Association between Pesticide Exposure and Childhood Leukaemia: A Systematic Literature Review of Epidemiological Studies

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ABSTRACT

Introduction: Cancer is the leading cause of death for children and adolescents globally with 300,000 children aged 0-19 are diagnosed with cancer every year, mainly leukaemia, lymphomas and brain cancers. Like other causes of cancer, the difficulty arises because of multi-factorial aetiologies involving the interaction between genetic factors as well as environmental exposures. **Aims**: This study aimed to analyse published studies on the relationship between childhood leukaemia and exposures to pesticides. **Methods**: The search on the literature database Ovid-MEDLINE search strategy was conducted for the period from 1995 to 2014. The quality of non-randomised studies was assessed by using Newcastle Ottawa Scale (NOS). **Results**: Six studies investigated the relationship related to parental residential exposure and one study, showed an association between childhood leukaemia and maternal exposure. Two studies investigated the relationship to maternal residential exposure. Two studies reported an association between childhood leukaemia and parental occupational exposure. One study showed a positive association out of two studies that evaluated the association related to parental occupational and residential exposure. This review provides evidence of weak to modest association between childhood leukaemia and pesticides exposure in most of the studies. **Conclusion**: Most studies showed an association; however, the causation remains unexplained because of limitations such as potential bias, faulty study design and sample frame, lack of statistical power and also ascertainment of exposure.

KEYWORDS: Children, Pesticide, Exposure, Cancer, Leukaemia

INTRODUCTION

Over recent decades, the incidence of childhood cancer has risen in developed countries. It is the leading cause of death for children and adolescents around the world, and about 300,000 children aged 0-19 are diagnosed with cancer particularly leukemia, brain cancers, lymphomas and solid tumours (1). In general, the cure rates for childhood cancer have improved as a result of better treatment options such as chemotherapy and radiotherapy. More than 80 per cent of children with cancer are cured in high - income countries, but in many low- and middle-income countries just 20 per cent are cured (2).

The risk factors for leukaemia in children are different from adults because of differences in exposure to hazards and higher exposure to pollutions such as water, air and food, and also a longer life expectancy as compared to adults. In contrast to cancer in adults, the majority of causes and infectious agents of childhood cancers are still unknown (3). It is assumed that cancer results from various causes, and is multigenerational involving many complex multistage and prolonged processes involving external and internal factors (4). Certain specific genetic syndromes will predispose an individual to cancer. Heritable retinoblastoma is a condition which can affect both eyes, and is passed from one generation to another; it is an example of cancer caused by an inherited genetic abnormality resulting from two mutations in the RB1 tumour suppressor gene (5).

Many epidemiological studies have been conducted to investigate the association between childhood leukaemia and environmental factors, including smoking habit, ionizing radiation, non-

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ionizing radiation, alcohol consumption, hydrocarbons, magnetic fields and pesticides (6–8). Among environmental chemicals, pesticides have been causing increased public concern because of various health effects (9,10).

Over the past decades, several studies have been carried out examining the association between childhood leukaemia and pesticides exposure, however, to date the research has not yet arrived at an absolute conclusion as to the details of these relationships. This review summarised existing research on the relationship between pesticides exposure and childhood leukaemia. Therefore, this review aimed to evaluate the quality evidence of published studies that examined any association between pesticides exposure and the risk of childhood leukaemia.

MATERIALS AND METHODS

A systematic literature review (SLR) guidelines proposed by Kitchenham and Charters (11) was adapted for this narrative review approach. This method used a broad automated search compared to a restricted manual search process with more than two researchers collecting and classifying data.

Literature search method

The literature searches and selection processes were conducted simultaneously for published English language studies that assess the risk of childhood leukaemia with parental occupational and residential exposure to pesticides. Study identification included both electronic and manual searching strategies. Ovid-MEDLINE and PubMed were used as electronic search databases and were searched for the period from 1996 to 2014. The initial search strategy was broad to ensure as many studies as possible were found. To allow a wide range of search results, the basic MeSH (Medical Subject Heading) term and keywords were used. The search keywords composed by term representing population, intervention and outcome. Finally, a manual search was also carried out on the reference lists of all potentially eligible studies to identify any studies that were not retrieved by the electronic search and to ensure as many studies as possible were assessed.

The inclusion criteria for the review were (a) Children exposed to pesticides either from parental occupational exposure and/or residential exposure (b) Outcome included all types of leukaemia (acute, chronic, lymphoid, or myeloid) (c) Studies published from 1996 to 2014 (d) Only full-text articles. The exclusion criteria were (a) Studies published in a non-English language (b) Studies that examined cancer types other than leukaemia (c) Studies that did not provide sufficient information (for example, study population, period of exposure) (d) Chapters of a book.

Quality assessment

The Newcastle Ottawa Scale (NOS) was used to assess the quality of non-randomised studies as recommended by the Cochrane Collaboration (12,13). Using the NOS, a maximum of ten stars can be obtained based on three domains (a) Selection (maximum of one star per item) (b) Comparability (maximum of two stars) (c) Exposure (maximum of one star per item).

RESULTS

Study selection

For the search using Ovid-MEDLINE, articles were searched using search terms separately to ensure no articles were missed. The terms used were "children", "pesticides" and "leukaemia" (Table 1).

Population	Intervention	Outcome
• exp child/OR • children.mp .OR • (age adj3 child).mp.OR • (pediatric$ adj3 age).mp	• Exp pestcides/OR • Exp agrochemicals /OR • chemosterilants.mp.OR • fungicides.mp. OR • herbicides.mp .OR • insecticides.mp	• Exp leukemia/OR • leukemia, myeloid,acute/,OR • leukemia$.mp.OR

Table 1: The search keywords composed by term representing population, intervention and outcome.

As a result, the Boolean operator "AND" was used to group the search terms and this resulted in 122 relevant studies. The search keywords are shown in Table 2.

The PubMed database was searched on the topic issues between January 1996 and 2014; the keywords included pesticide, childhood and leukaemia which yielded 112 studies. A total of 234 potentially relevant studies were retrieved. Most excluded studies were not aimed at the topic of interest or were irrelevant (n=153), systematic review and meta-analysis (n=20), or review articles (n=23). The Ovid database search accounted for 18 articles, and PubMed accounted for 20 articles. In total 12 studies were either unavailable in full text to assess,, were duplicate studies (n=6) or duplicate studies and unable to assess (n=8) and lastly, 12 studies were included in this review (Figure 1).

No	Searches	Results
1	exp Child/	1,591,180
2	CHILDREN.mp.	732,839
3	(age adj3 child).mp.	5,920
4	(pediatric$ adj3 age).mp.	4,771
5	1 or 2 or 3 or 4	1,745,897
6	exp Pesticides/	132,499
7	exp Agrochemicals/	135,029
8	chemosterilants.mp.	538
9	fungicides.mp.	7,352
10	herbicides.mp.	15,475
11	insecticides.mp.	40,584
12	6 or 7 or 8 or 9 or 10 or 11	143,504
13	expLeukemia/	202,107
14	Leukemia, Myeloid, Acute/	30,539
15	leukemia$.mp.	255,282
16	leukemic infiltration.mp.	1,653
17	acute lymphoblastic leukemia.mp.	18,022
18	acute myeloid leukemia.mp.	17,107
19	chronic lymphoblastic leukmia.mp.	36
20	13 or 14 or 15 or 16 or 17 or 18 or 19	256,897
21	Case Control Study.mp.	54,891
22	Studies, Case Control.mp.	218
23	Study, Case-Control.mp.	93
24	21 or 22 or 23	55,141
25	5 and 12 and 20	122

Table 2: The search keywords

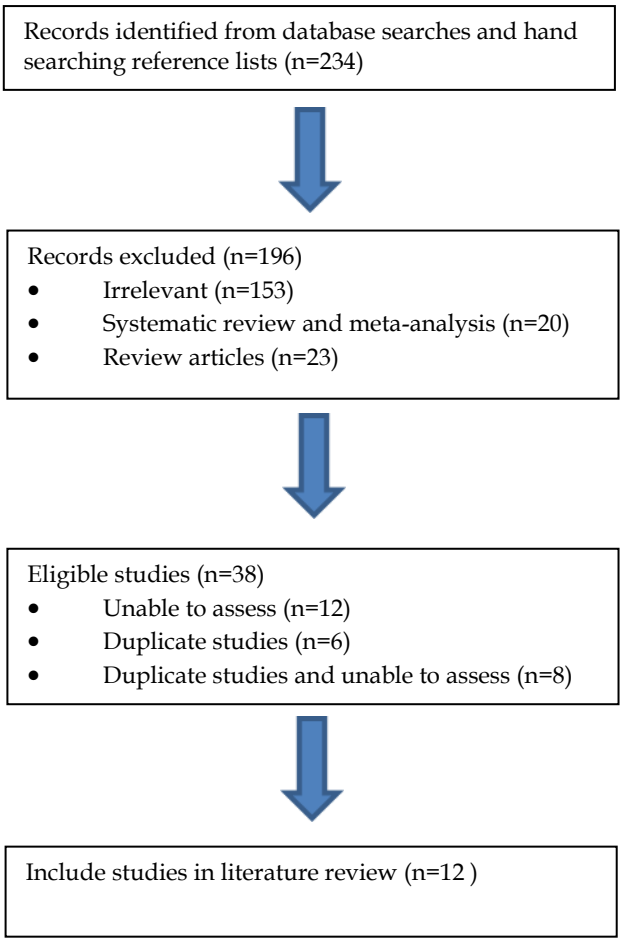

Figure 1: Breakdown of records identified from database searches

Study characteristic and data extraction

Given the relative rarity of childhood cancer, all the studies obtained were case-control studies. Three studies were obtained from the USA (14–16), two studies were obtained from Germany (17,18), France (19,20) and Australia (21,22) and one study was obtained from China (23), Costa Rica (24) and Canada (25). Table 3 shows a summary of the study characteristics, including the name of author and year, parental exposure, pesticide exposure, exposure assessment, age of children and type of pesticides.

Table 4 shows study characteristics including name of author, country and year, case and control sample, period of exposure, tool, type of pesticides and results. Although most of the studies examined cases among children below 15 years old (n=8)(14,17–24), one study examined children aged below 18 years (15), 10 years (25), 8 years and one was unspecific (16). Studies varied in sample size, ranging from a total of 41 up to 1,184 cases, and from 41 up to 2,588 controls. Most studies presented data restricted to acute lymphocytic leukaemia (n=7), and the remaining studies reported data for all types of acute leukaemia (n=5).

Eight studies included data for household or residential exposure (14–16,19,20,22,23,25), three studies included data for occupational exposure (17,18,24), and one study included data for both exposures (21). Two of the studies included data on maternal exposure only (22,25) , six studies included data for both (14,16,18,19,21,23), and four studies separated data for paternal and maternal exposure (15,17,20,24). Majority of the studies reported based on questionnaires. In case of any incomplete data on the exposure listed, phone call or face-to-face interview were done.

Glass et al., conducted a population-based case-control study in Australia to examine the relationship between ALL among children and parental occupational exposure to pesticides (21). The findings showed no statistical significance between paternal and maternal occupational exposure to pesticides and childhood cancer.

Another study by Bailey et al., conducted a population-based study with the purpose to determine whether professional pest treatments in or around the home, and before birth or during childhood, increasing the risk of childhood ALL (22). An association of childhood ALL and professional pest control treatments (the year before, during or after pregnancy) was not statistically significant. There was evidence of increased risk among cases with ETV6- Runx-1t (12, 21) translocation and Pre B cell ALL in any time period.

Author and Year	Parental exposure	Pesticide exposure	Exposure assessment	Age of children	Type of pesticides
Glass DC, 2011	Paternal Maternal	Occupational exposure Residential/ Household	Written questionnaire Telephone interview for further data	Under 15 years	Based on chemical class
Bailey HD,	Maternal	Residential/ Household	Questionnaire Telephoned interview for further data	Under 15 years	Based on type of pests
Soldin OP, 2009	Paternal Maternal	Residential/ Household	Questionnaire Urine for OP	Under 18 years	Based on type of pests
Rull RP, 2009	Paternal Maternal	Residential/ Household	Questionnaire In person interview for further data	Unspecific	Based on type of pests Based on chemical class
Ward MH, 2009	Paternal Maternal	Residential/ Household	Interview Blood sample for OC	Under 15 years	Based on type of pests
Rudant J, 2007	Paternal Maternal	Residential/ Household	Questionnaire: Telephone interview	Under 15 years	Based on type of pests
Monge P, 2007	Paternal Maternal	Occupational exposure	Questionnaire: Face to face interview	Under 15 years	Based on type of pests Based on chemical class
Menegaux F, 2005	Paternal Maternal	Residential/ Household	Questionnaire: Face to face interview	Under 15 years	Based on type of pests
Infante-Rivard C, 1999	Maternal	Residential/ Household	Questionnaire: Telephone interview	Under 10 years	Based on type of pests
Zhan Y, 2015	Paternal Maternal	Residential/ Household	Questionnaire: Face to face interview Urine for OP	Under 15 years	Based on type of pests
Meinert R, 2000	Paternal Maternal	Occupational exposure Residential/ Household	Questionnaire: Telephone interview	Under 15 years	Based on type of pests
Meinert R, 1996	Paternal Maternal	Occupational exposure	Questionnaire: Telephone interview	Under 15 years	Based on type of pests

Table 3: A summary of study characteristics

Table 4: Study characteristics including name of author, country and year, case and control sample, period of exposure, tool, type of pesticides and results

Title: Risk of childhood acute lymphoblastic leukaemia following parental occupational exposure to pesticides **Author:** Glass, DC **Country; Year** Australia; 2011	**Case sample:** ALL in children aged under 15 years in Australia diagnosed between 1 July 2003 and 31 December 2006 recruited from 10 paediatric oncology centres ***Participants:*** Mother (378) Father (327) **Control sample:** Control matched to cases on age, sex and state of residence. ***Participants:*** Mother (854) Father (748)	**Period of exposure:** Paternal occupational exposure before birth. Maternal occupational exposure from 2 years from birth up to 1 year after birth **Type of pesticides:** Based on chemical class: Organophosphates Organochlorides Phenoxy herbicides Other herbicides Other pesticides	**Tool:** Written questionnaire Socio demographic Occupational history Pesticides exposure Telephone interview To review job histories and job specific questions to assess exposure to pesticides	**Results:** Exposure to uncommon pesticides for paternal (cases 15%, control 14.4%) and maternal (cases 1%, control 1.8%) No statistically significant associations between the risk of ALL and maternal or paternal exposure to pesticide
Title: Exposure to professional pest control treatments and the risk of childhood ALL **Author:** Bailey, HD **Country; Year:** Australia; 2011	**Case sample:** ALL in children aged less than 15 years diagnosed between 1 July 2003 and 31 Dec 2006 recruited from 10 paediatric oncology centres ***Participants:*** 388 **Control sample:** Control matched to cases on age, sex and state of residence. ***Participants:*** 870	**Period of exposure:** Maternal residential exposure from professional pest treatments in three time periods: the year before, during and after delivery. **Type of pesticides:** Based on type of pest: Termites General insects and spiders Rodents or birds	**Tool:** Mailed questionnaire Socio demographic and potential pesticides exposure Computer Assisted Telephone Interview (CATI) To collect further data on exposure listed in questionnaire	**Results:** Exposure to uncommon pesticide around 11-18% Weak evidence of association between childhood ALL and professional pest control treatments in a year before pregnancy (OR 1.19 (0.83-1.69)), during pregnancy (OR 1.3(0.86-1.97)) and after delivery (OR 1.24(0.54-2.88)) Weak evidence association of childhood ALL and use of pesticide for insects and spiders in a year before pregnancy (OR 1.12 (0.74-1.68)), during pregnancy (OR 1.29(0.80-2.08)) and after delivery (OR 1.33(0.96-1.82))

Title: Paediatric acute lymphoblastic leukaemia and exposure to pesticides **Author:** Soldin, OP **Country; Year:** USA; 2009	**Case sample:** ALL diagnosed between January 2005 and January 2008 and aged less than 18 years old recruited from Georgetown University Medical Centre and Children's National Medical Centre in Washington DC. ***Participants:*** 41 **Control sample:** Control matches to cases by sex, age and place of residence. The control subjects were healthy. ***Participants:*** 41	**Period of exposure:** Residential environmental exposure to pesticides during period of preconception (6 months) and during pregnancy (9 months). Based on type of pest: Insecticides Rodent pesticides Weed pesticide Fungal pesticide Pet pesticide Urine bio specimen analysis of pesticides (OP) DMP,DMT,DMDTP, DMTP,DEP,DEDTP, DETP	**Tool:** Telephone interview using structured questionnaire Urine bio specimen analysis for pesticides	**Results:** Statistically significant associations between risk of ALL and maternal exposure to insecticides at residence area but not paternal site. Statistically significant associations between risk of ALL and maternal exposure to insect pesticides and weed pesticide based on urine sample.
Title: Residential proximity to agricultural pesticides applications and childhood ALL **Author:** Rull, RP **Country; Year:** USA; 2010	**Case sample:** ALL in children under 15 years diagnosed between August 1995 and November 1999 (phase 1) and between December 1999 and June 2002 (phase 2) in Northern California. ***Participants:*** 213 **Control sample:** Control matches to cases by sex, age and place of residence. The control subjects were no prior cancer diagnosis. ***Participants:*** 268	**Period of exposure:** Residential proximity to agricultural pesticide applications Unexposed = pesticide use density was less than 1 Ib/mi. Exposed = pesticide use density was more than 1 Ib/mi. These categories were defined as moderate (1st to 49th percentile) and high (50th percentile and above). Exposed subjects were divided into lifetime and first year of life exposure. **Type of pesticides:** Based on of target pests: Insecticides Herbicides fungi sites Plant growth regulars Fumigants Based on chemical class: Azoles Banzimidazoles Chlorinated Dinitroaniline Methyl carbamates Organochlorines Organophosphates Pyrethroids Substituted benzenes Thiocarbamates Triazines Ureas	**Tool:** Written questionnaire Extensive demographic and exposure information Interview In person followed by interview	**Results:** Elevated risks of ALL were observed for moderate lifetime exposure to fumigants (OR 1.7(1-3.10) and insecticides (1.5(0.9-2.4)). The risk for high exposure and exposure during the first year of life did not show any significance. Elevated risks were observed in moderate exposure groups for chlorinated phenol (OR 2.0 (1.0-3.8)), OP(1.6(1.0-2.7)) and triazines (OR 1.991.0-3.70) Elevated ALL risk was associated with lifetime moderate exposure but not high exposure in certain chemical classes and type of pest. Small numbers of exposed cases and controls obscured the analysis of results.

Title: Residential exposure to polychlorinated Biphenyls and organochloride pesticides and risk of childhood leukaemia **Author:** Ward, MH **Country; Year:** USA; 2009	**Case sample:** ALL in children aged below 8 years diagnosed in Dec recruited from nine major paediatric clinical centres in northern and central California. ***Participants:*** 184 **Control sample:** Control matches to cases by sex, age, race and place of residence. ***Participants:*** 212	**Period of exposure:** Residential exposure to pesticides from carpet dust. **Type of pesticides:** Chlordane DDE DDT PCB Lindane dieldrin	**Tool:** Interview Resident and parental occupational history Home and garden using pesticides Inventoried pesticides in storage Collect carpet dust samples Laboratory sample From dust Chlordane DDE DDT PCB Lindane dieldrin	**Results:** Elevated risks of ALL were observed in nay measured PCB congeners and the risk was higher in highest quartiles. Four of the six measured PCB congeners were associated with elevated risk of ALL (118, 138, 153, 170) No significant association between chlordanem DDT, DDE, Methoxychlor or pentachlorophenol
Title: Household exposure to pesticides and risk of childhood hematopoietic malignancies **Author:** Rudant, J **Country; Year:** France; 2004	**Case sample:** Acute leukaemia in children aged less than 15 years and diagnosed between 1 January 2003 and 31 December 2004 recruited from French paediatric oncology hospital. ***Participants:*** 764 **Control sample:** The controls were randomly selected from French population matches to cases by sex, age and place of residence ***Participants:*** 1681	**Period of exposure:** Household exposure to pesticides. **Type of pesticides:** Based on of target pests: Pesticides Insecticide Herbicides Fungicides	**Tool:** Telephone interview using structured questionnaire Information about demographic and socioeconomic status. Household use of pesticides during pregnancy by mother, and during pregnancy or childhood by father Insecticides used at homes, on pets or for garden crops. Herbicides used a weed killers Maternal exposed at work during pregnancy	**Results:** Maternal household exposure use of any pesticide (OR 2.2 (1.8-2.6)) during pregnancy significantly increases risk of AL. Maternal household exposure use of insecticide (OR 2.1 (1.7-2.5)) and herbicide (OR 1.5(1.0-2.2)) during pregnancy significantly increase risk of AL Paternal household exposure use of any pesticide (OR 1.5 (1.2-1.8)) and insecticide (OR 1.4 (1.2-1.7)) during pregnancy significantly increase risk of AL No risk observed between use of pesticide with maternal (OR 0.2(0.1-0.8)) or paternal (OR 0.6(0.4-1.1)) household use- of pesticide. Neither maternal agricultural occupation exposure during pregnancy nor paternal occupational was associated with AL This study showed an association between AL and household pesticides use.

Title: Parental occupational exposure to pesticides and risk of childhood leukaemia in Costa Rica **Author:** Monge, P **Country; Year:** Costa Rica, 2007	**Case sample:** Acute leukaemia in children aged less than 15 years, diagnosed between 1995 and 2000 and identified at the Cancer Registry and the Children's Hospital of Costa Rica. ***Participants:*** Both parents (267) Mother only (32) Father only (1) **Control sample:** Control matches to cases by birth year were drawn from National Birth Registry. ***Participants:*** Both parents (492) Mother only (85) Father (2)	**Period of exposure:** Paternal occupational exposure year before conception, 1st trimester and 1st year of life. Maternal occupational exposure from a year from conception, during pregnancy and 1st year of life. **Type of pesticides:** Based on of target pests: Insecticides Herbicides Fungicides Based on chemical group: Foxim Picloram Paraquat Benomyl Mancozeb Organophosphates Carbamate Chlorinated Pyrethroids	**Tool:** Interview (face to face) Using Icon Calendar Form (ICF) to collect demographic data and known and suspected risk factors of childhood leukaemia.	**Results:** Fathers' exposures showed an excess risk for all pesticides during second trimester (OR 1.5(1.0-2.3)), insecticides during third trimester (OR 2.2(1.2-4.1)), herbicides during second trimester (OR 1.6(1.0-2.5) and fungicides in most of the time periods and anytime. Mothers' exposures showed an excess risk for all pesticides during first trimester (OR 22(2.8-171.5)), insecticides during first and second trimester (OR 6.9(1.4-33.2)), herbicides during first and second trimester (OR 5.3(1.4-20) and fungicides in most of the time periods and anytime. In average, the OR was higher among mothers than fathers. In conclusion, there was an association between exposure of insecticides, herbicides and fungicides for fathers and mothers and risk of AL. An association between exposure to OP in most time periods: year before conception (OR 2.3 (0.9-6.0), OR 2.5(0.9-6.7)), first trimester (OR 3.5 (1.0-12.2), OR 3.7(1.0-13.1), second trimester (OR 2.5 (0.7-9.5), OR 3.0(0.8-11.5) , third trimester and first years of life (OR 1.8 (0.6-4.9), OR 1.8) in total AL and ALL, respectively. In conclusion , this study suggest that parental exposure to pesticides may increase risk of ALL or AL
Title: Household exposure to pesticides and risk of childhood acute leukaemia **Author:** Menegaux, F **Country; Year:** France; 2005	**Case sample:** ALL under 15 years old. Diagnosed between 1995 and 1999 in the hospitals of Lille, Lyon, Nancy and Paris. ***Participants:*** 280 **Control sample:** Controls were children hospitalised in the same hospital as cases but due to cancer and matches to cases by age, gender, hospital and ethnic origin. ***Participants:*** 288	**Period of exposure:** Household exposure included home insecticide and garden pesticide covered during pregnancy, use during childhood and both. **Type of pesticides:** Base on type of pest: Insecticides Fungicide Herbicide	**Tool:** Face to face interview with specific questionnaire The questionnaire included socio demographic characteristic and pesticide exposure.	**Results:** Significant association between childhood AL and home insecticide use during pregnancy (OR 1.8(1.2-1.8) and during childhood (OR 1.7(1.1-2.4) Significant association between childhood AL and garden pesticide, insecticide and herbicide use during pregnancy and during childhood. The study showed an association between type of pest exposure in garden and home risk of childhood AL.

Title: Risk of childhood leukaemia associated with exposure to pesticides and with gene polymorphisms **Author:** Claire, IR **Country; Year:** Canada, 1999	**Case sample:** ALL age less than 10 years diagnosed between 1980 and 1993 were recruited from tertiary centres in Quebec. ***Participants:*** 491 **Control sample:** Control matches to cases by age, gender and region of residence at the time of diagnosis. ***Participants:*** 491	**Period of exposure:** Residential exposure during pregnancy and during childhood. **Type of pesticides:** Based on type of pest: Herbicides Plant insecticides Products for trees Outdoor insects Products for slugs and snails	**Tool:** Interview and questionnaire The questionnaire include information about possible confounding variables and use of pesticides in and out of the home from 1 month before pregnancy to birth and from birth to date of diagnosis Genotyping In 123 cases genotyping sample were taken to detect mutants.	**Results:** Herbicides, plant insecticides, products for trees, products for slugs and snails used during and after pregnancy increase risk of childhood leukaemia. But the use of outdoor insects during and after pregnancy not associated with childhood leukaemia.
Title: Household pesticide exposure and the risk of childhood ALL in Shanghai **Author:** Zhang, Y **Country; Year:** China; 2014	**Case sample:** Acute Leukaemia under 15 years old diagnosed between January 2009 and December 2010 in Shanghai. ***Participants:*** 248 **Control sample:** Control subjects were healthy children, selected from the same hospital as cases , matches to cases by gender and age ***Participants:*** 111	**Period of exposure:** Household pesticide. **Type of pesticides:** Based on type of pest: Mothproofing Cockroach killer Termite control agent Mosquito repellent Rodenticide Herbicide Sanitizer Antiseptic germicide others Based on chemical group (nonspecific dialkylphospate (DAP) metabolites of OP) DMP DEP DMTP DETP DEDTP	**Tool:** Face to face interview via questionnaire The questionnaire contains information on the parents' socio demographic factors and information about pesticides. Urine sample Urine sample analysis of DAP metabolites.	**Results:** A significant association between household use of mosquito repellent and pesticides and childhood AL. However, no association observed use of mothproofing agent, cockroach killer, sanitizer and antiseptic germicide. In conclusion, showed an association between household pesticide exposure and childhood AL.

Title: Childhood leukaemia and exposure to pesticides **Author:** Meinert, R **Country; Year:** Germany; 1996	**Case sample:** Childhood leukaemia diagnosed in between July 1988 and 30 June 1993 in children aged less than 15 years old in Northern Germany. ***Participants:*** 173 **Control sample:** Control matches to cases by age and gender. ***Participants:*** 161	**Period of exposure:** Parental occupation as farmer, gardener and florist exposes to pesticides Year before, during and after pregnancy and ever. **Type of pesticides:** Based on type of pest: (combine)	**Tool:** Mailed questionnaire The questionnaire Possible occupational related health hazard for each parent among one item was insecticides, herbicides or fungicides A year before pregnancy, during pregnancy and/ or after child birth Telephone interview To verify the exposure	**Results:** Father, mother and both occupational exposure to insecticide, herbicides or fungicides year before, during and after pregnancy has increased risk of childhood leukaemia in local controls except for mother during and after pregnancy. Father and both occupational exposure to insecticide, herbicides or fungicides year before, during and after pregnancy has reduced risk of childhood leukaemia in state controls. Mother occupational exposure to insecticide, herbicides or fungicides year before, during and after pregnancy has increased risk of childhood leukaemia in state controls. This happen because of state controls more frequently lived in rural areas than leukaemia cases.
Title: Leukaemia and non-Hodgkin lymphoma in childhood and exposure to pesticides **Author:** Meinert, R **Country; Year:** Germany; 2000	**Case sample:** Acute leukaemia diagnosed between January 1980 and September 1994 in children aged 15 years or less in West Germany. ***Participants:*** 1,184 children with leukaemia **Control sample:** Control matches to cases by age , residency and gender. ***Participants:*** 2,588	**Period of exposure:** Residential use of pesticides between year of birth and date of diagnosis. Parental occupational exposure to pesticides year before, during and after pregnancy and ever. **Type of pesticides:** Based on type of pest: (combine)	**Tool:** Mailed questionnaire The questionnaire asked parents to list all of their occupational related hazard and demographic data Telephone interview The interviews were conducted to check any missing or discrepancy information.	**Results:** Mother occupational exposure to insecticide, herbicides or fungicides year before (OR 2.1(0.1-4.2)), during (OR 3.6(1.5-8.8)) and after (OR 2.5 (1.0-6.4)) pregnancy has increased risk of childhood leukaemia. Father occupational exposure to insecticide, herbicides or fungicides year before (OR 1.1(1 .1-2.2)), during (OR 1.1(1.1-2.3)) and after (OR 1.3(1.1-2.3)) pregnancy has increased risk of childhood leukaemia. Pesticide used on farm (OR 1.5(1.0-2.2)) increased risk of childhood AL but not in garden

Meanwhile, Soldin et al., conducted a hospital-based case-control study in the Washington DC metropolitan area with the main aim to determine the relationship between pesticides exposure in a residential environment and the risk of paediatric ALL (15). The fining of the study showed there were statistically significant associations between the risk of ALL and maternal exposure to insecticides in the residential area. In contrast, the urinalysis showed significant results of maternal urine containing weed pesticide. In another study by Rull et al., to explore the relationship between childhood ALL and residential proximity to agricultural pesticide applications (16). Elevated risks of ALL were observed for moderate lifetime exposure to fumigants and insecticides, but not for high exposure. Small numbers of exposed cases and controls obscured the analysis of results and the results did not show any dose-response trend.

Furthermore, Ward et al. (14) conducted a study to examine the association between residential exposure (carpet dust) to organochloride chemicals and childhood leukaemia. This study concluded that the risk of ALL was associated with increased residential concentrations of PCBs. Similar finding was found in the study by Rudent et al. (20) in France to investigate the relationship between household exposure to pesticides and the aetiology of childhood hematopoietic malignancies. This study concludes that both maternal and paternal household use of pesticides was associated with childhood AL.

Consistently, another France study by Menegaux et al. (19) showed a significant association between childhood AL and home insecticide use during pregnancy and childhood, and garden insecticide and herbicide use during pregnancy and childhood. Likewise, Monge et al. concluded that there is an elevated risk of childhood leukaemia in association with parents' exposure to pesticides prior to, and during, pregnancy, and over the first year of life in Costa Rica.

Additionally, Infante-Rivard et al. (25) conducted a population-based case-control study to evaluate the risk of childhood acute lymphoblastic leukaemia and household pesticides used. The showed a relationship between the use of pesticides in and around the home and childhood cancer. A similar study in Shanghai, conducted by Zhang et al.et al. (23) showed an association between household pesticides exposure and childhood AL.

Moreover, Meinert et al. (17) conducted a population-based study in Northern Germany to investigate the association between childhood leukaemia and pesticides exposure. These findings suggest that pesticide use in rural areas increases the risk of childhood leukaemia. Meinert et al. (18) conducted a study to assess the relationship between pesticides exposure and childhood cancer. This study provides evidence of an association between an increased risk of leukaemia and the use of household pesticides and living on farms. Table 4 shows the detail regarding study characteristics.

DISCUSSION

Several studies have reported a positive association between pesticides exposure and childhood leukaemia(14–16,18–20,23–25). The timing of exposure to pesticides appears to be critical, childhood exposure to residential exposure to pesticides before pregnancy and after pregnancy seems to present greatest risk. In studies with parental exposure, all studies showed an association between paternal and maternal exposure (17,18,20,24), except for only one study where maternal exposure has association but paternal exposure did not (15). In two studies that specifically examined the relationship with maternal residential exposure, one study showed a modest association (16) where the other showed a weak association (22). Inconsistencies among studies may be due to differences in data collection, classification of pesticides, age of children, type of pesticides and country. Dose-response relationships were observed in one study but unfortunately did not show any association, whether this observational association is causal remains questionable to date.

The Bradford Hill Criteria or Hill's criteria for causation was used in this study to assess whether any association between an exposure and disease is a causal component or not. Considerations are strength, consistency, specificity, temporality, biological gradients, plausibility/coherence.

Strength

To make decisions regarding causal relationships the larger the odds ratio (OR) in case-control studies the stronger the association (26). The OR observed from studies conducted range from weak evidence to strong evidence. In a study conducted by Rudant et al., paternal residential exposure during pregnancy showed a weak relationship with childhood ALL, but a modest relationship with maternal exposure (20). Weak to modest associations were found in studies conducted by Infante-Rivard et al. (25); Meinert et al. (17); and Meinert et al. (18). Modest associations were observed in studies conducted by Menegaux et al.

(19); Zhang et al. (23); Ward et al. (14); Rull et al. (16); and Monge et al. (24). The majority of studies showed weak to modest evidence, and the lower limits of confidence intervals are nearly null value, of which the significance can be questionable. Nevertheless, weak evidence, or small OR, does not mean no association exists, and does not rule out a cause and effect relationship. In a weak association between exposure and disease, it is possible due to potential uncontrolled confounders. In this case of pesticides exposure, other complements such as genetic component, smoking and drinking habit may play a role.

Consistency

The majority of studies showed an association between exposure and case, therefore the consistency reported of an association between pesticides exposure and childhood leukaemia tend to be the likelihood of an effect. This is the strongest evidence that supports the causal relationship between pesticide exposure and childhood leukaemia. Even though some of the studies showed consistency, different studies had different cause-effect involving different people, places and time that make the consistency observed questionable.

Specificity

The studies considered different pesticides exposure (household or occupation exposure and either from parental, maternal or paternal), different types of pesticide exposure (pesticides, insecticides, herbicides, so on), and different periods of exposure (before pregnancy, during pregnancy, after delivery or during childhood). For example, only a few studies classify a specific type of pesticides: Zhang et al. (23), DAP metabolites; Ward et al. (14), PCB's. All other studies used broad categories such as pesticides, insecticides and herbicides to classify the exposure type. For Bradford Hill, in the absence of specificity, there is no causal effect.

Temporality

In the relationship between pesticide exposure and childhood cancer, it is clear that exposure occurs prior to cancer development; nevertheless, the timeline for causative action is still lacking. In this study, increased risks were found in pre-pregnancy, pregnancy or childhood cases without a clear timeline window. Nevertheless, exposure during pregnancy was consistent with childhood leukaemia.

Biological gradients

Only one study attempted to assess childhood ALL in response to an increased risk of pesticide exposure. In a study conducted by Rull et al. (16), moderate exposure to insecticides and fumigates in a residential area showed an increased risk of childhood ALL, compared to greater residential exposure. This study did not support biological gradient and causal relationships. Furthermore, randomised controlled trial studies are useful in assessing the dose-response relationship because they avoid some biases such as selection bias compared to other studies design.

Plausibility / Coherence

Pesticide is a heterogeneous group of chemical agents or compounds for biological activity. Similar to other biologically active chemicals, it may play a role in the aetiology of cancer, but the explanation behind it remains unclear. Coherence between epidemiological studies and laboratory findings would increase the likelihood of a causal relationship, but the lack of coherence did not rule out the relationship. Four studies contained laboratory findings, but only some participants were involved.

LIMITATIONS

Ascertainment of exposure assessment and reporting

It has diverse etiologies for cancer to develop and may take many years before the disease is evident. Several studies have relied on self - reported exposure, which offers useful information, but the major weakness of the exposure information is inaccurate. Most of the studies did not identify a particular pesticide type or timing of exposure to the pesticide. It is very important to identify specific types of pesticides because each pesticide has its biochemical properties, which increase the risk of developing cancer. The timing of pesticide exposure during pregnancy, as well as during infancy, is important because of the dynamic developmental processes of children. Poor exposure measurement makes it more difficult to observe the effect; therefore, exposure assessment is important. Therefore, the focus is important not only on the pesticide type but also on the timing of exposure.

Genetic susceptibility

Childhood leukaemia is a heterogeneous disease that includes several cytogenetic subtypes.

Susceptibility to cancer may differ within a population due to genetic mutations of genes. To date, the studies regarding the role of genes such as multiple drug resistance (MDRI) genes, cytochrome P450 (CYP) genes and glutathione S-transferase (GST) in the aetiology of childhood leukaemia is mixed, likely due to small sample sizes.

Biological measurement

Only few studies demonstrated biological measurement, although without the involvement of all participants in which may cause flaws in the results. Moreover, long latency periods between cancer developments may not reflect the etiological agents, not all chemical measurements are routinely available and are also expensive.

Case definition

Most of the data provided were not specific to one type of leukaemia which comprised of heterogeneous subtypes such as ALL, AML, chronic lymphoblastic leukaemia and other forms. It may be important to investigate the different sub-types of leukaemia as they have a slightly different type of etiologies and grouping them may obscure the association.

Bias

Selection bias is one of the most powerful prejudices in an epidemiological study. Selection bias may be due to faulty sample frame, worried participants, or self - selection bias. In some of the studies conducted, the participant and the researchers were not blinded. This will overestimate or underestimate that association. One of the major concerns or limitations inherent in case-control studies using questionnaire data is recall bias. Recall of exposure to pesticide especially if it happened years back may be difficult and different and resulting potentially in recall bias. Parents with children with leukaemia will probably be more anxious and may over-report the exposure. Furthermore, parents may have emotional instability after their child has been diagnosed as having cancer and that will jeopardise the analysis. This will lead to false-positive association. General population controls may be under-reported because of failure to remember and report previous exposure very accurately. Misclassification bias is also a major potential bias in most of the studies. It occurs when either exposure status is incorrect or the disease status is incorrect. When dealing with pesticides exposure, and childhood leukaemia, misclassification bias can arise from incorrect exposure status where exposure was classified as a non-exposed group, and more likely to be non-differential, that will weaken the size of effect.

CONCLUSIONS

This review revealed the association between exposure to pesticides and childhood leukaemia. However, whether the causal association remains uncertain and doubtful and no specific conclusions can be drawn from existing studies. Childhood leukaemia is a fairly rare disease of multifactorial etiologies; more work needs to be done to validate results with larger sample size, to better quantify exposure assessments like occupational history, environmental exposure and biological measurement of pesticide metabolites, and to consider possible genetic changes. Although there is no causal relationship to date, children should be avoided to any exposure of pesticides.

CONFLICT OF INTEREST

Authors declare none.

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