*Journal of Exposure Science and Environmental Epidemiology* (2010) 20, 299–309


www.nature.com/jes

REVIEW

# Selection bias in case–control studies on household exposure to pesticides and childhood acute leukemia

JÉRÉMIE RUDANT[a,b], JACQUELINE CLAVEL[b] AND CLAIRE INFANTE-RIVARD[a]

[a]*Department of Epidemiology, Biostatistics and Occupational Health, Faculty of Medicine, McGill University, Montréal, Québec, Canada H3A 1A3*
[b]*Univ Paris-Sud, UMR-S754, INSERM, IFR69, Villejuif Cedex, France*

The goal of this study was to investigate the potential for selection bias in published case–control studies on household exposure to pesticides and childhood acute leukemia; most studies have reported positive findings. Items to evaluate the potential for selection bias were first developed. They focused on the source populations that gave rise to cases and controls, the probabilistic selection of subjects from the source, and the losses of the subjects actually selected. A quantitative assessment of bias was also carried out. Potential sources of selection bias were found in all the studies, but none of them were observed across all the studies. Main sources of potential bias were a non-concurrent selection of controls with respect to cases, the use of control diagnoses possibly caused by pesticide exposure in hospital-based studies, and non-participation of selected eligible subjects. A quantitative assessment of bias concluded that non-participation alone could not explain the reported positive associations. We conclude that overall, selection bias, as a likely source of bias in these studies, does not seem to explain their positive findings. Our analysis provides arguments strengthening the conclusions on associations reported in earlier studies.
*Journal of Exposure Science and Environmental Epidemiology* (2010) **20,** 299–309; doi:10.1038/jes.2009.61; published online 16 December 2009

**Keywords:** *acute leukemia, child, pesticides, selection bias, case–control study.*

## Introduction

Childhood acute leukemia (CAL) is the most common cancer among children, with an etiology that remains largely unknown. Acute lymphoblastic leukemia is the most common subtype in developed countries and acute myeloblastic leukemia accounts for nearly all the cases of non-acute lymphoblastic leukemia. The only established risk factors for CAL are ionizing radiation at high levels and some rare genetic disorders, in addition to age and sex. As CAL is a rare disease, most of the etiological studies have been of the case–control type.

A number of environmental risk factors have been studied as possible determinants of CAL (Belson et al., 2007), and among them household exposure to pesticides. Nearly all the case–control studies that investigated this exposure (Lowengart et al., 1987; Buckley et al., 1989; Schwartzbaum et al., 1991; Leiss and Savitz, 1995; Meinert et al., 1996; Infante-Rivard et al., 1999; Meinert et al., 2000; Ma et al., 2002; Alderton et al., 2006; Menegaux et al., 2006; Pombo-de-Oliveira and Koifman, 2006; Rudant et al., 2007) reported significant associations, with odds ratios close to two. It is known that one of the main challenges of case–control studies is the rigorous selection of controls. In case–control studies, the distribution of exposure among controls should be representative of the exposure in the study base, the population which has given rise to the cases (Miettinen, 1985; Savitz, 2003). Socio-demographic differences between the controls providing data and targeted controls for selection in the study base, can lead to selection distortion assuming these factors are associated with exposure, as was observed for household pesticides. A large survey recently carried out in the UK on 13,391 pregnant women investigated household exposure to pesticides during pregnancy and the four following years (Steer and Grey, 2006). They observed that the independent factors related to pesticide use were an older age at the time of pregnancy, a higher parental educational level, owning the housing tenure, and being white. Higher use of pesticide with higher socioeconomic status has also been reported in smaller surveys (Robbins et al., 2001; Robbins and Sharp, 2003) or in controls of a CAL study (Leiss and Savitz, 1995). On the contrary, other small surveys suggested no consistent trends in pesticide use with age, income, education, ethnicity, or home ownership (Adgate et al., 2000; Lu et al., 2001; Berkowitz et al., 2003), and another

1. Address all correspondence to: Dr. Jérémie Rudant, INSERM U754, 16 av. Paul Vaillant Couturier, F-94807 VILLEJUIF Cédex, France.
Tel.: +33 1 45 59 50 37. Fax: +33 1 45 59 51 51.
E-mail: jeremie.rudant@inserm.fr
Received 3 June 2009; accepted 20 October 2009; published online 16 December 2009

suggested higher use in poorer quality housing (Whyatt et al., 2002). Two CAL case–control studies (Meinert et al., 1996; Rudant et al., 2007) reported higher rates of use in rural areas than urban areas, in controls. The proportions of pesticide use also differed across surveys (Steer and Grey, 2006) and between control groups in the different CAL case–control studies, indicating differences in use between countries, regions, and calendar periods.

We believe that control selection has not been scrutinized enough in the CAL studies on household exposure to pesticides, possibly because of inadequate or incomplete reporting. A careful assessment of all the practical and conceptual steps involved in the identification and actual selection of controls would be useful to determine whether we can rely on the almost uniformly positive results showing an association between household exposure to pesticides and CAL.

In the present paper, we first developed a checklist of items to evaluate the potential for selection bias in case–control studies on CAL. Some tools for critical appraisal of epidemiologic studies have been developed (Sanderson et al., 2007), but seemed more suitable for clinical studies, or the listed criteria mainly address the accuracy of reporting (von Elm et al., 2007). Some of the available grids focused on all potential biases, which resulted in only a few general items on selection bias. Examples of such items are ''Were the subjects asked to participate representative of the entire population from which they were recruited'' (Macfarlane et al., 2001) or ''Is the study population considered adequate'' (Borghouts et al., 1998; Nguyen et al., 1999). Although these items are clearly appropriate, they may not be sufficiently detailed to allow appropriate scrutiny of potential sources of selection bias. After developing our checklist, we reviewed the studies on household exposure to pesticides and CAL to determine whether their reported methods were in agreement with the items of our list. We also carried out a quantitative assessment of bias (Kleinbaum et al., 1981; Greenland, 1996). Our objective was to determine whether selection bias was a likely factor for the mostly positive results reported for household exposure and CAL.

## Methods

Items to evaluate studies for selection bias were defined (Table 1), and are described below. The first four items focus on the source populations that give rise to cases and controls. The next two items concern probabilistic subject selection. The last five items focus on the losses of the subjects actually selected.

Articles published in English from 1960 to March 2008 on household exposure to pesticides and CAL were searched in Pubmed. A first set of articles was identified by using the following Mesh terms or key words: (1) child, infant, adolescent; (2) leukemia, hematopoietic malignancies, cancer; (3) pesticides, insecticides, herbicides, fungicides, and environmental exposure. Then, the papers that published estimates of association between CAL and household exposure to pesticides (whatever the pesticide exposure) were reviewed to determine whether their reported methods were in agreement with the items of our list. If the selected papers referred to another publication in which study methods were more detailed, we also reviewed that additional paper.

Finally, a sensitivity analysis, described below, was performed to quantify the effect of losses in term of selection bias for each of the reviewed study.

**Table 1.** Summary of items developed to evaluate the potential for selection bias in case–control studies on childhood acute leukemia.

| | |
|---|---|
| *Items 1–4: source of controls representative of the study base with respect to exposure* | |
| Item 1 | Concurrent selection based on calendar time and place of case diagnosis |
| Item 2 | Age matching |
| Item 3 | Same inclusion/exclusion criteria |
| Item 4 | For hospital controls, exclusion of diagnoses caused by the studied exposure |
| *Items 5 and 6: subject selection* | |
| Item 5 | Complete or probabilistic ascertainment of cases from the base |
| Item 6 | Probabilistic selection of controls from the source |
| *Items 7–11: losses* | |
| Items 7–10: accuracy of reporting of | |
| Item 7 | Number of eligible subjects |
| Item 8 | Number of non-participants |
| Item 9 | Number of participating subjects selected as first, second, or later choices |
| Item 10 | Number of missing data |
| Item 11 | Reporting of some characteristics of non-participants |

### *Items Developed to Evaluate Studies for Selection Bias*

*Items 1–4: Source of Controls Representative of the Study Base with Respect to Exposure* Selection bias would seem unlikely if controls are appropriately selected from a pool of eligible subjects at the calendar time and place of case diagnosis (i.e. concurrently, as opposed to at the end of or after the risk period). Calendar time and place are chosen as plausible matching variables because of the potential variability of the exposure over time and place, and because selection among those who live in an area several years after case diagnosis may result in a different exposure

profile than selection from the pool of those who are at risk at the time a case occurs (e.g. if moving in or out of an area is associated with exposure). The more time elapses between case diagnosis and control selection, the greater the likelihood for change in exposure prevalence, and thus for bias (Poole, 1996; Savitz, 2003).

Among the other eligibility criteria, age could be retained among the selection criteria, as a strong determinant of CAL and a likely one for exposure. Obviously, instead of matching for age, adjusting in the analysis will provide valid results. However, recall is more likely to be similar when case and controls are of the same age.

Finally, inclusion or exclusion criteria should be similar in both groups, as they simply refine the scope of the study base. An additional requirement when selecting hospital controls is to exclude diagnoses that would be caused by the studied exposure (Wacholder et al., 1992).

In summary, items 1–4 are (Table 1) concurrent selection of controls based on calendar time and place of case diagnosis (item 1); age matching (item 2); similar inclusion/exclusion criteria between cases and controls (item 3); and, for hospital controls, exclusion of diagnoses caused by the studied exposure (item 4).

*Items 5 and 6: Subject Selection* Although selecting representative cases is important mainly for generalizability, and lack of it may not affect internal validity if controls are appropriately selected, most CAL studies seemed to aim at selecting representative cases in a geographical area over a period of time. In our review, case ascertainment was considered complete if the ascertainment relied on a population-based cancer registry reported to be exhaustive. If case ascertainment was claimed to be population-based but hospital-based in practice, we expected that all the hospitals with childhood cancer services serving the study base were used to identify and select cases, and that all (or a random sample) incident cases over the study period were selected in each hospital.

The selection process for controls may be split into two steps. The first step consists in conceptually identifying a source of potential controls, as discussed earlier (items 1–4), and the second in their actual probabilistic selection from a data source. It is easy to see that the more favorable situation occurs when a complete roster is available, because otherwise it may be difficult to ensure that every eligible subject has the same chance of being selected. Using procedures to select controls that involve telephone number rosters, each phone number in the study area should have the same chance of being reached, implying that the roster should be complete and up-to-date. In the eventuality of incomplete phone coverage, as it has been described among the poor in the United States (Anderson et al., 1998), a sensitivity analysis may be carried out whereby cases without telephone are also excluded from the analysis. If the number of residences that can be reached by more than one phone number is expected to be non-negligible, the sampling process may be stratified by the number of telephone lines per household. An alternative is to collect this information both for cases and controls, to take it into account in the analysis. Bias in estimating exposure related to family size can be introduced when methods to select controls rely on the identification of households, such as with a phone call procedure or with procedures using a roster of families (Greenberg, 1990; Wacholder et al., 1992). An eligible child with other eligible siblings is less likely to be selected as a control than one with no siblings. Potential for this bias will be limited if cases and controls are individually and closely matched on age or if sampling is stratified by family size.

In summary, items 5 and 6 are (Table 1) complete or probabilistic ascertainment of cases from the base (item 5); and probabilistic selection of controls from the source (item 6).

*Items 7–11: Losses* Once eligible cases and controls have been selected, participation of study subjects in the form of providing biological samples or questionnaire information should be obtained for a maximum of subjects. In the study results, it is important to report the number of eligible subjects based on *a priori* criteria and not to reduce the list of eligible subjects a posteriori, for example by taking out those that have confidential telephone numbers, when access at one point or other involves a phone contact. Although it is conventional to report reasons for non-participation, it is most often the case that there can only be speculation as to whether one reason carries a higher potential for bias than another. Possibly more important, but much less often done, is reporting, for controls in particular, of how many of the participating subjects were selected as first, second, or later choices. Ideally also, some of the characteristics of non-participants should be reported. Finally, a substantial amount of missing data from participating subjects can also be problematic and result in bias.

In summary, items 7–11 are (Table 1) accuracy of reporting of the following numbers: eligible subjects (item 7); non-participants (item 8); participating control subjects selected as first, second, or later choices (item 9); missing data (item 10); reporting of some characteristics of non-participants (item 11).

*Sensitivity Analysis*

For each study, we aimed at quantifying the effect of losses in terms of selection bias, defining losses as per items 7 and 8, that is number of non-participants among number of eligible. We focused on the odds ratio for association between CAL and household exposure to pesticides that would have been observed with complete subject participation. Thus, this ''corrected'' odds ratio corresponds to the odds ratio for association between CAL and household exposure to

pesticides in all eligible subjects who were selected (participants and non-participants). For each study, in which the number of losses was adequately reported, we estimated a range of realistic values for this corrected odds ratio. Our method is detailed below.

By definition, the odds ratio for association between CAL and household exposure to pesticides in eligible subjects who were selected (participants and non-participants) is equal to:
Corrected odds ratio $= [PE_{Cases} *(1-PE_{Controls})]/[PE_{Controls} *(1-PE_{Cases})]$, where $PE_{Controls}$ denotes the prevalence of exposure among the eligible controls who were selected, and $PE_{Cases}$ denotes the prevalence of exposure among the eligible cases who were selected. We estimated a range of realistic values for $PE_{Controls}$ and $PE_{Cases}$. These prevalences can be estimated from participation rates, prevalence of exposure in participating subjects, and the odds ratio for association between household exposure to pesticides and participation status (yes/no) (see Appendix 1 for details of calculation). Participation rates and prevalence of exposure in participating subjects can be obtained from the articles (assuming accurate reporting). However, we hypothesized the likely values of the odds ratios for association between household exposure to pesticides and participation status. We assumed that the odds ratio for association between household exposure to pesticides and participation status could vary from 2.0 to 0.5, for both cases and controls. This range corresponds to the magnitude of the associations observed between household exposure to pesticides and socio-demographic factors (reduced to dichotomous variables) in the literature (Steer and Grey, 2006). An odds ratio for association between household exposure to pesticides and participation status greater than one means that participation in exposed subjects is higher than among unexposed subjects. An odds ratio for association between household exposure to pesticides and participation status lower than one means that participation among exposed subjects is lower than among unexposed subjects.

Participation rates were calculated from the papers by dividing the number of subjects who were interviewed by the total number of eligible subjects in the initial sample of selected subjects. The prevalence of exposure in participating controls was calculated by dividing the number of exposed controls by the total number of participating controls. The prevalence of exposure in participating cases was obtained from the prevalence of exposure in participating controls and the odds ratio for association between pesticide exposure and CAL reported in the paper.

## Results

Eleven articles on household exposure to pesticides and CAL were reviewed (Lowengart et al., 1987; Buckley et al., 1989; Schwartzbaum et al., 1991; Leiss and Savitz, 1995; Meinert et al., 1996; Infante-Rivard et al., 1999; Meinert et al., 2000; Ma et al., 2002; Menegaux et al., 2006; Pombo-de-Oliveira and Koifman, 2006; Rudant et al., 2007). Their features are summarized in Table 2. Three of these (Leiss and Savitz, 1995; Meinert et al., 1996; Menegaux et al., 2006) cited other papers (Savitz et al., 1988; Kaatsch et al., 1996; Perrillat et al., 2002) detailing the relevant study design. Schwartzbaum et al. (1991) in an exploratory study aimed at comparing several exposures across nine childhood cancer types rather than arbitrarily designating one diagnostic category as cases and the others as controls. Yet, as we are focusing here on CAL, we applied the items as if CAL was the case disease, and the other types of cancers the controls. Another study was excluded as only children with Down syndrome were included (Alderton et al., 2006). Nine of the 11 studies reported at least one significant association (Lowengart et al., 1987; Buckley et al., 1989; Leiss and Savitz, 1995; Meinert et al., 1996; Infante-Rivard et al., 1999; Ma et al., 2002; Menegaux et al., 2006; Pombo-de-Oliveira and Koifman, 2006; Rudant et al., 2007). Table 3 shows the main associations between CAL and household exposures to pesticides reported in the papers (insecticide/indoor use, herbicide/outdoor use, any pesticide use). Meinert et al. (2000) reported a non-significant association both for insecticide use and garden pesticide use; yet, the authors found an OR equal to 1.8 (1.0–3.3) for use of insecticides more than ten times per year compared to less than once per year. Schwartzbaum et al. (1991) did not report a stronger association for CAL than for the other types of cancer. Below, we report our assessment of the selected studies based on the approach described in the method section.

### *Items*

*Items 1–4: Concurrent Selection of Controls, Age Matching, Inclusion, and Exclusion Criteria for Cases and Controls, Exclusion Criteria for Hospital Controls* In four studies, two hospital-based (Schwartzbaum et al., 1991; Pombo-de-Oliveira and Koifman, 2006) and two population-based (Infante-Rivard et al., 1999; Ma et al., 2002) studies, controls were selected concurrently with respect to the time of case diagnosis. Yet, in the two hospital-based studies, the authors did not mention if cases and controls both had to reside in the same hospital catchment area. In Infante-Rivard et al. (1999), controls were selected in the same geographical region as where the cases were diagnosed, and in Ma et al. (2002), more than 90% of the controls were selected at the time and place of birth of cases. As they also had to live in the study area at the time of case diagnosis, they were considered as eligible at the time and place of case diagnosis.

The period of control recruitment was not clearly mentioned in six (Lowengart et al., 1987; Buckley et al.,

**Table 2.** Summary of studies on childhood acute leukemia and household exposure to pesticides.

| Reference | Location | Type of leukemia | Period (case ascertainment) | Age (year) | Case selection | Control selection |
|---|---|---|---|---|---|---|
| Lowengart et al., 1987 | Los Angeles county | AL | 1980–1984 | <10 | Population-based cancer registry | Friends (half of controls)<br>Call procedure (random digit dialing) |
| Buckley et al., 1989 | USA/Canada | ANLL | 1980–1984 | <18 | 100 hospitals (Children Cancer Study Group) | Call procedure (random digit dialing) |
| Schwartzbaum et al., 1991 | Memphis | ALL, ANLL | 1979–1986 | <18 | St. Jude hospital | St. Jude hospital (children with other childhood cancers) |
| Leiss and Savitz, 1995 | Denver metropolitan area | AL | 1976–1983 | <15 | Population-based cancer registry plus hospital records | Call procedure (random digit dialing) |
| Meinert et al., 1996 | Lower saxony | AL | 1988–1993 | <15 | Population based cancer registry | Files of local residence registration offices (two groups of controls: local controls from the same community as cases, and state controls from another community) |
| Infante-Rivard et al., 1999 | Quebec | ALL | 1980–1993 | <10 | Quebec tertiary cancer care centers | Family allowance files |
| Meinert et al., 2000 | West Germany | AL | 1980–1994 | <15 | Population based cancer registry | Files of local residence registration offices |
| Ma et al., 2002 | Northern California | AL, ALL | 1995–1999 | <15 | Major hospital centers | Birth certificate files |
| Menegaux et al., 2006 | Lille, Lyon, Paris, and Nancy | AL, ALL and AML | 1995–1999 | <15 | Hospitals of Lille, Lyon, Paris, and Nancy | Same hospitals as cases (mainly orthopedic and emergency units) |
| Pombo-de-Oliveira and Koifman, 2006 | 10 states in Brazil | AL | 1999–2005 | <1,75 | 15 hospital institutions | Same hospitals as cases (subjects with severe disease) |
| Rudant et al., 2007 | France | AL, ALL and AML | 2003–2004 | <15 | Population-based cancer registry | Call procedure (phone directory) |

Abbreviations: AL, acute leukemia; ALL, acute lymphoblastic leukemia; AML, acute myeloblastic leukemia; ANLL, acute non-lymphoblastic leukemia.

1989; Meinert et al., 1996; Meinert et al., 2000; Menegaux et al., 2006; Rudant et al., 2007) of the other seven papers (Lowengart et al., 1987; Buckley et al., 1989; Leiss and Savitz, 1995; Meinert et al., 1996; Meinert et al., 2000; Menegaux et al., 2006; Rudant et al., 2007), whereas the period of case ascertainment was always specified. Yet, the period for ''carrying out the study'' was specified in five papers (Lowengart et al., 1987; Meinert et al., 1996; Meinert et al., 2000; Menegaux et al., 2006; Rudant et al., 2007). We assumed that the controls were selected during this period.

In two studies (Menegaux et al., 2006; Rudant et al., 2007), the period for carrying out the study was the same as the period of case ascertainment, but it was not mentioned whether controls were selected concurrently with respect to cases or at the end of the study period. In these two studies (Menegaux et al., 2006; Rudant et al., 2007), controls were selected in the same geographic region as where cases were diagnosed.

In four studies (Lowengart et al., 1987; Leiss and Savitz, 1995; Meinert et al., 1996; Meinert et al., 2000), controls were selected in the same geographic region as where the cases were diagnosed, but the period for carrying out the study started after the beginning of the diagnosis period: these periods were 1983–1985 (Lowengart et al., 1987), 1984–1985 (Leiss and Savitz, 1995), 1992–1995 (Meinert et al., 1996), and 1993–1997 (Meinert et al., 2000), respectively, whereas the periods of case ascertainment for these same studies were 1980–1984 (Lowengart et al., 1987), 1976–1983 (Leiss and Savitz, 1995), 1988–1993 (Meinert et al., 1996), and 1980–1994 (with most cases diagnosed between 1992 and 1994) (Meinert et al., 2000), respectively. Thus, some controls may not have been included in the risk set at the calendar time the case occurred, either because they did not live in the study area at the time of case diagnosis, or because they were not even born. In three of these studies (Lowengart et al., 1987; Meinert et al., 1996; Meinert et al., 2000), bias could have arisen if the prevalence of exposure to pesticides differed between controls moving away from or into the study area in comparison with those who stayed, between the time of case diagnosis and the time of control selection. Leiss and Savitz (1995) selected controls who had lived in their current residence at the time the case was diagnosed (Savitz et al., 1988), so that in- and out-migration could not have occurred among eligible controls. In three studies (Lowengart et al., 1987; Meinert et al., 1996; Meinert et al., 2000), controls were matched to cases on date of birth; thus, the calendar period for exposure measurement was the same in the two groups and a potential change in pesticide

**Table 3.** Main odds ratios of association between CAL and household exposures to pesticides reported in selected studies, participation rates, and corrected odds ratios.

| | Hospital controls | | | Control selection relying on call procedures | | | | Control selection relying on population register | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Schwartzbaum et al., 1991 | Pombo-de-Oliveira and Koifman, 2006 | Menegaux et al., 2006 | Lowengart et al., 1987 | Buckley et al., 1989 | Leiss and Savitz, 1995 | Rudant et al., 2007 | Meinert et al., 1996 | Infante-Rivard et al., 1999 | Meinert et al., 2000 | Ma et al., 2002 |
| *Household exposure to pesticides and CAL (OR and 95% CI reported in the articles)* | | | | | | | | | | | |
| Insecticide/indoor pregnancy | — | | 1.8 (1.2–2.8) | 3.8 (1.4–13) | — | 3.0 (1.6–5.7) | 2.1 (1.7–2.5) | | 1.8 (1.3–2.4) | | 2.1 (1.3–3.5) |
| Insecticide/indoor childhood | — | | 1.7 (1.1–2.4) | — | — | 1.7 (1.2–2.4) | — | | 1.4 (1.1–1.8) | | 1.6 (1.0–2.7) |
| Herbicide/outdoor pregnancy | — | | 2.5 (0.8–7.2) | 6.5 (1.5–59) | — | 1.1 (0.6–1.9) | 1.5 (1.0–2.2) | | 1.8 (1.3–2.6) | | 1.6 (0.9–3.0) |
| Herbicide/outdoor childhood | ns | | 1.7 (1.1–2.7) | | — | 0.9 (0.5–1.8) | — | | 1.4 (1.1–1.8) | | 1.1 (0.7–2.0) |
| Pesticide pregnancy | | 2.2 (1.5–2.1) | | | 1.8 (1.1–2.8)[a] | | | | | | |
| Pesticide childhood | | | | | 1.7 (1.1–2.7)[a] | | | | | | |
| Insecticide/indoor | | | | | | | | Lo Co: 0.8 ns<br>St Co: 1.0 ns | | 1.2 (0.9–1.6) | |
| Herbicide/outdoor | | | | | | | | Lo Co: 2.5 (1.0–6.1)<br>St Co: 0.8 ns | | 1.0 (0.8–1.2) | |
| *Participation rates*[b] | | | | | | | | | | | |
| Cases | 100% | 96% | 95% | 74%[c] | 78% | 71% | 87%[c] | 73% | 96% | 77%[c] | 83% |
| Controls | 100% | 95% | 99% | — | — | — | — | Lo Co: 71%<br>St Co: 67% | 84% | 66% | — |
| *Refusal rates in controls*[d] | | | | — | 85%[d] | 80%[d] | 71%[d] | | | | 69%[d] |
| *Corrected odds ratios*[e] | | | | | | | | | | | |
| Insecticide/indoor pregnancy | | | 1.7; 1.9 | — | | 2.1; 4.2 | 1.6; 2.7 | | 1.5; 2.0 | | 1.5; 2.9 |
| Insecticide/indoor childhood | | | 1.6; 1.8 | | | 1.2; 2.4 | | | 1.2; 1.6 | | 1.2; 2.2 |
| Herbicide/outdoor pregnancy | | | 2.4; 2.6 | — | | 0.8; 1.5 | 1.1; 2.0 | | 1.6; 2.1 | | 1.1; 2.2 |
| Herbicide/outdoor childhood | — | | 1.6; 1.8 | | | 0.6; 1.3 | | | 1.2; 1.6 | | 0.8; 1.5 |
| Pesticide pregnancy | | 2.1; 2.3 | | | 1.4; 2,3 | | | | | | |
| Pesticide childhood | | | | | 1.3; 2.2 | | | | | | |
| Insecticide/indoor | | | | | | | | Lo Co: 0.6; 1.2<br>St Co: 0.7; 1.5 | | 0.8; 1.8 | |
| Herbicide/outdoor | | | | | | | | Lo Co: 1.7; 3.7<br>St Co: 0.5; 1.3 | | 0.7; 1.5 | |

Studies are grouped according to the method of control selection.

Abbreviations: CAL, childhood acute leukemia; Lo Co, local controls; ns, non-significant; St Co, state controls.

[a]These are crude odds ratios calculated from numbers given in the paper.

[b]The participation rates were calculated by dividing the number of subjects who were interviewed by the total number of eligible subjects in the initial sample of selected subjects, when available.

[c]Cases *a priori* excluded because of child's death or poor conditions were counted as losses to be homogenous across all the 11 studies. That led to participation rates lower than those reported in these articles.

[d]The refusal rates among eligible controls who could be approached were available in the articles.

[e]For each exposure, two corrected odds ratios are given. The first one corresponds to the hypothetical situation in which the odds ratios for association between household exposure to pesticides and participation status (yes/no) would have been equal to 2.0 in cases and to 0.5 in controls. The second one corresponds to the hypothetical situation in which the odds ratios for association between household exposure to pesticides and participation status (yes/no) would have been equal to 0.5 in cases and to 2.0 in controls.

use over time should not have been a problem. In Buckley et al. (1989), where the period for carrying out the study was not specified, controls were also matched on date of birth, minimizing the likelihood for bias. On the contrary, in Leiss and Savitz (1995) where cases and controls were not matched on date of birth, bias could have been introduced if pesticide use changed over time.

Cases of CAL and controls were matched on age in nine studies ( Lowengart et al., 1987; Buckley et al., 1989; Leiss and Savitz, 1995; Meinert et al., 1996; Infante-Rivard et al., 1999; Meinert et al., 2000; Ma et al., 2002; Menegaux et al., 2006; Pombo-de-Oliveira and Koifman, 2006). In Rudant et al. (2007) controls were frequency matched with cases of childhood leukemia, lymphoma, neuroblastoma, and brain tumor, so that cases of CAL and controls differed slightly with respect to age. In Schwartzbaum et al. (1991), cases of CAL were not matched on age with the other types of cancer. However, analyses were closely adjusted on age in these two studies (Schwartzbaum et al., 1991; Rudant et al., 2007).

Inclusion/exclusion criteria reported in the papers were similar for cases and controls in nine studies (Lowengart et al., 1987; Buckley et al., 1989; Schwartzbaum et al., 1991; Meinert et al., 1996; Infante-Rivard et al., 1999; Meinert et al., 2000; Menegaux et al., 2006; Pombo-de-Oliveira and Koifman, 2006; Rudant et al., 2007). In Ma et al. (2002), $<10\%$ of cases were born outside the study area, contrary to their controls selected from the statewide birth certificate files, providing an opportunity, albeit limited, for selection bias if pesticide exposure was associated with moving into the area. In Leiss and Savitz (1995), controls were restricted to those who had lived in their current residence at the time their matched case was diagnosed. This reflected an effort to select controls who would have been eligible at the time of case diagnosis. However, this strategy also led to the selection of residentially stable controls compared with cases (Savitz et al., 1988), because this criterion was not applied to cases who could have lived anywhere in the years prior to diagnosis. If residential mobility was linked to pesticide exposure, this may have contributed to selection bias.

In one hospital-based study (Schwartzbaum et al., 1991) controls had cancers that could have been caused by pesticide exposure (Infante-Rivard and Scott Weichenthal, 2007). In the two other hospital-based studies (Menegaux et al., 2006; Pombo-de-Oliveira and Koifman, 2006), many different diagnostic categories were included, which should have minimized the likelihood of a bias by a dilution effect if only few diseases were related to pesticide exposure.

In one study, half of controls were friends of cases (Lowengart et al., 1987). Although the nature of controls other than population- and hospital-based controls was not included as items in our evaluation criteria, a main limitation with this source of controls is that controls may be too similar to cases with regards to the exposure investigated.

*Item 5: Case Ascertainment* In five studies, cases were ascertained from population-based cancer registries reported to be exhaustive (Lowengart et al., 1987; Leiss and Savitz, 1995; Meinert et al., 1996; Meinert et al., 2000; Rudant et al., 2007). In the six studies in which case ascertainment was hospital-based (Buckley et al., 1989; Schwartzbaum et al., 1991; Infante-Rivard et al., 1999; Ma et al., 2002; Menegaux et al., 2006; Pombo-de-Oliveira and Koifman, 2006) the sampling strategy was not detailed enough to ensure that all the cases of CAL (or a random sample) diagnosed in the given hospitals during the study period were selected. Yet, as CAL is a rare disease that needs very specific care, we believe all cases were likely selected. In one study (Infante-Rivard et al., 1999), all possible cancer units in a determined geographic area were reported to be included, and, in two other studies, the authors compared the cases ascertained with those ascertained by a statewide population-based registry and found that the protocol successfully identified 88% (Ma et al., 2002) and 91% (Pombo-de-Oliveira and Koifman, 2006) of all the newly diagnosed CAL cases in the study area.

*Item 6: Selection of Controls from the Source* Four studies used population registers to identify potential controls: files of local residence registration offices (Meinert et al., 1996; Meinert et al., 2000), family allowance files (Infante-Rivard et al., 1999), and birth certificates files (Ma et al., 2002). In four studies, controls were selected using a phone call procedure (Lowengart et al., 1987; Buckley et al., 1989; Leiss and Savitz, 1995; Rudant et al., 2007). In each instance, the telephone numbers in the area were randomly dialed. Cases from households without phones were reported to have been excluded in only one study (Buckley et al., 1989), and, according to the information available in the papers, none of the studies took into account the possibility that a household could have several phone lines. Proportions of such households (with no phone or several phone lines) in the study area were not provided in the articles. However, not having home phone services is quite rare in the countries where these studies were done, (Anderson et al., 1998; Cloarec and Victor, 2004). The method to select controls relied on the identification of households in the four studies using a phone call procedure, and, potentially in three of the four studies using population registers in which it was not clearly mentioned if the children, rather than the families, had been randomly selected from the rosters (Meinert et al., 1996; Infante-Rivard et al., 1999; Meinert et al., 2000). As sampling was either stratified by family size (Rudant et al., 2007), or cases and controls were reported to be individually matched on age (Lowengart et al., 1987; Buckley et al., 1989; Leiss and Savitz, 1995; Meinert et al., 1996; Meinert et al., 2000), a bias should not have occurred even though family size was linked to pesticide use.

In the hospital-based studies (Schwartzbaum et al., 1991; Menegaux et al., 2006; Pombo-de-Oliveira and Koifman, 2006), a number of hospitalized children were identified as potential controls, but the process of selecting them was not reported in the reviewed papers.

*Items 7–11: Accuracy of Reporting for Eligibility, Participation Rate, Missing Data, Rank Choice for Controls, Characteristics of Non-Participants* The total number of eligible cases and the number of non-participating cases were reported or could be calculated in 10 papers (Lowengart et al., 1987;Buckley et al., 1989; Schwartzbaum et al., 1991; Leiss and Savitz, 1995; Meinert et al., 1996; Infante-Rivard et al., 1999; Ma et al., 2002; Menegaux et al., 2006; Pombo-de-Oliveira and Koifman, 2006; Rudant et al., 2007). In one paper, these numbers were given for all the types of childhood cancers together (Meinert et al., 2000), but not separately by cancer types. With respect to controls, the total number of eligible subjects and the number of non-participants in the initial selected sample were not provided in the Ma et al. (2002) paper and in the four studies relying on call procedures ( Lowengart et al., 1987; Buckley et al., 1989; Leiss and Savitz, 1995; Rudant et al., 2007). Indeed, with call procedure it is not possible to determine if there are some eligible children at telephone numbers that never respond. On the other hand, the number of refusals among subjects whose eligibility could be determined was available in three (Buckley et al., 1989; Leiss and Savitz, 1995; Rudant et al., 2007) of these four studies relying on call procedures. With respect to the Ma et al. (2002) paper, the rate of participation among controls that could be approached was provided.

The number of participating controls selected as first, second, or later choices was reported only in two studies (Buckley et al., 1989; Infante-Rivard et al., 1999). The number of subjects with missing data for pesticide exposure accounted for less than 2% of participating subjects in each of the six studies that reported the numbers of exposed and unexposed subjects (Buckley et al., 1989; Schwartzbaum et al., 1991; Infante-Rivard et al., 1999; Meinert et al., 2000; Ma et al., 2002; Menegaux et al., 2006;). In the other studies the number of subjects with missing data could not be determined.

There was little information provided on non-participants. In Leiss and Savitz (1995), Caucasian cases were more successfully interviewed than non-Caucasian cases. In Lowengart et al. (1987) and Meinert et al. (1996), cases in the study *versus* cases not in the study showed similar age and sex distributions. In two papers (Ma et al., 2002; Rudant et al., 2007), participating controls were compared with the control source population. In Rudant et al. (2007), birth order, region of residence, and maternal educational level were similar between participating controls and the control source population, but paternal educational level was higher for participating controls. In Ma et al. (2002), participating controls well represented the control source population with respect to maternal age and mother's reproductive history.

*Sensitivity Analysis*

The sensitivity analysis was not carried out for two studies. Lowengart et al. (1987) did not provide the numbers of eligible and non-participating controls, and in the Schwartzbaum et al. (1991) paper the odds ratio for association between CAL and pesticide use, using for control group all the other cancer types, was not provided.

With respect to the other nine studies (Buckley et al., 1989; Leiss and Savitz, 1995; Meinert et al., 1996; Infante-Rivard et al., 1999; Meinert et al., 2000; Ma et al., 2002; Menegaux et al., 2006; Pombo-de-Oliveira and Koifman, 2006; Rudant et al., 2007), participation rates in controls from the initial selected sample could not be calculated in Ma et al. (2002) or in the studies relying on call procedures (Buckley et al., 1989; Leiss and Savitz, 1995; Rudant et al., 2007). Yet, participation rates among subjects whose eligibility could be assessed were available in these four studies and were used for the calculation of the corrected odds ratios. Overall, participation rates ranged from 71% (Leiss and Savitz, 1995) to 96% (Pombo-de-Oliveira and Koifman, 2006) for cases and from 66% (Meinert et al., 2000) to 99% (Menegaux et al., 2006) for controls (Table 3). The corrected odds ratios shown in the lower part of Table 3 correspond to the two extreme situations in which the odds ratios of association between household exposure to pesticides and participation were assumed to be equal to 2.0 in cases and 0.5 in controls, or the reverse, that is 0.5 in cases and 2.0 in controls. With respect to the positive and significant associations reported in eight studies (Buckley et al., 1989; Leiss and Savitz, 1995; Meinert et al., 1996; Infante-Rivard et al., 1999; Ma et al., 2002; Menegaux et al., 2006; Pombo-de-Oliveira and Koifman, 2006; Rudant et al., 2007), the corrected odds ratios were still substantially greater than one when considering the first and more unfavorable scenario. For instance, the corrected odds ratios for the association between indoor insecticide use during pregnancy and CAL were consistently still high, equal to 1.7 (Menegaux et al., 2006), 2.1 (Leiss and Savitz, 1995), 1.6 (Rudant et al., 2007), 1.5 (Infante-Rivard et al., 1999), and 1.5 (Ma et al., 2002), in the five studies that reported this association (Table 3). Even in the Meinert et al. (1996) study, where participation rates for both cases and controls were on the low side in comparison with other studies, the corrected odds ratio for the association between outdoor use of pesticide and CAL (as compared to local controls) was much greater than one, equal to 1.7 (Table 3). With respect to the second extreme situation (odds ratios of association between household exposure to pesticides and participation assumed to be equal to 0.5 in cases and 2.0 in controls), the corrected odds ratios for household insecticide use and garden pesticide use were 1.8 and 1.5, respectively, in Meinert et al. (2000) where

non-significant associations were reported (Table 3). The corrected odds ratios for indoor insecticide use during pregnancy and CAL became equal to 1.9 (Menegaux et al., 2006), 4.2 (Leiss and Savitz, 1995), 2.7 (Rudant et al., 2007), 2.0 (Infante-Rivard et al., 1999), and 2.9 (Ma et al., 2002), in the five studies that reported this association (Table 3).

## Discussion

In this paper, we investigated the potential for selection bias for the mostly positive results reported in the eleven published case–control studies on household exposure to pesticides and CAL. Selection bias could have arisen if household exposure to pesticides changed over time or was linked to residential mobility in studies with a non-concurrent selection of controls with respect to cases (Lowengart et al., 1987; Leiss and Savitz, 1995; Meinert et al., 1996; Meinert et al., 2000), if control diagnoses were caused by pesticide exposure in the hospital-based studies (Schwartzbaum et al., 1991; Menegaux et al., 2006; Pombo-de-Oliveira and Koifman, 2006), or in case of differential participation among pesticide users and non-users.

### *What is the Impact of these Biases on the Results of the Studies on CAL and Household Pesticides?*

Concerning the hospital-based studies we reviewed, the association with CAL would rather have been underestimated if some control diagnoses were caused by pesticide exposure, as the control group would have been more exposed than the base. This may explain the null results observed in Schwartzbaum et al. (1991) where CAL were compared with other childhood cancers possibly caused by pesticides.

It is difficult to determine the impact of factors such as migrations or residential mobility, because it is not clear whether such factors resulted in the inclusion of controls more or less exposed than the base. Similarly, it is difficult to determine the impact of possible changes in pesticide use over time. Yet, in studies with a non-concurrent selection of controls with respect to cases (Lowengart et al., 1987; Leiss and Savitz, 1995; Meinert et al., 1996; Meinert et al., 2000), the majority of cases were diagnosed a few years before the controls, reducing the magnitude of a potential bias (Poole, 1996; Savitz, 2003). Moreover, five out of the six studies that recruited controls during the same period as that when cases were diagnosed (Schwartzbaum et al., 1991; Infante-Rivard et al., 1999; Ma et al., 2002; Menegaux et al., 2006; Pombo-de-Oliveira and Koifman, 2006; Rudant et al., 2007), reported positive and significant results. In two of these studies (Menegaux et al., 2006; Rudant et al., 2007), it was not mentioned if the controls were actually selected concurrently with respect to cases. However, the study period was short, and even if the controls had not been selected concurrently with respect to cases, the consequence of the lag would have been negligible (Poole, 1996; Savitz, 2003).

With respect to non-response, in most of the reviewed studies, socioeconomic status, race, and degree of urbanization were relatively similar between participating cases and participating controls and the analyses were adjusted for these factors. Yet, residual confounding could occur after adjusting for some markers of socioeconomic status. On the basis of a relatively scarce literature, it is noteworthy that groups using more pesticides (Steer and Grey, 2006) appear to have the same characteristics as people more willing to participate in epidemiologic studies (Richiardi et al., 2002; Galea and Tracy, 2007; Mezei et al., 2008; Shen et al., 2008) such as being of rather higher socioeconomic status and living in more rural areas. If this pattern applied to controls in the reviewed studies, users of pesticides would have tended to be more willing to participate than non-users, and odds ratios would have been somewhat underestimated as compared to the true odds ratios (assuming the participation in exposed cases was similar to that in unexposed cases). Nevertheless, the literature is scarce and both the determinants of pesticide use and of participation in case–control studies are not well known. Moreover, the reviewed studies provided very little information in that respect. Thus, in our sensitivity analysis we covered a broad range of situations, and even the more unfavorable scenario (odds ratios of association between household exposure to pesticides and participation assumed to be equal to 2.0 in cases and 0.5 in controls) led to corrected odds ratios still substantially greater than one (for the reported positive and significant associations), even in the studies with relatively low participation rates.

### *Reporting of Methods in Reviewed Manuscripts on Pesticides and Childhood Leukemia*

Our analysis confirms the results of earlier analyses that found that reporting on important methodological aspects of research is often too limited in epidemiology (Pocock et al., 2004). In our work, some items could not be fully ascertained because of lack of sufficient details. For a number of aspects, details should have been easy to provide: for example, the exact number of subjects with missing data, the time period of control selection, and the exact selection procedure of cases. Each of these limitations in reporting concerned about half of studies and we had to make some assumptions that seem realistic (e.g. that the period of control recruitment was the period for carrying out the study, that most cases diagnosed in a hospital were selected, or that there were few missing data). For other items, providing adequate information may be inherently more difficult: for instance, determination of eligibility with call procedures or the socio-demographic characteristics of non-participants.

### *Exposure Assessment in Studies on Pesticides and Childhood Leukemia*

The reviewed studies used broad categories of pesticides (such as insecticides or herbicides), with little specificity in pesticide type, and it is not possible to point out specific products.

The products used nowadays in a given country may be different from those used in the studies we reviewed; thus, results from such epidemiological studies may not be seen as highly relevant. However, even if many pesticides in use in the past have been banned in the last 15 years (Karabelas et al., 2009), most currently in use existed in the market before the 90s, in particular indoor insecticides. Moreover, current pesticides are unlikely to have a different mechanism of action, and thus past results may well apply to current investigations. Recall bias may also be of concern in the reviewed studies. Our review focused on selection bias and did not deal with recall bias. Yet, the rare studies examining recall bias in case–control studies of severe childhood diseases often do not conclude to strong differential parental recall between cases and controls (Infante-Rivard and Jacques, 2000). Moreover, in most of the reviewed studies, questionnaires were standardized and interviews were conducted in a similar way for cases and controls, which would have generated less differential error between cases and controls, if any (Mitchell et al., 1986; Teschke et al., 1994; Teschke et al., 2000).

*Assessment of Selection Bias in CAL and Electromagnetic Fields Studies*

Potential for selection bias in studies on CAL and magnetic fields has been initially raised mainly because some studies reported higher wire codes configuration among controls who refused to be interviewed or among families with lower income or social class (Hatch et al., 2000). Wartenberg (2001) explored the potential sources of bias in these studies, albeit without developing or applying evaluation criteria; the author concluded that given the wide variety of study populations and measurement protocols, it was unlikely that a single design flaw had resulted in consistent effects across all studies. Mezei and Kheifets (2006) explored the way socioeconomic status could distort the results, and showed that realistic scenarios could easily result in biased effect estimates in the magnitude of 1.2–1.7. In these two reviews, authors acknowledged that the evaluation of a potential for bias was difficult, as reporting of selection processes was incomplete. Greenland (2005) showed through a multiple-bias approach based on Bayesian analysis and Monte Carlo sensitivity analysis that non-response was a large source of uncertainty in studies on CAL and magnetic fields. Taking advantage of available information on non-participant controls in a Canadian study, Mezei et al. (2008) recently reported that the odds ratio for developing leukemia in the highest exposure category was 1.6 when the actual participating controls were used and 1.3 when the first-choice ideal controls were used, regardless of their participation.

## Conclusion

Potential sources of selection bias were found in all the studies, but none of theses sources were observed across all the studies. A quantitative assessment of bias concluded that non-participation alone could not explain the reported positive associations. We conclude that overall, selection bias, as a most likely source of bias in the studies on household exposure to pesticides and CAL, does not seem to explain their positive findings. Our analysis provides arguments strengthening the conclusions on associations reported in earlier studies.

## Conflict of interest

The authors declare no conflict of interest.

## Acknowledgements

This work was supported by a grant from the *Association pour la Recherche sur le Cancer* (ARC) and was partially carried out while Jérémie Rudant was on post-doctoral training with Claire Infante-Rivard in the Department of Epidemiology, Biostatistics and Occupational Health, Faculty of Medicine, McGill University, Canada.

## References

Adgate J.L., Kukowski A., Stroebel C., Shubat P.J., Morrell S., and Quackenboss J.J., et al. Pesticide storage and use patterns in Minnesota households with children. *J Expo Anal Environ Epidemiol* 2000: 10: 159–167.

Alderton L.E., Spector L.G., Blair C.K., Roesler M., Olshan A.F., and Robison L.L., et al. Child and maternal household chemical exposure and the risk of acute leukemia in children with Down's syndrome: a report from the Children's Oncology Group. *Am J Epidemiol* 2006: 164: 212–221.

Anderson J.E., Nelson D.E., and Wilson R.W. Telephone coverage and measurement of health risk indicators: data from the National Health Interview Survey. *Am J Public Health* 1998: 88: 1392–1395.

Belson M., Kingsley B., and Holmes A. Risk factors for acute leukemia in children: a review. *Environ Health Perspect* 2007: 115: 138–145.

Berkowitz G.S., Obel J., Deych E., Lapinski R., Godbold J., and Liu Z., et al. Exposure to indoor pesticides during pregnancy in a multiethnic, urban cohort. *Environ Health Perspect* 2003: 111: 79–84.

Borghouts J.A., Koes B.W., and Bouter L.M. The clinical course and prognostic factors of non-specific neck pain: a systematic review. *Pain* 1998: 77: 1–13.

Buckley J.D., Robison L.L., Swotinsky R., Garabrant D.H., LeBeau M., and Manchester P., et al. Occupational exposures of parents of children with acute nonlymphocytic leukemia: a report from the Childrens Cancer Study Group. *Cancer Res* 1989: 49: 4030–4037.

Cloarec N., and Victor P. Le marché des télécommunications en 2002. *Insee première* 2004: 968: 1–4.

Galea S., and Tracy M. Participation rates in epidemiologic studies. *Ann Epidemiol* 2007: 17: 643–653.

Greenberg E.R. Random digit dialing for control selection. A review and a caution on its use in studies of childhood cancer. *Am J Epidemiol* 1990: 131: 1–5.

Greenland S. Basic methods for sensitivity analysis of biases. *Int J Epidemiol* 1996: 25: 1107–1116.

Greenland S. Multiple-bias modelling for analysis of observational data. *J R Stat Soc Ser A* 2005: 168: 267–291.

Hatch E.E., Kleinerman R.A., Linet M.S., Tarone R.E., Kaune W.T., and Auvinen A., et al. Do confounding or selection factors of residential wiring codes and magnetic fields distort findings of electromagnetic fields studies? *Epidemiology* 2000: 11: 189–198.

Infante-Rivard C., Labuda D., Krajinovic M., and Sinnett D. Risk of childhood leukemia associated with exposure to pesticides and with gene polymorphisms. *Epidemiology* 1999: 10: 481–487.

Infante-Rivard C., and Jacques L. Empirical study of parental recall bias. *Am J Epidemiol* 2000: 152: 480–486.
Infante-Rivard C., and Scott Weichenthal S. Pesticides and childhood cancer: an update of Zahm and Ward's 1998 Review. *J Toxicol Environ Health B* 2007: 10: 81–99.
Kaatsch P., Kaletsch U., Krummenauer F., Meinert R., Miesner A., and Haaf G., et al. Case control study on childhood leukemia in Lower Saxony, Germany. Basic considerations, methodology, and summary of results. *Klin Padiatr* 1996: 208: 179–185.
Karabelas A.J., Plakas K.V., Solomou ESDrossou V., and Sarigiannis D.A. Impact of European legislation on marketed pesticides—a view from the standpoint of health impact assessment studies. *Environ Int* 2009: 35: 1096–1107.
Kleinbaum D.G., Morgenstern H., and Kupper L.L. Selection bias in epidemiologic studies. *Am J Epidemiol* 1981: 113: 452–463.
Leiss J.K., and Savitz D.A. Home pesticide use and childhood cancer: a case-control study. *Am J Public Health* 1995: 85: 249–252.
Lowengart R.A., Peters J.M., Cicioni C., Buckley J., Bernstein L., and Preston-Martin S., et al. Childhood leukemia and parents' occupational and home exposures. *J Natl Cancer Inst* 1987: 79: 39–46.
Lu C., Knutson D.E., Fisker-Andersen J., and Fenske R.A. Biological monitoring survey of organophosphorus pesticide exposure among pre-school children in the Seattle metropolitan area. *Environ Health Perspect* 2001: 109: 299–303.
Ma X., Buffler P.A., Gunier R.B., Dahl G., Smith M.T., and Reinier K., et al. Critical windows of exposure to household pesticides and risk of childhood leukemia. *Environ Health Perspect* 2002: 110: 955–960.
Macfarlane T.V., Glenny A.M., and Worthington H.V. Systematic review of population-based epidemiological studies of oro-facial pain. *J Dent* 2001: 29: 451–467.
Meinert R., Kaatsch P., Kaletsch U., Krummenauer F., Miesner A., and Michaelis J. Childhood leukaemia and exposure to pesticides: results of a case-control study in northern Germany. *Eur J Cancer* 1996: 32A: 1943–1948.
Meinert R., Schuz J., Kaletsch U., Kaatsch P., and Michaelis J. Leukemia and non-Hodgkin's lymphoma in childhood and exposure to pesticides: results of a register-based case-control study in Germany. *Am J Epidemiol* 2000: 151: 639–646.
Menegaux F., Baruchel A., Bertrand Y., Lescoeur B., Leverger G., and Nelken B., et al. Household exposure to pesticides and risk of childhood acute leukaemia. *Occup Environ Med* 2006: 63: 131–134.
Mezei G., and Kheifets L. Selection bias and its implications for case-control studies: a case study of magnetic field exposure and childhood leukaemia. *Int J Epidemiol* 2006: 35: 397–406.
Mezei G., Spinelli J.J., Wong P., Borugian M., and McBride M.L. Assessment of selection bias in the Canadian case-control study of residential magnetic field exposure and childhood leukemia. *Am J Epidemiol* 2008: 167: 1504–1510.
Miettinen O.S. The "case-control" study: valid selection of subjects. *J Chronic Dis* 1985: 38: 543–548.
Mitchell A.A., Cottler L.B., and Shapiro S. Effect of questionnaire design on recall of drug exposure in pregnancy. *Am J Epidemiol* 1986: 123: 670–676.
Nguyen Q.V., Bezemer P.D., Habets L., and Prahl-Andersen B. A systematic review of the relationship between overjet size and traumatic dental injuries. *Eur J Orthod* 1999: 21: 503–515.
Perrillat F., Clavel J., Auclerc M.F., Baruchel A., Leverger G., and Nelken B., et al. Day-care, early common infections and childhood acute leukaemia: a multicentre French case-control study. *Br J Cancer* 2002: 86: 1064–1069.
Pocock S.J., Collier T.J., Dandreo K.J., de Stavola B.L., Goldman M.B., and Kalish L.A., et al. Issues in the reporting of epidemiological studies: a survey of recent practice. *BMJ* 2004: 329: 883–887.
Pombo-de-Oliveira M.S., and Koifman S. Infant acute leukemia and maternal exposures during pregnancy. *Cancer Epidemiol Biomarkers Prev* 2006: 15: 2336–2341.
Poole C. Invited commentary: evolution of epidemiologic evidence on magnetic fields and childhood cancers. *Am J Epidemiol* 1996: 143: 129–132.
Richiardi L., Boffetta P., and Merletti F. Analysis of nonresponse bias in a population-based case-control study on lung cancer. *J Clin Epidemiol* 2002: 55: 1033–1040.
Robbins P., Polderman A., and Birkenholtz T. Lawns and toxins—an ecology of the city. *Cities* 2001: 18: 369–380.
Robbins P., and Sharp J.T. Producing and consuming chemicals: the moral economy of the American lawn. *Econ Geogr* 2003: 79: 425–451.
Rudant J., Menegaux F., Leverger G., Baruchel A., Nelken B., and Bertrand Y., et al. Household exposure to pesticides and risk of childhood hematopoietic malignancies: the ESCALE study (SFCE). *Environ Health Perspect* 2007: 115: 1787–1793.
Sanderson S., Tatt I.D., and Higgins J.P. Tools for assessing quality and susceptibility to bias in observational studies in epidemiology: a systematic review and annotated bibliography. *Int J Epidemiol* 2007: 36: 666–676.
Savitz D.A. Selection bias in case-control studies. In: Savitz D.A. (Ed.). *Interpreting Epidemiologic Evidence: Strategies for Study Design and Analysis*. Oxford University Press, Oxford, 2003, pp. 81–114.
Savitz D.A., Wachtel H., Barnes F.A., John E.M., and Tvrdik J.G. Case-control study of childhood cancer and exposure to 60-Hz magnetic fields. *Am J Epidemiol* 1988: 128: 21–38.
Schwartzbaum J.A., George S.L., Pratt C.B., and Davis B. An exploratory study of environmental and medical factors potentially related to childhood cancer. *Med Pediatr Oncol* 1991: 19: 115–121.
Shen M., Cozen W., Huang L., Colt J., De Roos A.J., and Severson R.K., et al. Census and geographic differences between respondents and nonrespondents in a case-control study of non-Hodgkin lymphoma. *Am J Epidemiol* 2008: 167: 350–361.
Steer C.D., and Grey C.N. Socio-demographic characteristics of UK families using pesticides and weed-killers. *J Expo Sci Environ Epidemiol* 2006: 16: 251–263.
Teschke K., Kennedy S.M., and Olshan A.F. Effect of different questionnaire formats on reporting of occupational exposures. *Am J Ind Med* 1994: 26: 327–337.
Teschke K., Smith J.C., and Olshan A.F. Evidence of recall bias in volunteered vs. prompted responses about occupational exposures. *Am J Ind Med* 2000: 38: 385–388.
Von Elm E., Altman D.G., Egger M., Pocock S.J., Gotzsche P.C., and Vandenbroucke J.P. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Epidemiology* 2007: 18: 800–804.
Wacholder S., Silverman D.T., McLaughlin J.K., and Mandel J.S. Selection of controls in case-control studies. II. Types of controls. *Am J Epidemiol* 1992: 135: 1029–1041.
Wartenberg D. The potential impact of bias in studies of residential exposure to magnetic fields and childhood leukemia. *Bioelectromagnetics* 2001: (Suppl 5): S32–S47.
Whyatt R.M., Camann D.E., Kinney P.L., Reyes A., Ramirez J., and Dietrich J., et al. Residential pesticide use during pregnancy among a cohort of urban minority women. *Environ Health Perspect* 2002: 110: 507–514.

## Appendix 1. Calculation of the prevalence of exposure among all the eligible controls who were selected (the method is similar for the cases).

Let $PR_{Controls}$ denotes the participation rate in controls, $PE_{PartControls}$ the prevalence of exposure in participating controls, $PE_{NPartControls}$ the prevalence of exposure in non-participating controls, $PE_{Controls}$ the prevalence of exposure among all the eligible controls who were selected and $OR_{ExpPartControls}$ the odds ratio for association between household exposure to pesticides and participation status in controls.

$PE_{NPartControls}$ is related to $PE_{PartControls}$ and $OR_{ExpPartControls}$ by

$$OR_{ExpPartControls} = [PE_{PartControls} * (1-PE_{NPartControls})]/[(1-PE_{PartControls}) * PE_{NPartControls}]$$

and hence, $$PE_{NPartControls} = 1/[1 + (OR_{ExpPartControls} * (1-PE_{PartControls})/PE_{PartControls})]$$

Then, $PE_{Controls}$ is obtained by the following equation:

$$PE_{Controls} = PE_{PartControls} * PR_{Controls} + PE_{NPartControls} *(1-PR_{Controls})$$