use of job specific questionnaires (JSQs).

The collected data were blindly reviewed by expert industrial hygienists (one or two for each area) to estimate exposure to a list of agents.

All experts had experience in industrial hygiene for industries located in the study areas from which the study subjects were drawn. Furthermore, they also had experience in retrospective exposure assessment and most of them had participated in another multicentre Italian study.[15] To ensure a standardised approach, the assessors were trained prior to (and periodically during) their independent evaluations of questionnaires and a training session was conducted before the job histories were reviewed. In order to reduce variability among experts, a job–exposure matrix developed for the previous study[15] and based on the minimum overall consensus for the most frequent job titles/sectors in the study areas, was used as baseline for individual exposure assessment. Protocols and specific guideline were also developed for assessing the different agents.

Exposures were rated on two scales: 'probability' represented the likelihood of exposure based on knowledge of the materials used and technologies applied in the particular activity/production process reported in a given calendar period; it was classified into three levels: low, medium and high. The second scale was 'intensity', which represented the estimated concentration of the agent in the work environment and was measured on a 4-point scale: very low, low, medium and high. Parental occupational exposures were assessed with reference to three time windows: 1 year before conception, during pregnancy, and from date of child's birth to diagnosis.

Exposure was estimated for classes of solvents and of other chemicals as well as certain individual substances or agents. The experts considered the following categories: a general category 'solvents' and the following specific categories: aromatic hydrocarbons, aliphatic hydrocarbons, chlorinated hydrocarbons, technical hydrocarbons and oxygenated derivatives of hydrocarbons. Furthermore, when there was sufficient information for assessing individual chemicals, the experts made exposure judgments for the following: benzene, styrene, xylene and toluene; dichloromethane, tetrachloroethylene, trichloroethylene, 1,1,1-trichloroethane and chloroform; and 1,4-dioxane. No specific individual agent was assessed for technical hydrocarbons (category including solvent naphtha, petroleum solvents, kerosene, etc).

Exposure to diesel and petrol exhaust, polycyclic aromatic hydrocarbons, bitumen, chromium, lead and nickel was also assessed.

Statistical analyses

The analyses were performed for each agent, separately for maternal and paternal exposures and for leukaemia and NHL. Only exposure periods with medium or high assigned probability of exposure were considered, for all levels of intensity and for different time windows using unconditional multivariable logistic regression models, taking into account design variables (sex, age, area). Point estimates of ORs and their corresponding CIs (95% CI) were calculated. Where the numbers were sufficient, analyses by acute lymphoblastic leukaemia (ALL) and acute non-lymphoblastic leukaemia (AnLL) and for immunophenotype (T cell and pre-B cell ALL) were performed. All

exposures were analysed with respect to the entire period from 1 year before conception to diagnosis and in the three different time windows. When data were sufficient, we also analysed intensity of exposure considering two classes of exposure: very low/low and medium/high. Parents who were never exposed to any of the listed chemicals were used as the referent population separately for leukaemia and NHL.

Possible confounding factors were considered, such as the mother's age at childbirth and level of education, but were not considered in the final model as we observed no difference in the magnitude of risk estimates.

RESULTS

A total of 683 leukaemia and 97 NHL cases and 1044 controls were interviewed. Participation rate was 91.4% for leukaemia, 83.6% for NHL and 69.2% for the control group. Among childhood leukaemia cases, 601 were ALL and 82 AnLL.

Solvent exposure

In table 1, adjusted ORs for maternal exposures to the general category of 'solvents' and to chemical classes of solvents are shown. An increased risk of childhood leukaemia was observed among children whose mothers were exposed to aromatic (OR 1.8) or aliphatic hydrocarbons (OR 2.4). Considering individual chemicals (data not shown in the table), a non-statistically significant increased risk of leukaemia was observed for mothers exposed to benzene (OR 3.1, 95% CI 0.8 to 12.4; 6 exposed cases), toluene (OR 1.8, 95% CI 0.8 to 4.0; 14 exposed cases) and xylene (OR 2.0, 95% CI 0.9 to 4.7; 13 exposed cases).

There was some correlation among chemicals. For instance, 63% of mothers exposed to aliphatic hydrocarbons were also exposed to aromatic hydrocarbons; 86% of mothers exposed to toluene were also exposed to xylene. Finally, an OR of 2.6 (95% CI 1.1 to 6.0; 15 exposed cases) was observed for mothers exposed to both aliphatic and aromatic hydrocarbons in the period from 1 year before pregnancy to diagnosis; for exposure to both toluene and xylene the OR was 2.0 (95% CI 0.9 to 4.7; 13 exposed cases).

Considering specific critical time windows, we found a statistically significant increased risk for childhood leukaemia after maternal exposure in the period '1 year before conception' to aliphatic (OR 4.3) and aromatic hydrocarbons (OR 3.8) and to oxygenated derivatives of hydrocarbons (OR 1.9). Increase risk was also observed for exposure during pregnancy (table 1). When individual solvents were considered, a higher risk was found in the preconception period for toluene (OR 4.3, 95% CI 1.4 to 13.7; 11 exposed cases) and xylene (OR 7.8, 95% CI 1.7 to 35.9; 10 exposed cases).

There was little or no evidence that paternal exposure to solvents was associated with childhood leukaemia risk in any time window (table 2). A non-statistically significant increased risk was observed for paternal exposure to styrene (OR 1.7, 95% CI 0.7 to 4.3; 10 exposed cases) and dichloromethane (OR 1.5, 95% CI 0.7 to 3.2; 14 exposed cases) with higher ORs during pregnancy and in the postnatal period.

Regarding ALL, maternal exposure to aliphatic hydrocarbons was significantly associated with the cancer, with the highest risk observed for exposure in the preconception period (OR 4.2) (table 1). Maternal exposure to aromatic hydrocarbons was also associated with an elevated risk of ALL but only the point

Table 1 SETIL study results for maternal exposure

		Leukaemia				ALL				AnLL			
Solvents	Time period*	Exp. cases	Exp. controls	OR	95% CI	Exp. cases	Exp. controls	OR	95% CI	Exp. cases	Exp. controls	OR	95% CI
Any solvent	Ever	58	80	1.1	0.8 to 1.6	48	80	1.3	0.6 to 2.8	10	80	1.8	0.9 to 3.6
	Preconception	46	52	1.4	0.9 to 2.1	39	52	1.3	0.9 to 2.0	7	52	1.8	0.8 to 4.2
	Pregnancy	43	55	1.2	0.8 to 1.8	36	55	1.1	0.7 to 1.8	7	55	1.7	0.8 to 4.0
	Postnatal	49	74	1.0	0.7 to 1.5	41	74	1.0	0.6 to 1.4	8	74	1.5	0.7 to 3.3
Aromatic	Ever	21	18	1.8	1.0 to 3.4	18	18	1.8	0.9 to 3.5	3	18	2.0	0.6 to 7.0
hydrocarbons	Preconception	17	7	3.8	1.6 to 9.2	15	7	3.8	1.5 to 9.5	2	7	3.2	0.6 to 16.0
	Pregnancy	14	10	2.2	1.0 to 4.9	12	10	2.2	0.9 to 5.0	2	10	2.3	0.5 to 10.6
	Postnatal	17	17	1.6	0.8 to 3.1	14	17	1.5	0.7 to 3.0	3	17	2.1	0.6 to 7.6
Chlorinated	Ever	24	33	1.1	0.7 to 1.9	19	33	1.0	0.6 to 1.8	5	33	2.1	0.8 to 5.6
hydrocarbons	Preconception	19	21	1.4	0.7 to 2.6	16	21	1.3	0.7 to 2.6	3	21	1.9	0.5 to 6.8
	Pregnancy	18	20	1.4	0.7 to 2.6	15	20	1.3	0.7 to 2.6	3	20	2.1	0.6 to 7.4
	Postnatal	19	29	1.0	0.6 to 1.8	16	29	0.9	0.5 to 1.8	3	29	1.4	0.4 to 4.7
Oxygenated	Ever	34	45	1.2	0.7 to 1.9	29	45	1.2	0.7 to 1.9	5	45	1.4	0.5 to 3.6
derivatives of	Preconception	32	27	1.9	1.1 to 3.2	27	27	1.8	1.0 to 3.1	5	27	2.3	0.9 to 6.4
hydrocarbons	Pregnancy	28	26	1.7	1.0 to 2.9	23	26	1.6	0.9 to 2.8	5	26	2.4	0.9 to 6.6
	Postnatal	29	39	1.2	0.7 to 1.9	24	39	1.1	0.6 to 1.8	5	39	1.6	0.6 to 4.3
Aliphatic	Ever	20	13	2.4	1.2 to 4.9	17	13	2.4	1.1 to 5.0	3	13	2.4	0.6 to 8.6
hydrocarbons	Preconception	19	7	4.3	1.8 to 10.4	16	7	4.2	1.7 to 10.3	3	7	4.2	1.0 to 17.2
	Pregnancy	14	9	2.4	1.0 to 2.7	11	9	2.2	0.9 to 5.5	3	9	3.2	0.8 to 12.4
	Postnatal	15	13	1.8	0.9 to 3.9	12	13	1.7	0.8 to 3.7	3	13	2.4	0.6 to 8.6

ORs (adjusted by gender, age and area) and 95% CIs are for leukaemia and leukaemia groups by maternal exposure to selected chemical classes of solvents at all intensity levels where probability of exposure is medium or high.
*Time periods: ever indicates exposed from 1 year before conception to diagnosis; preconception indicates exposure 1 year before conception; pregnancy indicates exposure during pregnancy; and postnatal indicates exposure from date of child's birth to diagnosis.
ALL, acute lymphoblastic leukaemia; AnLL; acute non-lymphoblastic leukaemia; Exp., exposed; SETIL, Italian Multicentric Epidemiological Study on Risk Factors for Childhood Leukaemia and Non-Hodgkin's Lymphoma.

Table 2 SETIL results for paternal exposure

		Leukaemia				ALL				AnLL			
Solvents	Time period*	Exp. cases	Exp. controls	OR	95% CI	Exp. cases	Exp. controls	OR	95% CI	Exp. cases	Exp. controls	OR	95% CI
Any solvent	Ever	131	189	1.1	0.8 to 1.4	117	189	1.1	0.8 to 1.4	14	189	1.0	0.5 to 1.8
	Preconception	113	166	1.1	0.8 to 1.4	100	166	1.1	0.8 to 1.4	13	166	1.0	0.5 to 1.9
	Pregnancy	119	167	1.1	0.9 to 1.4	106	167	1.1	0.9 to 1.5	13	167	1.0	0.5 to 1.9
	Postnatal	128	183	1.1	0.9 to 1.4	114	183	1.1	0.9 to 1.4	14	183	0.9	0.5 to 1.7
Aromatic	Ever	74	98	1.2	0.9 to 1.6	65	98	1.2	0.8 to 1.6	9	98	1.3	0.6 to 2.7
hydrocarbons	Preconception	61	83	1.1	0.8 to 1.6	53	83	1.1	0.8 to 1.6	8	83	1.3	0.6 to 2.9
	Pregnancy	64	86	1.2	0.8 to 1.6	56	86	1.1	0.8 to 1.6	8	86	1.3	0.6 to 2.8
	Postnatal	71	95	1.2	0.8 to 1.6	62	95	1.2	0.8 to 1.6	9	95	1.2	0.6 to 2.5
Chlorinated	Ever	40	61	1.0	0.7 to 1.5	35	61	1.0	0.6 to 1.5	5	61	1.1	0.4 to 2.8
hydrocarbons	Preconception	32	52	0.9	0.6 to 1.5	27	52	0.9	0.5 to 1.4	5	52	1.2	0.5 to 3.3
	Pregnancy	35	52	1.0	0.7 to 1.6	30	52	1.0	0.6 to 1.6	5	52	1.2	0.5 to 3.3
	Postnatal	38	59	1.0	0.7 to 1.5	33	59	1.0	0.6 to 1.5	5	59	1.0	0.4 to 2.7
Aliphatic	Ever	42	69	0.9	0.6 to 1.4	35	69	0.9	0.6 to 1.3	7	69	1.5	0.7 to 3.5
hydrocarbons	Preconception	37	56	1.0	0.7 to 1.6	31	56	0.9	0.6 to 1.5	6	56	1.5	0.6 to 3.8
	Pregnancy	38	60	1.0	0.6 to 1.5	32	60	0.9	0.6 to 1.4	6	60	1.4	0.6 to 3.5
	Postnatal	41	66	1.0	0.6 to 1.4	34	66	0.9	0.6 to 1.4	7	66	1.4	0.6 to 3.2
Technical	Ever	56	92	0.9	0.7 to 1.3	50	92	0.9	0.6 to 1.3	6	92	0.9	0.4 to 2.2
hydrocarbons	Preconception	49	77	1.0	0.7 to 1.4	44	77	1.0	0.7 to 1.4	5	77	0.8	0.3 to 2.2
	Pregnancy	51	80	1.0	0.7 to 1.4	46	80	1.0	0.7 to 1.4	5	80	0.9	0.3 to 2.2
	Postnatal	56	89	1.0	0.7 to 1.4	50	89	1.0	0.7 to 1.4	6	89	0.9	0.4 to 2.1
Oxygenated	Ever	55	75	1.2	0.8 to 1.7	49	75	1.1	0.8 to 1.7	6	75	1.2	0.5 to 2.9
derivatives of	Preconception	52	63	1.3	0.9 to 1.9	47	63	1.3	0.9 to 1.9	5	63	1.2	0.5 to 3.1
hydrocarbons	Pregnancy	52	66	1.2	0.8 to 1.8	47	66	1.2	0.8 to 1.8	5	66	1.1	0.4 to 2.9
	Postnatal	53	72	1.1	0.8 to 1.7	47	72	1.1	0.8 to 1.7	6	72	1.1	0.4 to 2.6

ORs (adjusted by gender, age and area) and 95% CIs are for leukaemia and leukaemia groups by paternal exposure to chemical classes at all intensity levels where probability of exposure is medium or high.
*Time periods: ever indicates exposed from 1 year before conception to diagnosis; preconception indicates exposure 1 year before conception; pregnancy indicates exposure during pregnancy; and postnatal indicates exposure from date of child's birth to diagnosis.
ALL, acute lymphoblastic leukaemia; AnLL; acute non-lymphoblastic leukaemia; Exp., exposed; SETIL, Italian Multicentric Epidemiological Study on Risk Factors for Childhood Leukaemia and Non-Hodgkin's Lymphoma.

estimate for the preconception period reached statistical significance (OR 3.8). Maternal exposure to oxygenated hydrocarbons in the preconception period showed an increasing risk of borderline statistical significance.

No increased risk for ALL was observed in relation to paternal exposure to the chemical classes of solvents considered (table 2) or individual solvents (data not presented).

Results for ALL by individual chemicals and maternal exposure are not shown in the tables: we found non-statistically significant increased risks for benzene (OR 2.9, 95% CI 0.7 to 12.4; 5 exposed cases), toluene (OR 1.8, 95% CI 0.8 to 4.2; 12 exposed cases) and xylene (OR 2.0, 95% CI 0.8 to 4.8; 11 exposed cases) exposure in the period from 1 year before conception to diagnosis. For toluene, the observed risk was statistically significant in the preconception period (OR 4.1, 95% CI 1.3 to 13.6; 9 exposed cases).

As reported in table 1, a non-statistically significant increased risk for AnLL was observed after maternal solvent exposure (OR 1.8). The highest OR was observed for chlorinated hydrocarbons (OR 2.1), but this was based on a small number of exposed cases and did not reach statistical significance. The risks for AnLL could not be estimated for individual solvents because of the small number of mothers who were exposed.

Considering paternal exposure and risk of AnLL, no statistically significant results were observed for exposure to solvents in general, for specific chemical classes or for individual chemicals (data not presented).

Risk of NHL appeared to be related to paternal exposure, particularly to oxygenated solvents (OR 2.2, 95% CI 1.1 to 4.5; 12 exposed cases), with higher risk for paternal exposure during pregnancy. Maternal exposure showed a modest increased risk for solvents (OR 1.3, 95% CI 0.6 to 2.8; 9 exposed cases). The analyses for individual chemicals were limited by the small numbers of exposed subjects.

Other groups of chemicals

Paternal exposure to diesel exhaust fumes (OR 1.4), mineral oils (OR 1.4) and lead (OR 1.7) appeared to increase the risk of childhood leukaemia (table 3). Increased risks of borderline statistical significance were observed for exposure at any time to petrol exhaust fumes (OR 1.5), polycyclic aromatic hydrocarbons (OR 1.2) and bitumen (OR 1.6, 95% CI 1.0 to 2.5; 43 exposed cases). Higher risks were observed particularly for exposure in the preconception period. Exposure to diesel and petrol exhausts was correlated, limiting the separate analyses of the two risk factors; among fathers the OR for exposure to diesel but not to petrol exhaust was 1.4 (95% CI 1.0 to 1.9; based on 83 exposed cases) and to petrol but not to diesel exhaust was 1.9 (95% CI 0.7 to 5.2; based on 8 exposed cases).

Paternal exposure to chromium in preconception and during pregnancy was associated with an increased risk of borderline significance. There was also some suggestion that maternal exposure to exhausts might increase the risk of childhood cancer (table 3).

Table 3 SETIL results for parental exposure

		Father								Mother							
		Leukaemia				ALL				Leukemia				ALL			
	Time period*	Exp. cases	Exp. controls	OR	95% CI	Exp. cases	Exp. controls	OR	95% CI	Exp. cases	Exp. controls	OR	95% CI	Exp. cases	Exp. controls	OR	95% CI
Diesel	Ever	134	154	1.4	1.1 to 1.8	120	174	1.5	1.1 to 1.9	18	20	1.4	0.7 to 2.6	17	20	1.5	0.8 to 2.9
exhaust	Preconception	120	128	1.5	1.2 to 2.0	107	128	1.6	1.2 to 2.1	13	11	1.8	0.8 to 4.0	13	11	2.0	0.9 to 4.5
	Pregnancy	119	135	1.4	1.1 to 1.9	106	135	1.4	1.1 to 1.9	14	12	1.8	0.8 to 3.9	14	12	2.0	0.9 to 4.4
	Postnatal	131	153	1.4	1.1 to 1.8	117	153	1.4	1.1 to 1.8	17	16	1.6	0.8 to 3.2	16	16	1.7	0.8 to 3.5
Petrol	Ever	59	63	1.5	1.0 to 2.2	53	63	1.5	1.6 to 2.2	10	9	1.7	0.7 to 4.2	9	9	1.7	0.7 to 4.4
exhaust	Preconception	50	49	1.6	1.1 to 2.4	45	49	1.7	1.1 to 2.5	7	4	2.7	0.8 to 9.2	7	4	2.9	0.8 to 10.0
	Pregnancy	51	53	1.5	1.0 to 2.3	46	53	1.6	1.0 to 2.4	6	5	1.8	0.6 to 6.0	6	5	2.0	0.6 to 6.7
	Postnatal	57	63	1.4	1.0 to 2.1	51	63	1.5	1.0 to 2.2	9	7	2.0	0.7 to 5.3	8	7	1.9	0.7 to 5.3
PAH	Ever	124	160	1.2	1.0 to 1.6	108	160	1.2	0.9 to 1.6	21	28	1.1	0.6 to 2.1	18	28	1.1	0.6 to 2.1
	Preconception	111	133	1.3	1.0 to 1.8	97	133	1.3	1.0 to 1.8	14	13	1.7	0.8 to 3.6	12	13	1.6	0.7 to 3.6
	Pregnancy	112	144	1.2	1.0 to 1.6	98	144	1.2	0.9 to 1.7	13	17	1.2	0.6 to 2.4	11	17	1.1	0.5 to 2.4
	Postnatal	121	156	1.2	1.0 to 1.6	105	156	1.2	0.9 to 1.6	20	25	1.2	0.7 to 2.2	17	25	1.1	0.6 to 2.2
Mineral	Ever	97	109	1.4	1.1 to 1.9	85	109	1.4	1.1 to 2.0	10	17	0.9	0.4 to 2.0	9	17	0.9	0.4 to 2.1
oils	Preconception	85	92	1.5	1.1 to 2.0	75	92	1.5	1.1 to 2.1	10	12	1.3	0.5 to 3.0	9	12	1.3	0.6 to 3.2
	Pregnancy	89	93	1.6	1.1 to 2.1	79	93	1.6	1.1 to 2.2	9	14	0.9	0.4 to 2.3	9	14	1.1	0.5 to 2.6
	Postnatal	97	103	1.5	1.1 to 2.1	85	103	1.5	1.1 to 2.1	9	17	0.8	0.4 to 1.8	9	17	0.9	0.4 to 2.0
Chromium	Ever	30	32	1.6	0.8 to 3.2	27	32	1.8	0.9 to 3.8	3	5	1.0	0.2 to 4.5	3	5	1.2	0.3 to 5.4
	Preconception	24	24	2.1	1.0 to 4.2	21	24	2	1.0 to 4.2	3	3	1.7	0.3 to 9.0	3	3	2.1	0.4 to 10.9
	Pregnancy	25	27	2	1.0 to 3.9	23	27	2.1	1.0 to 4.3	3	4	1.3	0.3 to 5.8	3	4	1.5	0.3 to 6.8
	Postnatal	30	32	1.6	0.8 to 3.3	27	32	1.8	0.9 to 3.7	3	5	0.9	0.2 to 4.1	3	5	1.1	0.3 to 4.9
Nickel	Ever	15	23	1	0.5 to 1.9	13	23	1	0.5 to 2.0	5	3	2.5	0.6 to 10.7	5	3	2.9	0.7 to 12.5
	Preconception	14	17	1.2	0.6 to 2.5	12	17	1.2	0.6 to 2.5	5	1	–	–	5	1	–	–
	Pregnancy	14	17	1.2	0.6 to 2.5	12	17	1.2	0.6 to 2.6	3	2	2.2	0.4 to 13.5	3	2	1.7	0.3 to 8.6
	Postnatal	15	22	1	0.5 to 2.0	13	22	1	0.5 to 2.0	3	3	1.5	0.3 to 7.5	3	3	1.7	0.3 to 8.6
Lead	Ever	49	47	1.7	1.1 to 2.5	6	9	1	0.4 to 2.8	6	9	1.0	0.4 to 2.8	5	9	0.9	0.3 to 2.9
	Preconception	44	40	1.7	1.1 to 2.7	5	3	2.5	0.6 to 10.6	5	3	2.5	0.6 to 10.6	5	3	2.8	0.7 to 12.0
	Pregnancy	43	43	1.6	1.0 to 2.4	5	5	1.5	0.4 to 5.3	5	5	1.5	0.4 to 5.3	5	5	2.0	0.5 to 5.9
	Postnatal	48	47	1.6	1.1 to 2.5	6	7	1.3	0.4 to 3.9	6	7	1.3	0.4 to 3.9	5	7	1.2	0.4 to 3.9

ORs (adjusted by gender, age and area) and 95% CIs are for leukaemia and ALL by parental exposure to agents other than solvents at all intensity levels where probability of exposure is medium or high.
*Time periods: ever indicates exposed from 1 year before conception to diagnosis; preconception indicates exposure 1 year before conception; pregnancy indicates exposure during pregnancy; and postnatal indicates exposure from date of child's birth to diagnosis.
ALL, acute lymphoblastic leukaemia; Exp., exposed; PAH, polycyclic aromatic hydrocarbons; SETIL, Italian Multicentric Epidemiological Study on Risk Factors for Childhood Leukaemia and Non-Hodgkin's Lymphoma.

Considering ALL, statistically significant ORs were observed for paternal exposure in any period to diesel exhaust fumes and to mineral oils; increased risks of borderline statistical significance were also observed for paternal exposure to petrol exhaust fumes and bitumen (OR 1.6, 95% CI 1.0 to 2.5; 38 exposed cases). Non-statistically significant increased risks were found for maternal exposure to exhausts.

Risk of NHL appeared to be related to paternal exposure to petrol exhaust (OR 2.5, 95% CI 1.2 to 5.1; 12 exposed cases); a borderline statistically significant risk was also observed for lead (OR 2.2, 95% CI 1.0 to 4.8; 10 exposed cases) and chromium exposure (OR 8.1, 95% CI 1.3 to 49.6; 8 exposed cases). For maternal exposure, risks could not be estimated due the lack of exposed cases and the small numbers.

The analysis by immunophenotype (T cell and pre-B cell) showed an higher risk for the pre-B cell immunophenotype for paternal exposure to diesel and petrol exhaust (ever exposed to diesel exhaust: OR 1.6, 95% CI 1.2 to 2.1; petrol exhaust: OR 1.7, 95% CI 1.1 to 2.5) and for maternal exposure to aliphatic hydrocarbons (OR 2.6, 95% CI 1.2 to 5.6).

The analysis considering exposure intensity was performed for all leukaemias. For most of the exposures, we did not find a dose–response relationship except for maternal exposure in the preconception period to solvent in general (very low/low: OR 1.1, 95% CI 0.7 to 1.9; medium/high: OR 2.1, 95% CI 1.0 to 4.2) and among the classes aliphatic (very low/low: OR 3.6, 95% CI 1.2 to 10.5; medium/high: OR 6.0, 95% CI 1.3 to 28.7) and oxygenated hydrocarbons (very low/low: OR 1.5, 95% CI 0.8 to 2.9; medium/high: OR 2.9, 95% CI 1.1 to 7.2), but the p for trend was not statistically significant.

DISCUSSION

This paper addresses the relationship between parental occupational exposure to a selected group of agents used in industrial activities, defined a priori on the basis of current evidence and hypotheses, and the risk of childhood leukaemia and NHL.

Evidence on the association between parental occupational exposure and risk of childhood cancer has been summarised in some reviews.[16–19] Pesticides and hydrocarbons were the chemical classes most commonly associated with childhood leukaemia.[1] Many studies have evaluated leukaemia risk and paternal exposure to paint and pigments in occupations that may also involved solvent exposures.[19] Exposure to paint and petroleum solvents at home and the risk of childhood leukaemia was also examined and a possible association was reported.[4 20 21] Maternal exposures have received much less attention, but studies have yielded strongly suggestive results linking a variety of occupational exposures to childhood leukaemia.[18]

Results from studies that investigated the role of parental occupational exposure and cancer in their offspring have

showed limited consistency. Possible reasons are the small numbers of subjects[4 6] or exposure inferred on the basis of occupational title or industrial activity.[3 22 23]

Exposure classification is, in our opinion, the most critical limitation which might affect research on this topic. The most recent studies are characterised by well designed methods for assessing exposure, but unfortunately there are few of them.[9–11]

The SETIL study provides data on a large number of cases of childhood leukaemia and NHL, diagnosed according to current standards.[14] The study investigated occupational exposures to chemicals using the expert assessment procedure, that is, the state-of-the-art method to assess occupational exposures in retrospective communities based on case–control studies when measured exposure data are not available.[24–26] The use of JSQs is the core feature of the process. This method has been used successfully for three decades and has produced many useful insights into the occupational causes of disease. In our study, occupational exposures were assessed by local experts with long-standing industrial hygiene experience in the study regions. Nevertheless, it is safe to say that non-differential misclassification of exposure may have occurred and reduced our ability to uncover significant findings.

The evidence of association with childhood leukaemia was stronger for maternal exposure to some chemical classes of solvents. Solvents are a very broad category of chemicals. Benzene, toluene, xylene and styrene are among the most prominent members of the aromatic hydrocarbon family in term of occurrence and exposure in occupational environments. The International Agency for Research on Cancer has classified benzene as carcinogenic to humans (Group 1), while xylene and toluene were not classifiable (Group 3).[27]

Our results showed increased risks of childhood leukaemia among children whose mothers were exposed in the preconception period and during pregnancy to aromatic and aliphatic hydrocarbons. This suggestion was confirmed in the analyses for the childhood leukaemia groups. However, we did not find such an association between paternal solvent exposure and childhood leukaemia. Numbers were too small to examine each individual chemical solvent, particularly for mothers, but we found a suggestion of increased risk of childhood leukaemia for maternal exposure to benzene, toluene and xylene. Exposures to benzene, xylene and toluene were correlated and so caution must be exercised when interpreting the evidence for any one of these three solvents separately.

Few studies have investigated childhood cancer in relation to chemical classes or individual solvents. In a large study conducted in Canada,[10] an increasing risk for maternal exposure to toluene was found for the two periods considered (2 years before pregnancy up to birth, and during pregnancy); as regards chemical families, stronger indications were found for 'mononuclear aromatic hydrocarbons' and alkanes (C5–C17); a borderline non-significant risk was also observed for aliphatic ketones in the two periods considered. McKinney *et al*[8] found a twofold increase in risk for childhood leukaemia for maternal hydrocarbon exposure at periconception; in the same study no increased risk was observed for paternal exposure. In the recent study conducted in Australia,[9] no increased risk was observed for maternal exposure to benzene, other aromatic compounds, or chlorinated and aliphatic solvents, while an increased risk was found for paternal exposure to aromatic solvents other than benzene prior to the child's birth.

In a large US study,[7] maternal self-reported exposure to 'solvents, degreaser or cleaning agents' during preconception (OR 1.8) or during pregnancy (OR 1.6) was associated with ALL.

When the individual chemicals were considered, we found a significantly increased risk for maternal exposure to toluene in the preconception period, and elevated ORs for maternal exposure to xylene and benzene. In the study from the USA by Shu *et al*,[7] a non-statistically significant OR of 1.5 was reported for maternal toluene exposure in the preconception period, but no increased risk was found for benzene exposure. Other studies reported results for exposure to the broad category of solvents. McKinney *et al*[11] reported the results of a UK study characterised by expert assessments according to three exposure indices in which only maternal exposure to eight specific agent groupings was considered: a significant risk of ALL was observed for solvent exposure during pregnancy (OR 2.7) and the postnatal period (OR 1.9). A study in Germany[28] reported a non-statistically significant OR of 1.2 for solvent exposure in the preconception period and an OR of 1.3 during pregnancy

The different ways of classifying exposure, the agents considered and the critical time windows are serious limitations in comparing results across different studies. The more recent studies[9–11] used 'experts' to review exposure, but in the McKinney[11] study broad categories of agents such as 'solvents' or 'paints' are considered, while the Canadian study[10] investigated broad categories of chemicals as well as individual chemicals, and both studies considered maternal but not paternal exposure. The Australian study[9] considered both parents, exposure up to 2 years before birth, up to 1 year up to birth and 1 year after birth, 'solvents' in general and also aromatic and aliphatic hydrocarbons.

There are also differences in the prevalence of parental exposure among studies. Among earlier studies, Buckley *et al*[5] estimated paternal solvent exposure in 61/178 controls, Schüz *et al*[28] estimated the prevalence of exposure to solvents as 5% for mothers and 12.9% for fathers, while the estimates of Reid *et al*[9] were 13% and 51%, respectively. In our study, as regards controls, the experts assigned exposure to solvents to 7% of mothers and 18.3% of fathers. The different prevalences of exposure may reflect true differences or the different sensitivity of raters.

Among the other chemical agents investigated, we found increased risks of childhood leukaemia for paternal exposures to diesel exhaust, with higher ORs in the preconception period. This increased risk was also observed for maternal exposure to diesel exhaust fumes, particularly in the preconception period, although our estimate lacked precision. Parental exposure to petrol exhaust was also associated with increased risk of childhood leukaemia.

Diesel engine exhaust is a complex mixture and was recently classified by the IARC as carcinogenic to humans (Group 1).[27] Few studies have specifically examined parental exposure to exhaust fumes and childhood leukaemia risk. The Australian study found increased risk of ALL with parental exposure to diesel exhausts before the child's birth, but the estimate lacked precision.[9] A slight excess risk was observed in the US study.[7] A small but significant increased risk was observed in the UK study[8] for paternal exposure to exhaust fumes at periconception, while a raised but not statistically significant risk was present for maternal exposure.

Statistically significant risks were also observed for paternal exposures to mineral oil and lead. Oil products were considered in the US[7] and German studies,[28] but only in the latter was a slight, non-significant increased risk found for maternal exposure in the preconception period and also for paternal exposure during pregnancy. A study that used a job exposure matrix to evaluate parental exposure and childhood cancer[6] found a slight non-statistically significant OR for ALL for fathers exposed to

mineral oil during the year prior to the child's birth (OR 1.2). In the most recent UK study,[11] lead exposure was not associated with maternal exposure, while a previous study from the same author considered only the broad category of metals.[8]

Few studies on parental occupational exposure investigated the risk for NHL. We found children whose fathers were exposed to oxygenated hydrocarbons and to petrol exhausts were at risk, while a result of borderline significance was observed for metal exposure. Too few exposed mothers were observed for risks to be investigated. In adults, an association between exposure to solvents and NHL subtypes was observed.[15]

In conclusion, the results of our study indicate an increased leukaemia risk with maternal exposure to occupational aromatic and aliphatic hydrocarbons and with paternal exposure to occupational diesel exhaust fumes, lead and mineral oils. The exposure varied with the time window and the association appeared to be determined by the nature of the chemicals. For maternal exposure, the critical time windows were the preconception year and pregnancy, while for fathers the preconception period seems to carry the highest risk.

The analysis taking intensity into account level did not present a clear dose–response relationship as reported in other studies.[7 10] Our data reflect exposures that occurred at the end of the 1990s, when occupational exposure to solvents was under control and therefore exposure likely occurred at low levels and so exposure frequency might be an important issue.

Our results underline the risks associated with prenatal exposure. This observation is consistent with the two-hit model proposed for leukaemia by Graves. According to this hypothesis, prenatal chromosome alterations and postnatal genetic alterations are both necessary for the development of childhood leukaemia.[29] Genetic susceptibility and environmental factors may play a role in this process.[30] From twin studies and the use of neonatal blood spots, it was possible to identify the first initiating genetic events in critical haematopoietic cells during fetal development for most precursor B cell ALL and some cases of acute myeloid leukemia (AML). These events may occur as part of normal fetal development, and it is unclear whether other factors (eg, environmental) are also involved to increase the number of genetic changes and how these genetic events happen. For the majority of ALL and AML, a further genetic change is required and this change can also happen postnatally. The risk of developing leukaemia is determined by complex interactions between genetic and environmental factors and chance.[31] Our results support the suggestion that parental occupational exposures, including those in the prenatal period, may increase the risk of childhood leukaemia and NHL. This supports the hypothesis that cell damage occurring before or after pregnancy is also an important factor. A recent study[21] that examined the association between home use of solvents and paints and the risk of childhood leukaemia suggested that exposure to paints conferred an increased risk of t(12;21) ALL. Parental exposure to specific chemicals was associated with distinct ras mutations in children who developed ALL in one study,[32] suggesting that ras mutations may occur during pregnancy or preconceptionally in germ cells.

However, potential mechanisms of action that may arise from pre- or post-conception occupational paternal or maternal exposure are currently poorly understood and, due to power limitations in analyses addressing leukaemia subtypes, it is likely that coordinated multinational efforts will be needed to elucidate them.

The study also suggests that paternal occupational exposure to selected chemical classes of solvents and exhausts might be a risk factor for childhood NHL.

The present study provides data on childhood leukaemia and NHL, with good quality diagnoses and detailed expert rating of exposure. The expert method used here has been found to have good validity and the use of the JSQs to obtain detailed information reduces differential reporting.[33 34] Exclusion from the analyses of subjects with work periods categorised by low probability of exposure reduces the potential for exposure misclassification. Although this is a large study, power is still an issue, and particularly for mothers, the prevalence of some exposures is very low. Another limitation of the study was that assessing exposure to individual chemicals entails a considerable degree of uncertainty, even though the most up-to-date methodology was used, and some misclassification cannot be totally excluded. Although it would be desirable to isolate the effects of any chemical agent from the effects of others, the high degree of correlation among some exposures and the limited numbers of exposed subjects precluded statistical adjustment for the effects of different agents. In addition, these findings should be interpreted with caution because the large number of comparisons may result in some statistically significant associations arising by chance. However, our findings of increased risk associated with maternal exposure to solvents and aromatic and aliphatic hydrocarbons and paternal exposure to diesel exhaust confirm associations observed in previous studies.

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Funding The SETIL study was financially supported by research grants received from AIRC (the Italian Association on Research on Cancer) Coordinated Grant 1998–2002 N. 954, MIUR (the Ministry for Instruction, University and Research) (Grant 2001164379), Ricerca Finalizzata 2009-Grant n.30258/DB2001 and the Ministry of Health and the Ministry of Labour, Piedmont Region.

Competing interests None.

Ethics approval The SETIL study was authorised by the ethics committee for the Piedmont Region (authorization n. 2886, on 15/2/1999; letter n. 1852/28.3 on 17/2/1999) and later by the corresponding board of each participating research unit.

Provenance and peer review Not commissioned; externally peer reviewed.

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Risk of childhood leukaemia and non-Hodgkin's lymphoma after parental occupational exposure to solvents and other agents: the SETIL Study

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Occup Environ Med published online June 1, 2013
doi: 10.1136/oemed-2012-100951