ORIGINAL ARTICLE

Household exposure to pesticides and risk of childhood acute leukaemia

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Objectives: To investigate the relation between childhood acute leukaemia and household exposure to pesticides.

Methods: The study included 280 incident cases of acute leukaemia and 288 controls frequency matched on gender, age, hospital, and ethnic origin. The data were obtained from standardised face to face interviews of the mothers with detailed questions on parental occupational history, home and garden insecticide use, and insecticidal treatment of pediculosis. Odds ratios were estimated using unconditional regression models including the stratification variables parental socioeconomic status and housing characteristics.

Results: Acute leukaemia was observed to be significantly associated with maternal home insecticide use during pregnancy (OR = 1.8, 95% CI 1.2 to 2.8) and during childhood (OR = 1.7, 95% CI 1.1 to 2.4), with garden insecticide use (OR = 2.4, 95% CI 1.3 to 4.3), and fungicide use (OR = 2.5, 95% CI 1.0 to 6.2) during childhood. Insecticidal shampoo treatment of pediculosis was also associated with childhood acute leukaemia (OR = 1.9, 95% CI 1.2 to 3.3).

Conclusion: The results reported herein support the hypothesis that various types of insecticide exposure may be a risk factor for childhood acute leukaemia. The observed association with insecticidal shampoo treatment of pediculosis, which has never been investigated before, requires further study.

L eukaemia is the most common cancer in childhood with an incidence rate of 43.1 per 1 000 000 per year in France[1] and, with the exception of ionising radiation and certain rare genetic syndromes, its aetiology remains largely unknown. Several studies[2–8] and two reviews of epidemiological studies[9][10] have suggested that household pesticide exposure may be associated with childhood leukaemia. The studies considered different definitions of exposure (home or garden pesticide use, pesticides overall, insecticides), different periods of exposure (pregnancy, childhood, or both), different subtypes of the cases included (acute lymphoblastic leukaemia: ALL or acute non-lyphoblastic leukaemia: ANLL) and different age groups (<9 years, <10 years, <15 years, <18 years). Residential pesticide exposure has also been associated with other childhood cancers (lymphoma, brain tumour, neuroblastoma, Wilm's tumour, and Ewing's sarcoma). Moreover, the International Agency for Research on Cancer (IARC) considers the ''spraying and application of non-arsenical insecticides entailing exposures'' to be, as a whole, probably carcinogenic to humans.[11]

The present study was designed to assess the role of environmental and genetic factors in the aetiology of childhood acute leukaemia. This paper analyses the relation between pesticide exposure and childhood acute leukaemia.

METHODS

Cases and controls

The detailed study design has been reported elsewhere.[12] Briefly, the cases were children under the age of 15 years hospitalised following recent diagnosis (<2 months) of primary leukaemia between 1995 and 1999 in the hospitals of Lille, Lyon, Nancy, and Paris (France). Special care was paid to selecting an appropriate hospitalised control group. The hospital based design of the study was chosen because case and control blood samples were required. Controls were children hospitalised in the same hospital as cases, mainly in orthopaedic and emergency departments, and mainly residing in the same area as cases (that is, the catchment area of the hospital). Many different diagnostic categories were included in order to avoid selection biases in the event that a particular disease was related to the exposures of interest. However, children hospitalised for cancer or a major congenital malformation were not eligible for the study, because those diseases may share risk factors with leukaemia.

Recruitment was frequency matched by age, gender, hospital, and ethnic origin (white, North African, other). Two case and two control mothers refused to participate. The physicians requested that the interviewers refrain from contacting the mothers of 13 cases (nine ALL and four ANLL) whose condition was critical. All the control mothers were contacted. One control child who had been adopted was excluded. Thus, a total of 280 incident cases of acute leukaemia confirmed by cytology and 288 controls were included in the study.

Data collection

The mothers of the cases and controls were interviewed face to face by specifically trained medical doctors using a standard questionnaire. The questions addressed the parents' sociodemographic characteristics, the child's pre- and postnatal characteristics and medical history, the familial history of cancer and autoimmune diseases, and the parents' occupations and habits.

The questions relating to pesticide exposure covered pregnancy and the period from birth to diagnosis, and included home insecticide and garden pesticide (insecticides,

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Abbreviations: ALL, acute lymphoblastic leukaemia; ANLL, acute non-lymphoblastic leukaemia; IARC, International Agency for Research on Cancer

herbicides, and fungicides) use by the mother. The questions on pesticide use at home and in the garden were closed questions: ''Did you regularly use insecticides at home?'', ''Did you use, yourself, gardening chemicals: fertilizer, herbicides, insecticides, fungicides, others?''. The questionnaire also addressed the parents' occupations during pregnancy and during childhood of study subjects.

The index child's direct pesticide exposure to pediculosis treatments during childhood was also determined through an open question on the types of treatment received.

Statistical analysis

All the analyses were performed using the SAS software packages (version 9.1, Cary, NC, USA). Odds ratios (OR) were estimated using unconditional logistic regression models including the stratification variables: gender, age, hospital,

Table 1 Sample description for the cases and controls

	Cases (%) (n = 280)	Controls (%) (n = 288)	p Value
Diagnostic categories			
Acute lymphoblastic leukaemia	240 (86)	–	
Acute non-lymphoblastic leukaemia	40 (14)	–	
Injury (fractures, wounds, burns, etc)	–	154 (54)	
Osteoarticular diseases (osteomyelitis, arthritis, etc)	–	100 (35)	
Gastrointestinal, genitourinary	–	17 (6)	
Minor congenital disorders	–	6 (2)	
Other	–	11 (4)	
Gender			NS
Male	166 (59)	168 (58)	
Age (years)			*
<2	33 (12)	51 (18)	
2–3	85 (30)	53 (18)	
4–6	83 (30)	79 (27)	
7–10	41 (15)	63 (22)	
≥11	38 (14)	42 (15)	
Hospital			NS
Lille	39 (14)	26 (9)	
Lyon	36 (13)	35 (12)	
Nancy	23 (8)	22 (8)	
Paris	182 (65)	205 (71)	
Ethnic origin			NS
White	244 (87)	236 (82)	
North African	15 (5)	25 (9)	
Caribbean	4 (1)	5 (2)	
African	2 (1)	6 (2)	
Asian, Middle Eastern	2 (1)	6 (2)	
Mixed, other	13 (5)	10 (3)	
Maternal education			NS
≤ High school	190 (68)	176 (62)	
> High school	90 (32)	108 (38)	
Paternal education			NS
≤ High school	181 (68)	171 (63)	
> High school	87 (32)	99 (37)	
Working mother at time of interview			NS
Yes v no	173 (62)	191 (67)	
Socioprofessional categories†			NS
Professional, technical workers, administrators, and managers	147 (52)	160 (56)	
Clerical, sales, and services workers	55 (20)	49 (17)	
Factory and agricultural workers	78 (28)	76 (27)	
Place of residence (number of inhabitants)			NS
<5000	40 (14)	37 (12)	
5000–9999	10 (4)	5 (2)	
10000–19999	5 (2)	4 (1)	
20000–49999	13 (5)	5 (2)	
50000–99999	8 (3)	2 (1)	
100000–199999	13 (5)	3 (1)	
200000–199999	41 (15)	46 (16)	
≥2000000	148 (53)	186 (65)	

NS, p>0.05.
*p<0.01.
†Socioprofessional categories: best occupational activity of child's mother or father.

and ethnic origin. Potential confounding by sociodemographic characteristics (maternal educational level and parental socioprofessional category), place of residence (rural: ≤5000 inhabitants and urban: >5000 inhabitants), and type of housing (apartment or house) was considered in the various analyses. Adjustments were also performed on other variables previously identified as related to acute leukaemia in this study (familial history of cancer or autoimmune disease, early common infections, daycare attendance, prolonged breast feeding, and residence in the vicinity of a gas station or garage).[12–16]

Only seven cases and four controls came from outside the catchment area of the hospital (3% v 1%, p = 0.37). When we restricted the analyses to cases and controls residing inside the catchment area of the hospital, the results were unchanged. Thus, we decided to present results on the entire study population.

RESULTS

Study population

Out of the 280 cases included in the study, acute lymphoblastic leukaemia (ALL) was diagnosed in 240 and acute non-lymphoblastic leukaemia (ANLL) in 40 cases.

Most of the controls (89%) were recruited in an orthopaedic or emergency department (table 1). Sixty per cent of the cases were 2–6 years old, versus 55% of the controls. Good case control comparability of maternal and paternal schooling was obtained after adjustment for stratification variables (table 1). The case and control groups contained the same proportion of working mothers and had similar socioprofessional category distributions.

Parental occupational exposure to pesticides

Five cases and three controls had a parent (mother or father) who was occupationally exposed to pesticide during the childhood of the index child. Only two cases and one control had a mother who was occupationally exposed to pesticide during the pregnancy of the index child.

Home insecticide use

We observed a significant association between childhood acute leukaemia and home insecticide use (OR = 1.8, 95% CI 1.2 to 2.8) during pregnancy and OR = 1.7 (95% CI 1.1 to 2.4) during childhood) (table 2). When the exposure periods were considered individually, home insecticide use was only significantly associated with childhood acute leukaemia when exposure occurred during both pregnancy and childhood (OR = 1.6 (95% CI 0.8 to 3.3) during pregnancy only, OR = 1.4 (95% CI 0.8 to 2.3)) during childhood only, and OR = 2.0 (95% CI 1.2 to 3.1) during pregnancy and childhood).

Garden pesticide use

Overall, pesticide use for gardening during childhood (OR = 1.7, 95% 1.1 to 2.7) was associated with acute leukaemia. Garden insecticide use during childhood and garden fungicide use during childhood were associated with childhood acute leukaemia (OR = 2.4 (95% 1.3 to 4.3), OR = 2.5 (1.0 to 6.2), respectively), while garden herbicide use was not (OR = 1.4, 95% CI 0.8 to 2.4). When the periods of exposure were considered individually, garden pesticide use was associated with childhood acute leukaemia when exposure occurred during both pregnancy and childhood (OR = 1.2 (95% CI 0.5 to 3.0) during pregnancy only, OR = 1.5 (95% 0.9 to 2.5) during childhood only, and OR = 5.6 (95% CI 1.6 to 20) during pregnancy and childhood. Garden insecticide use remained associated with acute leukaemia only when the period of exposure was during childhood (OR = 0.6 (95% CI 0.1 to 7.6) during pregnancy only, OR = 1.4 (95% CI 1.3 to 4.7)

Table 2 Home and garden pesticide use and childhood acute leukaemia by period of exposure

	Pesticide use during pregnancy*				Pesticide use during childhood†			
	Cases (n = 280)	Controls (n = 288)	OR‡	95% CI	Cases (n = 280)	Controls (n = 288)	OR‡	95% CI
Home insecticide use								
Never	188	223	1.0	Reference	164	198	1.0	Reference
Ever	92	60	1.8	(1.2–2.8)	111	84	1.7	(1.1–2.4)
Missing	0	5			5	6		
Garden pesticide use								
Never	252	272	1.0	Reference	191	198	1.0	Reference
Ever	14	7	2.5	(0.8–7.2)	70	45	1.7	(1.1–2.7)
Missing	0	6			2	6		
Insecticide	9	4	1.9	(0.6–6.5)	47	20	2.4	(1.3–4.3)
Herbicide	6	3	5.9	(0.7–52)	40	31	1.4	(0.8–2.4)
Fungicide	3	0	–		17	8	2.5	(1.0–6.2)

*Exposure of the mother during pregnancy.
†Exposure of the child from birth to diagnosis.
‡Odds ratios adjusted for age, gender, hospital, ethnic origin, and maternal educational level.

during childhood only, and OR = 3.4 (95% CI 0.7 to 17) during pregnancy and childhood).

Insecticide treatments for pediculosis
Pediculosis during childhood was more frequently reported for cases than for controls with ORs of 1.5 (95% CI 0.9 to 2.5) for one episode and 1.9 (95% CI 1.1 to 3.3) for two or more episodes (table 3). Overall, the use of shampoos to treat pediculosis was associated with childhood leukaemia (OR = 1.9, 95% CI 1.1 to 3.2). Various insecticidal shampoos were reported and were pyrethroid based (65 cases and 55 controls, OR = 2.0 (95% CI 1.1 to 3.4)), organochlorine based (six cases and four controls, OR = 2.1 (95% CI 0.5 to 8.7)), and organophosphorus based (five cases and 10 controls, OR = 0.7 (95% CI 0.2 to 2.4)). The estimates were similar for ALL and ANLL.

Adjustments
The estimates were unchanged when the use of insecticides at home, for gardening, and to treat pediculosis were considered together in the same model. There was no change in the results after adjustment for parental socioprofessional categories, parental educational levels, place of residence (urban or rural), or type of housing (apartment or house). Moreover, adjusting separately or simultaneously for familial history of cancer or

autoimmune disease, frequent early common infections, daycare attendance, prolonged breastfeeding, and residence in the vicinity of a gas station or garage—factors which were previously related to childhood acute leukaemia in the present study—did not modify the results.

The results remained stable over the age groups and were similar for ALL and ANLL.

Missing values
The data on the shampoos used to treat pediculosis were missing from about 10% of the questionnaires. A sensitivity analysis was carried out to evaluate the potential impact of those missing data on the estimates. When the missing data were all considered exposures and then all considered non-exposures, the odds ratios remained greater than 1, and were close to significance or significant: OR = 1.5 (95% CI 0.9 to 2.5) and OR = 2.0 (95% CI 1.2 to 3.3), respectively. In the extreme and unlikely scenario that the missing data were non-exposures for cases and exposures for controls, the odds ratio would be 1.2 (95% CI 0.7 to 1.9).

DISCUSSION
The present study evidenced associations between childhood acute leukaemia and three sources of exposure to insecticides: home insecticide use, garden insecticide use, and insecticide use for pediculosis. The number of parents who were occupationally exposed to pesticides was too small to allow further analyses.

The size of the present study enabled detection of minimum odds ratios of 1.6, 1.9, and 2.2 for control exposure prevalences of 20%, 10%, and 5%, respectively. These prevalences are of the same order of magnitude as those for home insecticide use during pregnancy and during childhood (21% and 29%, respectively), garden insecticide use during pregnancy and during childhood (1% and 5%, respectively), and insecticidal pediculosis treatment during childhood (25%).

The oncology departments recruit patients from more distant places than do control departments, and this could have introduced bias. In order to keep cases and controls comparable in terms of socioeconomic category and rural/urban status, most of the children (all but seven cases and four controls) were living in the same administrative region as the hospital location.

The case and control mothers were very similar with respect to education, occupation, socioeconomic status, and place of residence. The results were unchanged after additional adjustment for the parents' socioprofessional categories, educational levels, place of residence (urban or rural), or type of housing

Table 3 Pediculosis during childhood and risk of childhood acute leukaemia

	Cases (n = 280)	Controls (n = 288)	OR*	95% CI
Pediculosis				
Never	180	195	1.0	Reference
Ever	98	90	1.6	(1.0–2.6)
Missing	2	3		
Once	51	48	1.5	(0.9–2.5)
Twice or more	47	42	1.9	(1.1–3.3)
Pediculosis treatments				
No treatment†	179	194	1.0	Reference
Insecticidal shampoo	70	60	1.9	(1.1–3.2)
Other (vinegar, sweet almond oil)	1	3	0.3	(0.03–2.9)
Missing	30	31		
Pyrethroid	65	55	2.0	(1.1–3.4)
Pyrethroid only	59	46	2.2	(1.2–3.8)
Lindane (organochlorine)	6	4	2.1	(0.5–8.7)
Malathion (organophosphorus)	5	10	0.7	(0.2–2.4)

*Odds ratios adjusted for age, gender, hospital, ethnic origin, and maternal educational level.
‡Two children received preventive treatment without having pediculosis.

(apartment or house). The use of standardised questionnaires and similar interviewing conditions for case and control mothers reduced potential differential misclassifications.

Pesticide exposure is a growing public concern which might induce recall bias. However, our study took place in the period 1995–99 when the subject was far less in the media in France than it is now. Nevertheless, a recall bias cannot strictly be ruled out. The information on shampoos to treat pediculosis may be unreliable, but probably in the same way for the cases and controls.

A variety of possible confounding factors were incorporated in the model in order to test the consistency of the association between insecticide exposure and acute leukaemia. The factors included variables that had previously been shown to be related to childhood acute leukaemia in the present study. The variables related to home or garden insecticide use and pediculosis treatment were also incorporated simultaneously. Adjusted for separately or taken together, none of those variables had any influence on the results. With respect to shampoos for pediculosis, sensitivity analyses showed that loss of association would only occur for unlikely distributions of missing data and that the OR would still be 1.2 in the extreme scenario, in which all the missing case data consisted of non-exposures and all the missing control data consisted of exposures.

The shampoos used to treat pediculosis could have contained three types of insecticide, possibly in combination: pyrethroid, organochlorinated (lindane), and organophosphorus (malathion) insecticides. To the authors' knowledge, no previous study has investigated direct childhood pesticide exposure due to insecticidal shampoos. The results reported herein therefore need to be replicated and investigated further.

The results for residential pesticide exposure are consistent with previously published studies. Home pesticide use during pregnancy or childhood was associated with childhood acute leukaemia in the six studies which investigated that exposure.[2–6 8] Leiss and Savitz (1995) reported an association with pesticide strip use during pregnancy and childhood.[4] The authors cited dichlorvos, a specific insecticide used in pesticidal strips, which is carcinogenic in animals and classed as possibly carcinogenic for humans by the IARC. In addition, "spraying and application of non-arsenical insecticides entailing exposures" have been classified as probably carcinogenic by the IARC.[11]

The association with garden pesticide use is less consistent: two studies found an association between childhood leukaemia and garden pesticide use during pregnancy,[3 5] one study found an association with garden pesticide use during childhood,[3] and three studies did not find any association irrespective of the period of exposure.[4 6 8] The incidence of childhood cancer was not related to local agricultural pesticide use in an ecological study.[17] However, the same authors subsequently conducted a case control study and reported associations between childhood leukaemia and local agricultural use of two common types of pesticide, metham sodium (OR = 2.05 (95% CI 1.01 to 4.17)), and difocol (OR = 1.83 (95% CI 1.0 to 3.22)).[18]

In conclusion, the findings of the present study reinforce the hypothesis already suggested by the literature that household pesticide exposure may play a role in the aetiology of childhood acute leukaemia. At this stage, no specific product can be singled out and a causal relation remains questionable. However, the consistency of our results and the results from previous studies suggests that it may be opportune to consider preventive action.

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