Household exposure to pesticides and risk of childhood acute leukaemia

F Menegaux, A Baruchel, Y Bertrand, B Lescoeur, G Leverger, B Nelken, D Sommelet, D Hémon and J Clavel

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METHODS

Cases and controls

The detailed study design has been reported elsewhere. Briefly, the cases were children under the age of 15 years hospitalised following recent diagnostic periods (≤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, non-arsenical insecticides entailing exposures’ to be, as a whole, probably carcinogenic to humans.

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

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, 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 leukemia 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).

Only seven cases and four controls came from outside the catchment area of the hospital (3% ± 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 leukemia (ALL) was diagnosed in 240 and acute non-lymphoblastic leukemia (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 leukemia 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 leukemia when exposure occurred during both pregnancy and childhood (OR = 1.6 (95% CI 1.1 to 2.4)) 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% CI 1.1 to 2.7) was associated with acute leukemia. Garden insecticide use during childhood and garden fungicide use during childhood were associated with childhood acute leukemia (OR = 2.4 (95% CI 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 leukemia 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% CI 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 leukemia 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)

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

<table>
<thead>
<tr>
<th>Diagnostic categories</th>
<th>Cases (%)</th>
<th>Controls (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 280)</td>
<td>(n = 288)</td>
<td></td>
</tr>
<tr>
<td>Acute lymphoblastic leukemia</td>
<td>240 (86)</td>
<td>154 (54)</td>
<td></td>
</tr>
<tr>
<td>Acute non-lymphoblastic leukemia</td>
<td>40 (14)</td>
<td>38 (14)</td>
<td></td>
</tr>
<tr>
<td>Injury (fractures, wounds, burns, etc)</td>
<td>154 (54)</td>
<td>6 (2)</td>
<td></td>
</tr>
<tr>
<td>Osteoarticular diseases</td>
<td>– 100 (55)</td>
<td>12 (4)</td>
<td></td>
</tr>
<tr>
<td>(osteoarthritis, arthritis, etc)</td>
<td>– 100 (50)</td>
<td>17 (6)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal, genitourinary</td>
<td>– 17 (6)</td>
<td>6 (2)</td>
<td></td>
</tr>
<tr>
<td>Minor congenital disorders</td>
<td>– 6 (2)</td>
<td>– 1 (1)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>– 11 (4)</td>
<td>– 1 (1)</td>
<td></td>
</tr>
</tbody>
</table>

Gender: Male 166 (59) 168 (58)  NS
Age (years):
< 2 33 (12) 51 (18)  NS
2–3 85 (30) 53 (18)  NS
4–6 83 (30) 79 (27)  NS
7–10 41 (15) 63 (22)  NS
> 11 38 (14) 42 (15)  NS
Hospital NS 12 (1) 9 (1)  NS
Lille 39 (14) 26 (9)  NS
Nancy 36 (13) 35 (12)  NS
Paris 182 (65) 205 (71)  NS
Ethnic origin: White 244 (87) 236 (82)  NS
North African 15 (5) 25 (9)  NS
Caribbean 4 (1) 5 (2)  NS
African 2 (1) 6 (2)  NS
Asian, Middle Eastern 2 (1) 6 (2)  NS
Mixed, other 13 (5) 10 (3)  NS
Maternal education:
< High school 190 (68) 176 (62)  NS
> High school 90 (32) 108 (38)  NS
Paternal education:
< High school 181 (63) 171 (63)  NS
> High school 87 (32) 99 (37)  NS
Working mother at time of interview: Yes = 173 (62) 191 (67)  NS
Socioprofessional categories:
Professional, technical workers, doctors, and managers 147 (52) 160 (56)  NS
Clerical, sales, and services workers 55 (20) 49 (17)  NS
Factory and agricultural workers 78 (26) 70 (27)  NS
Place of residence (number of inhabitants):< 5000 40 (14) 37 (12)  NS
5000–9999 10 (4) 5 (2)  NS
10000–19999 5 (2) 4 (1)  NS
20000–49999 13 (5) 5 (2)  NS
50000–99999 8 (3) 2 (1)  NS
100000–199999 13 (5) 3 (1)  NS
200000–199999 41 (15) 46 (16)  NS
> 2000000 148 (53) 186 (65)  NS

NS, p > 0.05.
*p < 0.01.
†Socioprofessional categories: best occupational activity of child’s mother or father.
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 2). Various insecticidal shampoos were reported and were pyrethroid based (65 cases and 55 controls, OR = 2.1 (95% CI 0.5 to 8.7)), organochlorine based (six cases and four controls, OR = 0.7 (95% CI 0.2 to 2.4)), and organophosphorus based (five cases and 10 controls, OR = 2.1 (95% CI 0.5 to 8.7)). Various insecticidal shampoos were reported and were pyrethroid based (65 cases and 55 controls, OR = 2.1 (95% CI 0.5 to 8.7)), organochlorine based (six cases and four 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 was 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**

<table>
<thead>
<tr>
<th>Pediculosis</th>
<th>Cases [n = 280]</th>
<th>Controls [n = 288]</th>
<th>OR* 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>180</td>
<td>195</td>
<td>1.0</td>
</tr>
<tr>
<td>Ever</td>
<td>98</td>
<td>90</td>
<td>1.6 (1.0–2.6)</td>
</tr>
<tr>
<td>Missing</td>
<td>5</td>
<td>3</td>
<td>2.1 (1.1–3.3)</td>
</tr>
<tr>
<td>Once</td>
<td>51</td>
<td>48</td>
<td>1.5 (0.9–2.5)</td>
</tr>
<tr>
<td>Twice or more</td>
<td>47</td>
<td>42</td>
<td>1.9 (1.1–3.3)</td>
</tr>
</tbody>
</table>

*Odds ratios adjusted for age, gender, hospital, ethnic origin, and maternal educational level.

†Two children received preventive treatment without having pediculosis.

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**Table 2**

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

<table>
<thead>
<tr>
<th>Pesticide use during pregnancy*</th>
<th>Cases [n = 280]</th>
<th>Controls [n = 288]</th>
<th>OR† 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Home insecticide use</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>188</td>
<td>223</td>
<td>1.0</td>
</tr>
<tr>
<td>Ever</td>
<td>92</td>
<td>60</td>
<td>1.8 (1.2–2.8)</td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td><strong>Garden pesticide use</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>252</td>
<td>272</td>
<td>1.0</td>
</tr>
<tr>
<td>Ever</td>
<td>14</td>
<td>7</td>
<td>2.5 (0.8–7.2)</td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

*Exposure of the mother during pregnancy.
†Exposure of the child from birth to diagnosis.

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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.

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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: permethroid, 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. 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.

The association with garden pesticide use is less consistent: two studies found an association between childhood leukaemia and garden pesticide use during pregnancy, and one study found an association with garden pesticide use during childhood, and three studies did not find any association irrespective of the period of exposure. The incidence of childhood cancer was not related to local agricultural pesticide use in an ecological study. 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 dicofol (OR = 1.83 (95% CI 1.0 to 3.22)).

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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