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## **Household exposure to pesticides and risk of childhood acute leukaemia**

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### **Short title**

Pesticide exposure and childhood leukaemia

### **Key words**

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## **Abstract**

**Objectives:** Investigating the relationship between childhood acute leukemia (AL) 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 [1.2-2.8]) and during childhood (OR=1.7 [1.1-2.4]), with garden insecticide use (OR=2.4 [1.3-4.3]) and fungicide use (OR=2.5 [1.0-6.2]) during childhood. Insecticidal shampoo treatment of pediculosis was also associated with childhood acute leukaemia (OR=1.9 [1.2-3.3]).

**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 replications.

## **Introduction**

Leukaemia is the most common cancer in childhood with an incidence rate of 43.1 per 1 000 000 per year in France<sup>1</sup> and, with the exception of ionizing radiation and certain rare genetic syndromes, its etiology remains largely unknown. Several studies<sup>2-8</sup> and two reviews of epidemiological studies<sup>9, 10</sup> 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 lymphoblastic 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 tumor, neuroblastoma, Wilm's tumor 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<sup>11</sup>.

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 relationship between pesticide exposure and childhood acute leukaemia.

## **Material and Methods**

### *Cases and controls*

The detailed study design has been reported elsewhere<sup>12</sup>. 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 since 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 (i.e 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, since those diseases may share risk factors with leukaemia. Recruitment was frequency matched by age, gender, hospital and ethnic origin (Caucasian, 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 (9 ALL and 4 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 AL confirmed by cytology and 288 controls were included in the study.

### *Data collection*

The mothers of the cases and controls were face-to-face interviewed by specifically trained medical doctors using a standard questionnaire. The questions addressed the parents' sociodemographic characteristics, the child's pre- and post-natal characteristics and medical history, the familial history of cancer and auto-immune 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, 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, North Carolina). Odds ratios (OR) were estimated using unconditional logistic regression models including the stratification variables: gender, age, hospital and ethnic origin. Potential confounding by sociodemographic characteristics (maternal educational level and parental socioprofessional category), place of residence (rural:  $\leq 5000$  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 AL in this study (familial history of

cancer or autoimmune disease, early common infections, day-care attendance, prolonged breast feeding and residence in the vicinity of a gas station or garage)<sup>12-16</sup>. Only 7 cases and 4 controls came from outside the catchment area of the hospital (3% vs 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 percent of the cases were two to six 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 3 controls had a parent (mother or father) who was occupationally exposed to pesticide during the childhood of the index child. Only 2 cases and 1 control had a mother who was occupationally exposed to pesticide during the pregnancy of the index child.

**Table 1:** Sample description for the cases and controls

	<b>Cases (%)</b> n = 280	<b>Controls (%)</b> n = 288	<b>p</b>
<b>Diagnostic categories</b>			
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)	
<b>Gender</b>			
Male	166 (59)	168 (58)	ns
<b>Age (years)</b>			
< 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)	
<b>Hospital</b>			
Lille	39 (14)	26 (9)	ns
Lyon	36 (13)	35 (12)	
Nancy	23 (8)	22 (8)	
Paris	182 (65)	205 (71)	
<b>Ethnic origin</b>			
Caucasian	244 (87)	236 (82)	ns
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)	
<b>Maternal education</b>			
≤ high school	190 (68)	176 (62)	ns
> high school	90 (32)	108 (38)	
<b>Paternal education</b>			
≤ high school	181 (68)	171 (63)	ns
> high school	87 (32)	99 (37)	
<b>Working mother at time of interview</b>			
Yes vs. no	173 (62)	191 (67)	ns
<b>Socioprofessional categories†</b>			
Professional, technical workers, administrators and managers	147 (52)	160 (56)	ns
Clerical, sales and services workers	55 (20)	49 (17)	
Factory and agricultural workers	78 (28)	76 (27)	
<b>Place of residence (number of inhabitants)</b>			
< 5 000	40 (14)	37 (12)	ns
5 000-9 999	10 (4)	5 (2)	
10 000-19 999	5 (2)	4 (1)	
20 000-49 999	13 (5)	5 (2)	
50 000-99 999	8 (3)	2 (1)	
100 000-199 999	13 (5)	3 (1)	
200 000-199 999	41 (15)	46 (16)	
≥ 2 000 000	148 (53)	186 (65)	

ns:  $p > 0.05$  ; \*\*  $p < 0.01$  ; † Socioprofessional categories: best occupational activity of child's mother or father

### *Home insecticide use*

We observed a significant association between childhood acute leukaemia and home insecticide use (OR=1.8 [1.2-2.8] during pregnancy and OR=1.7 [1.1-2.4] 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 [0.8-3.3] during pregnancy only, OR=1.4 [0.8-2.3] during childhood only, and OR=2.0 [1.2-3.1] during pregnancy and childhood).

### *Garden pesticide use*

Overall, pesticide use for gardening during childhood (OR=1.7 [1.1-2.7]) was associated with AL. Garden insecticide use during childhood and garden fungicide use during childhood were associated with childhood acute leukaemia (OR=2.4 [1.3-4.3], OR=2.5 [1.0-6.2], respectively), while garden herbicide use was not (OR=1.4 [0.8-2.4]). When the periods of exposure were considered individually, garden pesticide use was associated with childhood acute leukaemia with childhood acute leukaemia when exposure occurred during both pregnancy and childhood (OR=1.2 [0.5-3.0] during pregnancy only, OR=1.5 [0.9-2.5] during childhood only, and OR=5.6 [1.6-20] during pregnancy and childhood). Garden insecticide use remained associated with acute leukaemia only when the period of exposure was during childhood (OR=0.6 [0.1-7.6] during pregnancy only, OR=1.4 [1.3-4.7] during childhood only, and OR=3.4 [0.7-17] during pregnancy and childhood).

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

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

† Exposure of the mother during pregnancy

‡ Exposure of the child from birth to diagnosis

<sup>a</sup> Odds ratios adjusted for age, gender, hospital, ethnic origin and maternal educational level<sup>b</sup> 95%CI: 95% Confidence interval

### *Insecticide treatments for pediculosis*

Pediculosis during childhood was more frequently reported for cases than for controls with ORs of 1.5 [0.9-2.5] for one episode and 1.9 [1.1-3.3] for two or more episodes (Table 3). Overall, the use of shampoos to treat pediculosis was associated with childhood leukaemia (OR=1.9 [1.1-3.2]). Various insecticidal shampoos were reported and were pyrethroid-based (65 cases and 55 controls, OR=2.0 [1.1-3.4]), organochlorine-based (6 cases and 4 controls, OR=2.1 [0.5-8.7]), and organophosphorus-based (5 cases and 10 controls, OR=0.7 [0.2-2.4]). The estimates were similar for ALL and ANLL.

**Table 3:** Pediculosis during childhood and risk of childhood acute leukaemia

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

<sup>†</sup> Two children received preventive treatment without having pediculosis

<sup>a</sup> Odds ratios adjusted for age, gender, hospital, ethnic origin and maternal educational level

<sup>b</sup> 95% CI: 95% Confidence interval

### *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, day-care attendance, prolonged breast-feeding 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 then all considered non-exposures, the odds ratios remained greater than 1, and were close to significance or significant: OR = 1.5 [0.9-2.5] and OR = 2.0 [1.2-3.3], 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 [0.7-1.9].

## **Discussion**

The present study evidenced associations between childhood acute leukaemia and 3 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 socio-economic category and rural/urban status, most of the children (all but 7 cases and 4 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 (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 1995-1999 when the subject was far less mediatised in France than it is presently. Nevertheless, a recall bias cannot be strictly 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 in non-exposures and all the missing control data consisted in exposures.

The shampoos used to treat pediculosis could have contained 3 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 previous published studies. Home pesticide use during pregnancy or childhood was associated with childhood acute leukaemia in the 6 studies having investigated that exposure<sup>2-6, 8</sup>. Leiss and Savitz (1995) reported an association with pesticide strip use during pregnancy and childhood<sup>4</sup>. The authors cited dichlorvos, a specific insecticide used in pesticidal strips, which is carcinogenic in animals and classed as possibly carcinogenic for humans by IARC. In addition, “spraying and application of non-arsenical insecticides entailing exposures” have been classified as probably carcinogenic by IARC<sup>11</sup>.

The association with garden pesticide use is less consistent: two studies found an association between childhood leukaemia and garden pesticide use during pregnancy<sup>3, 5</sup>, one study found an association with garden pesticide use during childhood<sup>3</sup> and three studies did not find any association irrespective of the period of exposure<sup>4, 6, 8</sup>. The incidence of childhood cancer was not related to local agricultural pesticide use in an ecologic study<sup>17</sup>. 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 [1.01-4.17]) and difocol (OR = 1.83 [1.05-3.22])<sup>18</sup>.

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 etiology of childhood acute leukaemia. At this stage, no specific product can be singled out and a causal relationship remains questionable. However, the

consistency of our results and the results from previous studies suggests that it may be opportune to consider preventive action.

## **Competing interest statement**

No competing interests

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## **Ethics approval**

The present study has been approved by the National Commission for Data protection and the Liberties (n°339392) and by the ethic committee (n° 94.0356).

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