Aetiology of childhood acute lymphoblastic and myeloid leukaemia: an overview of reviews (evidence summary)

EC van Dalen[1], I Kreis[2], E van Rongen[2], E Leclercq[1], WA Kamps[3], N van Larebeke[4], R Pieters[3], LCM Kremer[1]

[1]Cochrane Childhood Cancer Group; [2]Gezondheidsraad; [3]Stichting Kinderoncologie Nederland; [4]Universiteit Gent

Introduction

Leukaemias, cancers of the haematopoietic system, are the most common malignancies in childhood. The majority (approximately 80%) of childhood leukaemia cases are acute lymphoblastic leukaemia (ALL), with the remainder being almost exclusively acute myeloid leukaemia (AML). Chronic forms of childhood leukaemia, either myeloid or lymphoid, are rare [1].

ALL and AML have distinct origins. They involve malignant transformation of lymphoid progenitor cells and myeloid progenitor cells, respectively. [1, 2]. Furthermore, the major morphological division into ALL and AML is supplemented by the identification of a range of subsets based on gene expression, antigens that delineate cell type or differentiation status, and chromosomal and molecular abnormalities [3].

Children with certain genetic syndromes, such as Down syndrome, neurofibromatosis, Klinefelter syndrome or Fanconi anaemia, have an increased risk of developing childhood ALL and/or AML [1]. Childhood leukaemia can also develop as a so-called secondary malignancy after exposure to, for example, specific chemotherapy agents. Secondary leukaemias are mostly AML, but treatment-related ALL does occur [1]. The precise aetiology of childhood leukaemia remains unclear, although it is certain that acquired and/or inherited mutations play a central role and both genetic susceptibility and environmental exposures are likely to be involved. Different possible aetiological factors, like infectious exposure, pesticide exposure and ionizing radiation [4-6], have been mentioned in the literature. Different cell types, i.e. lymphoid or myeloid, may respond differently to aetiological factors [1, 2].

Objective

The objective of this study was to give an overview of the available evidence on the aetiology of ALL and AML as published in systematic reviews and evidence summaries of (international) guidelines.

Methods

Identification of eligible publications:

The database of PubMed/MEDLINE (from 1990 to March 2nd 2010) was searched for potentially relevant articles, combining subject headings and text words for ALL and AML, children, aetiology and relevant publication types (see Appendix 1 for the complete search strategy). The reason for choosing the year 1990 as the starting point of the search was that before the 1980s diagnostic methods to reliably differentiate between ALL and AML were not available and due to a different aetiology it is not appropriate to pool data on ALL and AML. It was expected that the first eligible publications would be available from 1990 onwards. Furthermore, we searched for guidelines using the following sources: (1) the National Guideline Clearinghouse™ (http://www.guideline.gov; searched on March 8th 2010), (2) the Scottish Intercollegiate Guidelines Network (SIGN) (http://www.sign.ac.uk/guidelines; searched on March 9th 2010), (3) the National Institute for Clinical Excellence – a Special Health Authority for England and Wales (NICE) (http://www.nice.org.uk; searched on March 9th 2010; NICE guidelines only) and (4) Dutch guidelines from several sources (http://www.artsenapotheker.nl/richtlijn; searched on March 9th 2010). Finally, information on additional publications was located by scanning the reference lists of included publications and through experts in the field.

In the protocol it was stated that if necessary, and depending on the available time, we would search for original studies published after the search of the most appropriate systematic review or guideline on a certain aetiological factor has been performed. However, due to the large amount of available data this has not been done.

Selection of eligible publications:

Eligible publications were selected on the basis of title and abstract by two independent reviewers, using the following inclusion criteria: provision of data on any type of aetiological factor for childhood ALL and AML (i.e. patients < 18 years at diagnosis); if a study included both children with ALL and AML data on patients with ALL and AML should be presented separately. If the abstract of the publication was unavailable electronically or in case it provided insufficient information, full papers were retrieved for more detailed examination. The screening of guidelines from the different sources and the screening of the reference lists of included reviews were performed by one reviewer (also based on the above mentioned inclusion criteria).

In the protocol it was stated that depending on the number of eligible publications we would only include high quality publications. During the selection process it became clear that there was a large amount of available data and therefore, it was decided to limit the inclusion to publications of systematic reviews and meta-analyses with a systematic literature search; narrative reviews were thus excluded. Furthermore, it was decided to only include publications evaluating external aetiological factors, thus excluding syndromes and other genetic factors. Also, non-English language publications and publications on leukaemia as a secondary malignancy were excluded.

All retrieved publications were screened by two reviewers to ensure that they met the inclusion criteria. When more than 1 publication was available for an aetiological factor the most appropriate publication was selected, i.e. either the publication with the most recent literature search or the publication with

the largest search period (to be decided by two independent reviewers). In case of double publication only one study was included.
We resolved most discrepancies between reviewers by consensus. If this was impossible, we achieved final resolution using a third-party arbitrator.

Data extraction:
From each publication, information on clinical and methodological characteristics was abstracted by one reviewer and checked by another reviewer. We resolved discrepancies between reviewers by consensus. If this was impossible, we achieved final resolution using a third-party arbitrator.

Assessment of methodological quality of included publications:
To determine the methodological quality of the included publications, one reviewer assessed the design and execution of each publication; this was checked by another reviewer. The used quality criteria were based on the AMSTAR tool to assess the methodological quality of systematic reviews [7, 8] (see Appendix 2). While assessing the methodological quality of an included publication we focussed only on the studies and results eligible for our overview (i.e. with presentation of ALL and/or AML separately). We resolved discrepancies between reviewers by consensus. No third party arbitration was needed.

Data analyses:
The results were summarised descriptively (for ALL and AML separately).

Results

Selection of articles

The PubMed/MEDLINE search identified a total of 2674 potentially relevant publications. Screening of the titles and abstracts of these publications excluded 2613 studies which clearly did not met the inclusion criteria. The remaining 61 articles were retrieved in full for more detailed information. A total of 15 studies fulfilled all inclusion criteria [2, 4-6, 9-19]. The other 46 studies were excluded for reasons described in Appendix 3 [20-65]. Two additional publications were identified by experts in the field [66, 67]. No additional eligible publications were identified by screening the different guideline sources and reference lists of included reviews. In total 17 studies were included.

Description of the included articles

In Table 1 study characteristics and results of all included publications are stated; in table 2 a short summary of main results is provided.

Sixteen different aetiological factors were evaluated: parental occupational pesticide exposure [9], residential pesticide use [5], arsenic exposure in drinking water [10], nuclear facilities/power plant [6], diagnostic X-rays [11], parental alcohol consumption [12], marijuana (cannabis) smoking by parents [13], exposure to passive smoking from the parents [14], maternal folate and vitamin supplementation [15], different types of allergy [16], birth weight [2], breast feeding [17], day-care attendance and other early social contacts [18], different infectious exposures [4], socioeconomic status [19] and static and extremely low-frequency (ELF) electric and magnetic fields [66, 67].

Methodological quality of included articles

In Table 2 the assessment of the methodological quality of all included publications is presented. All studies had methodological limitations. The total percentage of criteria scored as yes out of applicable criteria ranged between 0 and 67% (i.e. for 33 to 100% of the applicable criteria in a publication either a no or can’t answer was scored).

Rating

- If all results (OR, RR, etc.) were significantly different from 1 and in the same direction (i.e. positive or negative), this was indicated as a significantly higher/lower risk.
- If more than 75% of the results (OR, RR, etc.) were significantly different from 1 and in the same direction (i.e. positive or negative), this was indicated as a mostly significantly higher/lower risk.
- If all results (OR, RR, etc) were significantly different from 1 but in different directions, this was indicated as conflicting risks.
- If more than 75% of the results (OR, RR, etc) were significantly different from 1 but in different directions, this was indicated as mostly conflicting risks.
- If more than 75% of the results (OR, RR, etc.) included 1 with a close to even distribution of the means around 1, this was indicated as neither higher or lower risk.
- If more than 75% of the results included 1, but all means were on one side, this was indicated as a non-significantly higher/lower risk.
- If the pattern of results was none of the above, this was indicated as an inconsistent risk.

Conflict of interest

Dr. E van Rongen was a member of the task group on extremely low-frequency (ELF) electric and magnetic fields of the WHO publication [67].

References

1. Smith MA, Ries LA, Gurney JG, Ross JA. Leukemia. In: Smith MA, Ries LA, Gurney JG et al (eds). Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975-1995. Pub no 99-4649 ed. Bethesda, MD: National Cancer Institute, SEER Program, 1999, pp. 17-34.
2. Caughey RW, Michels KB. Birth weight and childhood leukaemia: a meta-analysis and review of the current evidence. Int J Cancer 2009;124:2658-70.
3. Greaves M. Childhood leukaemia. BMJ 2002;324:283-7.
4. McNally RJ, Eden TO. An infectious aetiology for childhood acute leukaemia: a review of the evidence. Br J Haematol 2004;127:243-63.
5. Turner MC, Wigle DT, Krewski D. Residential pesticides and childhood leukaemia: a systematic review and meta-analysis. Environ Health Perspect 2010;118:33-41.
6. Laurier D, Jacob S, Bernier MO, Leuraud K, Metz C, Samson E, et al. Epidemiological studies of leukaemia in children and young adults around nuclear facilities: a critical review. Radiat Prot Dosimetry 2008;132:182-90.
7. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol 2007;7:10.
8. Shea BJ, Hamel C, Wells GA, Bouter LM, Kristjansson E, Grimshaw J, et al. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. J Clin Epidemiol 2009;62:1013-20.
9. Wigle DT, Turner MC, Krewski D. A systematic review and meta-analysis of childhood leukaemia and parental occupational pesticide exposure. Environ Health Perspect 2009;117:1505-13.
10. Engel A, Lamm SH. Arsenic exposure and childhood cancer-a systematic review of the literature. J Environ Health 2008;71:12-6.
11. Schulze-Rath R, Hammer GP, Blettner M. Are pre- or postnatal diagnostic X-rays a risk factor for childhood cancer? A systematic review. Radiat Environ Biophys 2008;47:301-12.
12. Infante-Rivard C, El-Zein M. Parental alcohol consumption and childhood cancers: a review. J Toxicol Environ Health B Crit Rev 2007;10:101-29.
13. Hashibe M, Straif K, Tashkin DP, Morgenstern H, Greenland S, Zhang ZF. Epidemiologic review of marijuana use and cancer risk. Alcohol 2005; 35:265-75.
14. Boffetta P, Trédaniel J, Greco A. Risk of childhood cancer and adult lung cancer after childhood exposure to passive smoke: A meta-analysis. Environ Health Perspect 2000;108:73-82.
15. Milne E, Royle JA, Miller M, Bower C, de Klerk NH, Bailey HD, et al. Maternal folate and other vitamin supplementation during pregnancy and risk of acute lymphoblastic leukaemia in the offspring. Int J Cancer 2010;126:2690-9.
16. Dahl S, Schmidt LS, Vestergaard T, Schüz J, Schmiegelow K. Allergy and the risk of childhood leukaemia: a meta-analysis. Leukaemia 2009; 23:2300-4.
17. Martin RM, Gunnell D, Owen CG, Smith GD. Breast-feeding and childhood cancer: A systematic review with metaanalysis. Int J Cancer 2005;117:1020-31.

18. Urayama KY, Buffler PA, Gallagher ER, Ayoob JM, Ma X. A meta-analysis of the association between day-care attendance and childhood acute lymphoblastic leukaemia. Int J Epidemiol 2010;39:718-32.
19. Poole C, Greenland S, Luetters C, Kelsey JL, Mezei G. Socioeconomic status and childhood leukaemia: a review. Int J Epidemiol 2006;35:370-84.
20. Infante-Rivard C. Chemical risk factors and childhood leukaemia: a review of recent studies. Radiat Prot Dosimetry 2008;132:220-227.
21. Raaschou-Nielsen O. Indoor radon and childhood leukaemia. Radiat Prot Dosimetry 2008;132:175-181.
22. Lee KM, Ward MH, Han S, Ahn HS, Kang HJ, Choi HS, et al. Paternal smoking, genetic polymorphisms in CYP1A1 and childhood leukemia risk. Leuk Res 2009;33:250-258.
23. Dockerty JD, Herbison P, Skegg DC, Elwood M. Vitamin and mineral supplements in pregnancy and the risk of childhood acute lymphoblastic leukaemia: a case-control study. BMC Public Health 2007; 7:136.
24. Schuz J, Svendsen AL, Linet MS, McBride ML, Roman E, Feychting M, et al. Nighttime exposure to electromagnetic fields and childhood leukemia: an extended pooled analysis. Am J Epidemiol 2007;166: 263-269.
25. Kheifets L, Shimkhada R. Childhood leukemia and EMF: review of the epidemiologic evidence. Bioelectromagnetics 2005; Suppl 7:S51-S59.
26. Laurier D, Grosche B, Hall P. Risk of childhood leukaemia in the vicinity of nuclear installations--findings and recent controversies. Acta Oncol 2002;41: 14-24.
27. Ahlbom IC, Cardis E, Green A, Linet M, Savitz D, Swerdlow A. Review of the epidemiologic literature on EMF and Health. Environ Health Perspect 2001;109 Suppl 6:911-933.
28. Wartenberg D. Residential EMF exposure and childhood leukemia: meta-analysis and population attributable risk. Bioelectromagnetics 2001; Suppl 5:S86-104.
29. Ahlbom A, Day N, Feychting M, Roman E, Skinner J, Dockerty J, et al. A pooled analysis of magnetic fields and childhood leukaemia. Br J Cancer 200; 83:692-698.
30. Wartenberg D. Residential magnetic fields and childhood leukemia: a meta-analysis. Am J Public Health 1998;88:1787-1794.
31. McBride ML. Childhood cancer and environmental contaminants. Can J Public Health 1998; 89 Suppl 1:S53-S68.
32. Colt JS, Blair A. Parental occupational exposures and risk of childhood cancer. Environ Health Perspect 1998;106 Suppl 3:909-925.
33. Feychting M, Schulgen G, Olsen JH, Ahlbom A. Magnetic fields and childhood cancer-a pooled analysis of two Scandinavian studies. Eur J Cancer 1995;31A:2035-2039.
34. Levallois P. Do power frequency magnetic fields cause leukemia in children? Am J Prev Med 1995;11:263-270.
35. Feychting M, Ahlbom A. Electromagnetic fields and childhood cancer: meta-analysis. Cancer Causes Control 1995;6:275-277.

36. Shleien B, Ruttenber AJ, Sage M. Epidemiologic studies of cancer in populations near nuclear facilities. Health Phys 1991;61:699-713.
37. Bates MN. Extremely low frequency electromagnetic fields and cancer: the epidemiologic evidence. Environ Health Perspect 1991;95:147-156.
38. Savitz DA, Chen JH. Parental occupation and childhood cancer: review of epidemiologic studies. Environ Health Perspect 1990;88:325-337.
39. Bhopal RS, Rankin J. Cancer in minority ethnic populations: priorities from epidemiological data. Br J Cancer 1996;Suppl 29:S22-S32.
40. Redaelli A, Laskin BL, Stephens JM, Botteman MF, Pashos CL. A systematic literature review of the clinical and epidemiological burden of acute lymphoblastic leukaemia (ALL). Eur J Cancer Care (Engl) 2005;14:53-62.
41. Juutilainen J, Kumlin T, Naarala J. Do extremely low frequency magnetic fields enhance the effects of environmental carcinogens? A meta-analysis of experimental studies. Int J Radiat Biol 2006;82:1-12.
42. Meinert R, Michaelis J. Meta-analyses of studies on the association between electromagnetic fields and childhood cancer. Radiat Environ Biophys 1996;35:11-18.
43. Hardell L, Holmberg B, Malker H, Paulsson LE. Exposure to extremely low frequency electromagnetic fields and the risk of malignant diseases-an evaluation of epidemiological and experimental findings. Eur J Cancer Prev 1995;4 Suppl 1:3-107.
44. Miller MA, Murphy JR, Miller TI, Ruttenber AJ. Variation in cancer risk estimates for exposure to powerline frequency electromagnetic fields: a meta-analysis comparing EMF measurement methods. Risk Anal 1995;15:281-287.
45. Washburn EP, Orza MJ, Berlin JA, Nicholson WJ, Todd AC, Frumkin H, et al. Residential proximity to electricity transmission and distribution equipment and risk of childhood leukemia, childhood lymphoma, and childhood nervous system tumors: systematic review, evaluation, and meta-analysis. Cancer Causes Control 1994;5:299-309.
46. Greenland S, Sheppard AR, Kaune WT, Poole C, Kelsh MA. A pooled analysis of magnetic fields, wire codes, and childhood leukemia. Childhood Leukemia-EMF Study Group. Epidemiology 2000;11:624-634.
47. Angelillo IF, Villari P. Residential exposure to electromagnetic fields and childhood leukaemia: a meta-analysis. Bull World Health Organ 1999;77:906-915.
48. Salvesen KA, Eik-Nes SH. Ultrasound during pregnancy and birthweight, childhood malignancies and neurological development. Ultrasound Med Biol 1999;25:1025-1031.
49. Blot WJ, Henderson BE, Boice JD Jr. Childhood cancer in relation to cured meat intake: review of the epidemiological evidence. Nutr Cancer 1999;34:111-118.
50. Wang H, Diepgen TL. Atopic dermatitis and cancer risk. Br J Dermatol 2006;154:205-210.
51. Wang H, Diepgen TL. Is atopy a protective or a risk factor for cancer? A review of epidemiological studies. Allergy 2005; 60:1098-1111.

52. Hjalgrim LL, Westergaard T, Rostgaard K, Schmiegelow K, Melbye M, Hjalgrim H, et al. Birth weight as a risk factor for childhood leukemia: a meta-analysis of 18 epidemiologic studies. Am J Epidemiol 2003;158:724-735.
53. Kwan ML, Buffler PA, Abrams B, Kiley VA. Breastfeeding and the risk of childhood leukemia: a meta-analysis. Public Health Rep 2004;119:521-535.
54. Davis MK. Review of the evidence for an association between infant feeding and childhood cancer. Int J Cancer 1998;Suppl 11:29-33.
55. Goh YI, Bollano E, Einarson TR, Koren G. Prenatal multivitamin supplementation and rates of pediatric cancers: a meta-analysis. Clin Pharmacol Ther 2007;81:685-691.
56. Baker PJ, Hoel DG. Meta-analysis of standardized incidence and mortality rates of childhood leukaemia in proximity to nuclear facilities. Eur J Cancer Care (Engl) 2007;16:355-363.
57. Sali D, Cardis E, Sztanyik L, Auvinen A, Bairakova A, Dontas N, et al. Cancer consequences of the Chernobyl accident in Europe outside the former USSR: a review. Int J Cancer 1996;67:343-352.
58. Adam M, Rebholz CE, Egger M, Zwahlen M, Kuehni CE. Childhood leukaemia and socioeconomic status: what is the evidence? Radiat Prot Dosimetry 2008;132:246-254.
59. Sasco AJ, Vainio H. From in utero and childhood exposure to parental smoking to childhood cancer: a possible link and the need for action. Hum Exp Toxicol 1999;18:192-201.
60. Daniels JL, Olshan AF, Savitz DA. Pesticides and childhood cancers. Environ Health Perspect 1997;105:1068-1077.
61. Infante-Rivard C, Weichenthal S. Pesticides and childhood cancer: an update of Zahm and Ward's 1998 review. J Toxicol Environ Health B Crit Rev 2007;10:81-99.
62. Bassil KL, Vakil C, Sanborn M, Cole DC, Kaur JS, Kerr KJ. Cancer health effects of pesticides: systematic review. Can Fam Physician 2007;53:1704-1711.
63. Nasterlack M. Pesticides and childhood cancer: an update. Int J Hyg Environ Health 2007;210:645-657.
64. Jurewicz J, Hanke W. Exposure to pesticides and childhood cancer risk: has there been any progress in epidemiological studies? Int J Occup Med Environ Health 2006;19:152-169.
65. Ip S, Chung M, Raman G, Chew P, Magula N, DeVine D, et al. Breastfeeding and maternal and infant health outcomes in developed countries. Evid Rep Technol Assess 2007;153:1-186.
66. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Non-ionizing radiation, Part 1: Static and extremely low-frequency (ELF) electric and magnetic fields. Lyon, IARC, 2002 (Monographs on the Evaluation of Carcinogenic Risks to Humans, 80).
67. WHO - World Health Organization. Extremely low frequency fields. Environmental Health Criteria, Vol. 238. Geneva, World Health Organization, 2007.

Appendix 1 Search strategy for PubMed/MEDLINE

For leukaemia the following subject headings and text words were used:

Acute myeloid leukaemia (AML):

acute myeloid leukemia OR acute myelogenous leukemia OR acute myelocytic leukemia OR acute myeloid leukemi* OR acute myelogenous leukemi* OR acute myelocytic leukemi* OR AML OR ((akut* OR acut*) AND (myelomonocytic OR myeloid OR myelogenous)) OR ((akut* OR acut*) AND (leukemi* OR leukaemi*) AND (myeloid* OR myelogenous* OR myelocytic*))

Combined using OR with acute lymphoblastic leukaemia (ALL):

acute lymphocytic leukemia OR acute lymphoblastic leukemia OR acute lymphocytic leukemi* OR acute lymphoblastic leukemi* OR ((akut* OR acut*) AND (leukemi* OR leukaemi*) AND (lymphocyt* OR lymphoblast*))

Combined using OR with leukaemia general:

acute leukemia OR acute leukemias OR acute leukemia* OR acute leukaemia OR acute leukaemias OR acute leukaemia* OR leukemia

[* = 1 of more letters]

For children the following subject headings and text words were be used:

infant OR infan* OR newborn OR newborn* OR new-born* OR baby OR baby* OR babies OR neonat* OR perinat* OR postnat* OR child OR child* OR schoolchild* OR schoolchild OR school child OR school child* OR kid OR kids OR toddler* OR adolescent OR adoles* OR teen* OR boy* OR girl* OR minors OR minors* OR underag* OR under ag* OR juvenil* OR youth* OR kindergar* OR puberty OR puber* OR pubescen* OR prepubescen* OR prepuberty* OR pediatrics OR pediatric* OR paediatric* OR peadiatric* OR schools OR nursery school* OR preschool* OR pre school* OR primary school* OR secondary school* OR elementary school* OR elementary school OR high school* OR highschool* OR school age OR schoolage OR school age* OR schoolage* OR infancy OR schools, nursery OR infant, newborn

For aetiology the following subject headings and text words were used:

Etiology OR etiolog* OR aetiology OR aitiology OR causation* OR Causality OR Causalities or Multifactorial Causality OR Causalities, Multifactorial OR Causality, Multifactorial OR Multifactorial Causalities OR Multiple Causation OR Causation, Multiple OR Causations, Multiple OR Multiple Causations OR Causation OR Causations OR Etiology/Narrow[filter] OR “causes” OR environmental exposure OR environmental exposures OR environmental exposur* OR Exposure, Environmental OR Environmental Exposures OR Exposures, Environmental OR residential exposure OR residential exposures OR residential exposure* OR Maternal exposure[MeSH] OR paternal exposure[MeSH] OR Inhalation exposure[MeSH] OR Occupational exposure[MeSH] OR leukemia/etiology

For (systematic) reviews and guidelines the following subject headings and text words were used:

metaanalysis OR meta-analysis OR meta analysis OR meta analys* OR metaanalys* OR meta-analys* OR review literature OR review[pt] OR Review Literature as Topic[MeSH] OR Meta-Analysis as Topic[MeSH] OR Meta Analysis as Topic OR meta-analysis[pt] OR technology assessment OR systematic review[tiab] OR review[pt] OR systematic literature review[tiab] OR Review, Systematic OR Review, Academic OR guideline[pt] OR Guidelines as Topic[MeSH] OR Practice Guideline[pt]

The searches for leukaemia, children, aetiology and (systematic) reviews/guidelines were combined using AND.

Appendix 2 Criteria list for the assessment of methodological quality of included reviews

	Description	**Implementation** *Note: all criteria were scored "Yes", "No', "Can't answer" (when the item is relevant but not described by the authors) or "Not applicable" (when the item is not relevant, such as when a meta-analysis has not been possible or was not attempted by the authors).*
1	Was an 'a priori' design provided?	The research question and inclusion criteria should be established before the conduct of the review.
2	Was there duplicate study selection and data extraction?	There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.
3	Was a comprehensive literature search performed?	At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.
4	Was the status of publication (i.e. grey literature) used as an inclusion criterion?	The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.
5	Was a list of studies (included and excluded) provided?	A list of included and excluded studies should be provided.
6	Were the characteristics of the included studies provided?	In an aggregated form such as a table, data from the original studies should be provided on the participants, etiologic factors and outcomes. The ranges of characteristics in all the studies analyzed e.g. age, relevant socioeconomic data, and disease should be reported.
7	Was the scientific quality of the included studies assessed and documented?	'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.
8	Was the scientific quality of the included studies used appropriately in formulating conclusions?	The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.
9	Were the methods used to combine the findings of studies appropriate?	For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).

Appendix 3 Characteristics of excluded studies

Reference	Reason for exclusion	Evaluated aetiological factor
20	No systematic review or meta-analysis with a systematic literature search	Chemical risk factors
21	No systematic review or meta-analysis with a systematic literature search	Indoor radon
22	No systematic review or meta-analysis with a systematic literature search	Paternal smoking
23	No systematic review or meta-analysis with a systematic literature search	Vitamin and mineral supplements in pregnancy
24	No systematic review or meta-analysis with a systematic literature search	Night-time exposure to electromagnetic fields
25	No systematic review or meta-analysis with a systematic literature search	Electromagnetic fields
26	No systematic review or meta-analysis with a systematic literature search	Nuclear installations
27	No systematic review or meta-analysis with a systematic literature search	Electromagnetic fields
28	No systematic review or meta-analysis with a systematic literature search	Residential electromagnetic fields
29	No systematic review or meta-analysis with a systematic literature search	Magnetic fields
30	No systematic review or meta-analysis with a systematic literature search	Residential electromagnetic fields
31	No systematic review or meta-analysis with a systematic literature search	Environmental contaminants
32	No systematic review or meta-analysis with a systematic literature search	Parental occupational exposures
33	No systematic review or meta-analysis with a systematic literature search	Magnetic fields
34	No systematic review or meta-analysis with a systematic literature search	Power frequency magnetic fields
35	No systematic review or meta-analysis with a systematic literature search	Electromagnetic fields
36	No systematic review or meta-analysis with a systematic literature search	Nuclear facilities
37	No systematic review or meta-analysis with a systematic literature search	Extremely low frequency electromagnetic fields
38	No systematic review or meta-analysis with a systematic literature search	Parental occupation
39	No aetiological factor evaluated	Not applicable
40	No aetiological factor evaluated	Not applicable
41	No human data	Extremely low frequency magnetic fields
42	Results for ALL and AML not presented separately	Electromagnetic fields
43	Results for ALL and AML not presented separately	Extremely low frequency electromagnetic fields
44	Results for ALL and AML not presented separately	Powerline frequency electromagnetic fields

45	Results for ALL and AML not presented separately	Residential proximity to electricity transmission and distribution equipment
46	Results for ALL and AML not presented separately	Magnetic fields and wire codes
47	Results for ALL and AML not presented separately	Residential exposure to electromagnetic fields
48	Results for ALL and AML not presented separately	Ultrasound during pregnancy
49	Results for ALL and AML not presented separately	Cured meat intake
50	Not the most appropriate publication for the evaluated aetiological factor	Atopic dermatitis/allergy
51	Not the most appropriate publication for the evaluated aetiological factor	Atopy/allergy
52	Not the most appropriate publication for the evaluated aetiological factor	Birth weight
53	Not the most appropriate publication for the evaluated aetiological factor	Breast feeding
54	Not the most appropriate publication for the evaluated aetiological factor	Infant feeding
55	Not the most appropriate publication for the evaluated aetiological factor	Prenatal multivitamin supplementation
56	Not the most appropriate publication for the evaluated aetiological factor	Proximity to nuclear facilities
57	Not the most appropriate publication for the evaluated aetiological factor	Chernobyl accident
58	Not the most appropriate publication for the evaluated aetiological factor	Socioeconomic status
59	Not the most appropriate publication for the evaluated aetiological factor	Parental smoking
60	Not the most appropriate publication for the evaluated aetiological factor	Pesticides
61	Not the most appropriate publication for the evaluated aetiological factor	Pesticides
62	Not the most appropriate publication for the evaluated aetiological factor	Pesticides
63	Not the most appropriate publication for the evaluated aetiological factor	Pesticides
64	Not the most appropriate publication for the evaluated aetiological factor	Pesticides
65	Not the most appropriate publication for the evaluated aetiological factor	Breast feeding

Table 1 Study characteristics and results of included systematic reviews

Description of aetiological factor [reference]	**Parental occupational pesticide exposure; critical exposure time windows were defined as pregnancy for mothers and up to 2 years before conception for fathers** [9]	**Residential pesticide use during pregnancy and childhood** [5]	**Arsenic exposure in drinking water** [10]
Type of acute leukaemia evaluated	ALL and AML	ALL and AML	ALL and AML
Number of included studies	ALL: n=11[@] AML: n=7[@]	ALL: n=5 AML: n=3	ALL: n=1
Design(s) of included studies	ALL and AML: unclear (only case-control and cohort studies were included in the review)[@] Unclear if population- or hospital based	Case-control studies ALL: n=4 population-based; n=1 part population-based and part hospital based AML: all population based No cohort studies	Case-control study (unclear if population- or hospital based)
Number of included children	ALL and AML: unclear[@]	ALL: unclear (at least 742 cases and 998 controls) AML: unclear (at least 475 cases and 526 controls)	491 cases and 491 controls
Age included children	ALL and AML: unclear[@]	ALL: < 15 years AML: < 18 years	0-9 years
Gender of included children	ALL and AML: unclear[@]	ALL and AML: unclear	Unclear

Description of literature search (i.e. sources, dates, search strategy provided yes/no, additional information)	Ovid Medline (1950 to March 2009); Ovid Medline database of in process and other non-indexed citations (1950 to March 2009); Ovid Embase (1980 to 2009); Toxnet (2009); Open Sigle (2009); Proquest digital dissertations and theses (2009); reference lists of all included studies. Search strategy provided No language restrictions	Ovid Medline (1950 to March 2009); Ovid Medline database of in process and other non-indexed citations (1950 to March 2009); Ovid Embase (1980 to March 2009); Toxnet (March 2009); Open Sigle (March 2009); Proquest digital dissertations and theses (March 2009); reference lists of all included studies; hand search of journal websites (not mentioned which). Search strategy provided No language restrictions	PubMed (dates not provided); references from selected papers were searched for additional studies. Search strategy not provided
Meta-analysis performed?; If yes: heterogeneity present?	Yes; heterogeneity in paternal ALL and AML results, no heterogeneity in maternal ALL and AML results	Yes; heterogeneity was defined as low (I^2 < 25%), moderate (I^2 50%) or high (I^2 75%); see results for presence of heterogeneity in different analyses.	No

Results as presented in article	*Paternal:* ALL: OR 1.30 (95% CI 0.86-1.94); 8 studies AML: OR 1.12 (95% CI 0.60-2.13); 4 studies[@] *Maternal:* **ALL: OR 2.64 (95% CI 1.40-5.00)**; 5 studies **AML: OR 2.64 (95% CI 1.48-4.71)**; 4 studies[@]	*Unspecified residential pesticides:* *Pregnancy:* **ALL: OR 2.04 (95% CI 1.54-2.68)**; 5 studies; I^2 19% AML: OR 1.44 (95% CI 0.81-2.59); 3 studies; I^2 80% *Childhood:* ALL: OR 1.40 (95% CI 0.90-2.16); 4 studies; I^2 32% AML: OR 1.71 (95% CI 0.77-3.80); 2 studies; I^2 41% *Residential insecticides:* *Pregnancy:* **ALL: OR 2.14 (95% CI 1.83-2.50)**; 4 studies; I^2 0% **AML: OR 1.85 (95% CI 1.29-2.64)**; 2 studies; I^2 0% *Childhood:* ALL: OR 1.35 (95% CI 0.76-2.38); 3 studies; I^2 51% *Residential herbicides:* *Pregnancy:* **ALL: OR 1.73 (95% CI 1.28-2.35)**; 4 studies; I^2 0% *Childhood:* ALL: OR 0.85 (95% CI 0.43-1.66); 3 studies; I^2 78%	ALL: Used cut off points: 5 µg/litre for average exposure in pre-and postnatal periods and for cumulative exposures 1.46 or 10.78 mg/litre-days for pre-and postnatal periods respectively. *Prenatal period:* Fewer cases than controls had arsenic exposure above cut off point: 18 versus 19 for average exposure; OR 0.94, not significant 20 versus 27 for cumulative exposure; OR 0.70, not significant. *Postnatal period:* More cases than controls above cut off point: 20 versus 14 for average exposure; OR 1.39 (95%CI 0.70-2.76) 19 versus 17 for cumulative exposure; OR 1.14 (95% CI 0.59-2.12)

Conclusion of article	Both ALL and AML were associated with prenatal maternal occupational pesticide exposure; associations of ALL and AML with paternal preconceptual occupational pesticide exposure were not identified. Research needs include improved pesticide exposure indices, continued follow-up of existing cohorts, genetic susceptibility assessment and basic research on childhood leukaemia initiation and progression.	Positive associations were observed between ALL and residential pesticides exposure during pregnancy (for all three types of pesticides). The same is true for residential insecticides during pregnancy and AML. For other exposures no significant effect was identified. Further work is needed to confirm previous findings based on self-report, to examine potential exposure-response relationships and to assess specific pesticides and toxicologically related subgroups of pesticides in more detail.	The literature, while limited, does not seem to support an association between arsenic exposure and ALL. This might be due to long latency periods for cancer development (i.e. cancer does not occur in childhood) or arsenic-induced childhood cancers are too infrequent to have been detected with the current study design.
Notes	Unfortunately, the online supplemental material of this review is not available; it is possible that data missing in the article are stated there. In this review also studies which did not present results on AML and ALL separately were included, but those studies were not eligible for our publication; in total 35 studies reporting on leukaemia only were included (it was unclear how many of those reported AML and/or ALL separately).	In this review also studies which did not present results on AML and ALL separately were included, but those studies were not eligible for our publication; in total 17 studies reporting on leukaemia only were included, of which 7 (also) presented results on AML and/or ALL separately.	In this review also studies which did not present results on AML and ALL separately were included, but those studies were not eligible for our publication; in total 5 studies reporting on leukaemia only were included, of which 1 (also) presented results on ALL separately.

Table 1 Study characteristics and results of included systematic reviews (continued)

Description of aetiological factor [reference]	**Nuclear facilities/power plant** [6]	**Pre-and postnatal diagnostic X-rays** [11]	**Parental alcohol consumption** [12]
Type of acute leukaemia evaluated	ALL	ALL and AML	ALL and AML
Number of included studies	n=1	ALL: n=1 AML: n=1	ALL: n=7 AML: n=4
Design(s) of included studies	Multi-site study (4 sites in Sweden; radius to plant: Sweden)	ALL and AML: case-control studies ALL and AML: unclear if population- or hospital based	ALL: all case-control studies (n=5 population-based, n=1 hospital-based and n=1 both hospital- and population-based) AML: all case-control studies (all population-based)
Number of included children	Unclear (656 observed cases)	ALL: 1842 cases; 1986 controls AML: 80 cases; 240 controls; 517 children with ALL (unclear if these were used as controls)	ALL maternal: 1946 cases; 2222 controls ALL paternal: 691 cases; 1085 controls AML maternal: 355 cases; 985 controls AML paternal: 346 cases; 985 controls
Age included children	Range 0-14 years	ALL: < 15 years AML: < 14 years	ALL: 0-14 years AML: 0-17 years
Gender of included children	Unclear	ALL and AML: unclear	Unclear

Description of literature search (i.e. sources, dates, search strategy provided yes/no, additional information)	PubMed, Scopus (no dates provided); additional documents from Institute of Radiological Protection and Nuclear Safety Archives and direct contact with researchers. Search strategy not provided	PubMed (January 1990 to December 2006); Current Contents; Cochrane; Scirus MedPilot; Kinderkrebsinfo; Deutsches Medizin-Forum (no search date provided unless otherwise stated); reference lists of identified papers; hand search journals "International Journal of Epidemiology" and "British Journal of Radiology" (2001 and 2002). Search strategy provided Published in English	PubMed (1960-2003); relevant references were obtained from selected articles. Search strategy provided Written in English
Meta-analysis performed?; If yes: heterogeneity present?	Not applicable	ALL and AML: not applicable	No
Results as presented in article	Observed cases n=656; expected cases not mentioned (no further information provided)	*X-rays versus no/number of X-rays (target organs not specified):* ALL: *Prenatal* crude OR 0.95 (95% CI 0.73-1.23) ***Postnatal*** **crude OR 1.63 (95% CI 1.43-1.85)** *X-rays versus no X-rays (target organs not specified):* AML: *Prenatal* crude OR 2.35 (95% CI 0.79-7.00) *Postnatal:* not evaluated	*Maternal alcohol consumption*[¥]*:* ALL: No pooling, individual study results: *Year before pregnancy:* OR 1.2 (95% CI 0.9-1.5) *Month prior to pregnancy:* OR 1.1 (95% CI 0.8-1.6) OR 0.8 (95% CI 0.6-1.1) *During pregnancy:* OR 1.0 (95% CI 0.8-1.2) OR 1.4 (95% CI 1-2) OR 0.7 (95% CI 0.5-0.9) OR not stated, no significant effect 0-4 years^: OR 1.1 (95% CI 0.8-1.9) 5-9 years^: OR 0.8(95% CI 0.5-1.5)

			10-14 years^: OR 1.0 (95% CI 0.4-2.1) 1st trimester: OR 1.2 (95% CI 0.8-1.7) OR 0.7 (95% CI 0.5-1.0) 2nd trimester: OR 1.2 (95% CI 0.8-2) **OR 0.7 (95% CI 0.5-0.9)** 3rd trimester: OR 1.1 (95% CI 0.7-1.8) **OR 0.7 (95% CI 0.5-0.9)** 1-4 wine glasses/mo: OR 1.4 (95% CI 0.9-2.3) > 4 wine glasses/mo: OR 0.7 (95% CI 0.3-1.5) 1-4 beer cans/mo: OR 1.2 (95% CI 0.7-2.3) > 4 beer cans/mo: OR 0.7 (95% CI 0.3-1.5) 1-4 liquor drinks/mo: OR 1.9 (95% CI 1-3.7) > 4 liquor drinks/mo: OR 0.5 (95% CI 0.2-1.7) **1-20 total drinks: OR 1.8 (95% CI 1.1-2.7)** ≥ 20 total drinks: OR 0.9 (95% CI 0.5-1.6) ≥ 2 glasses/week: **OR 0.57 (95% CI 0.34-0.95)** < 1 drink/d (wine, beer, spirits): OR 0.7 (95% CI 0.5-1.0) ≥ 1 drink/d (wine, beer, spirits): OR 0.8 (95% CI 0.5-1.6) **Wine: OR 0.7 (95% CI 0.5-0.9)** Beer: OR 0.7 (95% CI 0.5-1.1) Spirits: OR 0.9 (95% CI 0.5-1.3) *During breastfeeding:* OR 1.0 (95% CI 0.61-1.7) **OR 0.5 (95% CI 0.3-0.8)**

			Paternal alcohol consumption[¥]*:* ALL: No pooling, individual study results: *Month prior to conception:* OR 1.2 (95% CI 0.8-1.9) **OR 1.4 (95% CI 1-2)** 1-15 wine glasses/mo: OR 0.9 (95% CI 0.6-1.4) ≥ 16 wine glasses/mo: OR 0.6 (95% CI 0.2-1.6) 1-15 beer cans/mo: OR 0.9 (95% CI 0.6-1.5) 16-30 beer cans/mo: OR 1.6 (95% CI 0.9-2.8) ≥ 31 beer cans/mo: OR 1.5 (95% CI 0.9-2.6) 1-15 liquor drinks/mo: OR 0.7 (95% CI 0.4-1.1) ≥ 16 liquor drinks/mo: OR 0.7 (95% CI 0.3-1.4) 1-30 total drinks/mo: OR 1.0 (95% CI 0.7-1.7) 31-45 total drinks/mo: OR 0.5 (95% CI 0.2-1.1) ≥ 46 total drinks/mo: OR 1.6 (95% CI 0.9-2.9) < 1 drink of any alcohol/d: OR 1.4 (95% CI 1-2) 1-2 drinks of any alcohol/d: OR 1.6 (95% CI 1.1-2.5) ≥ 3 drinks of any alcohol/d: OR 1.7 (95% CI 1.1-2.7) Wine: OR 1.2 (95% CI 0.8-1.5)

			Beer: OR 1.5 (95% CI 1.1-2.0) **Spirits: OR 1.5 (95% CI 1.1-1.9)** *Exposure period not stated:* 60 g/d: OR 1.8 (95% CI 0.2-19.5) *Maternal alcohol consumption[¥]:* AML: No pooling, individual study results: *Month prior to pregnancy:* **OR 1.8 (95% CI 1-3.3)** *During pregnancy[†]:* OR 2.6 (95% CI 1.4-5.1) Wine, beer or spirits: OR 1.4 (95% CI 0.9-2.2) for all types of AML OR 1.4 (95% CI 0.8-2.7) for myeloblastic leukaemia OR 0.5 (95% CI 0.05-3.5) for promyelocytic leukaemia OR 0.6 (95% CI 0.2-1.8) for myelomonocytic leukaemia **OR 11 (95% CI 1.6-473.4) for monocytic leukaemia** **OR 3 (95% CI 1.2-8.4) for children diagnosed at 0-2 years** **OR 9 (95% CI 1.2-394.5) for children diagnosed with myelomonocytic leukaemia or monocytic leukaemia at 0-2 years** **1st trimester: OR 1.9 (95% CI 1-3.6)** **2nd trimester: OR 2.5 (95% CI 1.2-5.3)** **3rd trimester: OR 2.4 (95% CI 1.1-5.5)**

			1-4 wine glasses/mo: OR 2.0 (95% CI 0.8-4.7) > 4 wine glasses/mo: OR 2.3 (95% CI 0.7-7.5) 1-4 beer cans/mo: OR 1.2 (95% CI 0.4-3.6) > 4 beer cans/mo: OR 2.2 (95% CI 0.7-7.0) 1-4 liquor drinks/mo: **OR 6.4 (95% CI 2-20.8)** > 4 liquor drinks/mo: No data provided **1-20 total drinks: OR 2.4 (95% CI 1.1-5.0)** **≥ 20 total drinks: OR 3.1 (95% CI 1.2-8.1)** *During breast feeding:* OR 0.8 (95% CI 0.3-1.9) *Paternal alcohol consumption*[¥]*:* AML: No pooling, individual study results: *One year prior to conception:* OR 1.5 (95% CI 0.6-3.5) *Month prior to conception:* OR 0.8 (95% CI 0.4-1.6) Wine, beer or spirits: OR not mentioned, no significant effect 1-15 wine glasses/mo: OR 1.0 (95% CI 0.4-2.0) ≥ 16 wine glasses/mo: OR 1.0 (95% CI 0.2-5.7) 1-15 beer cans/mo: OR 0.9 (95% CI 0.4-2.0) 16-30 beer cans/mo: OR 0.7 (95% CI 0.3-2.0)

			≥ 31 beer cans/mo: OR 0.9 (95% CI 0.4-2.0) 1-15 liquor drinks/mo: OR 0.8 (95% CI 0.3-1.8) ≥ 16 liquor drinks/mo: OR 1.4 (95% CI 0.4-5.4) 1-30 total drinks/mo: OR 0.6 (95% CI 0.3-1.4) 31-45 total drinks/mo: OR 0.6 (95% CI 0.2-2.0) ≥ 46 total drinks/mo: OR 0.9 (95% CI 0.4-2.2)
Conclusion of article	Risk of ALL is higher close to nuclear power plant than elsewhere.	No association of ALL and AML with prenatal diagnostic X-ray exposures observed; postnatal diagnostic X-ray exposures were associated with a significant increase in ALL (for AML not evaluated). Most studies had limitations; computed tomography is not covered in this review.	Inconsistencies in the results and the low risks reported do not suggest an association between ALL and AML and parental alcohol consumption. However, before reaching any definitive conclusions, methodological issues need to be addressed in future studies, as well as the role of genetic susceptibility.
Notes	In this review also studies which did not present results on AML and ALL separately were included, but those studies were not eligible for our publication; in total 198 single-site studies (unclear if leukaemia only was analysed) and 22 multi-site studies (of which 1 presented results on ALL) were included.	In this review also studies which did not present results on AML and ALL separately were included, but those studies were not eligible for our publication; in total 9 studies reporting on leukaemia only were included, of which 1 (also) presented results on AML and 1 (also) presented results on ALL separately.	In this review also studies which did not present results on AML and ALL separately were included, but those studies were not eligible for our publication; in total 11 studies reporting on leukaemia only were included, of which 8 (also) presented results on AML and/or ALL separately.

Table 1 Study characteristics and results of included systematic reviews (continued)

Description of aetiological factor [reference]	**Marijuana (cannabis) smoking by parents** [13]	**Exposure to passive smoking from the parents** [14]	**Maternal folate and vitamin supplementation before and / or during pregnancy** [15]
Type of acute leukaemia evaluated	AML	ALL and AML	ALL
Number of included studies	n=1	Exposure to tobacco smoke from mother during pregnancy: ALL: n=6 AML: n=2 Exposure to maternal tobacco smoke before pregnancy: ALL: n=1 Exposure to paternal tobacco smoke: ALL: n=6 AML: n=3	n=7
Design(s) of included studies	Case-control study; population-based	ALL and AML: case-control studies ALL and AML: unclear if population- or hospital based	Case-control studies (all population-based)
Number of included children	204 cases; 204 controls	Exposure to tobacco smoke from mother during pregnancy: ALL: n=1684 cases; n=2488 controls AML: n=110 cases; n=865 controls Exposure to maternal tobacco smoke before pregnancy: ALL: n=73 cases; n=196 controls Exposure to paternal tobacco smoke: ALL: unclear in two studies, in the other 4 studies n=787 cases; n=1428 controls AML: unclear in one study, in the other 2 studies n=110 cases; n=865 controls	n=3965 cases and n=6728 controls

Age included children	AML diagnosed < 18 years; age controls unclear	ALL: 0-16 years AML: 0-15 years	0-14 years
Gender of included children	Unclear	Unclear	Cases: unclear (at least 177 girls and 216 boys) Controls: unclear (at least 558 girls and 661 boys)
Description of literature search (i.e. sources, dates, search strategy provided yes/no, additional information)	PubMed/Medline (published up to November 2004); literature citations of each of the publications identified. Search strategy provided	Medline (dates nor mentioned); recent reviews; reference lists from papers identified through Medline. Search strategy not provided No restrictions regarding language and type of publication.	PubMed (1966 to 2008); reference lists of two recent meta-analyses. Search strategy provided
Meta-analysis performed?; If yes: heterogeneity present?	Not applicable	Yes, for 1 etiologic factor (i.e. exposure to paternal tobacco smoke); yes, but unclear in which analyses (in the method section the following is stated: the authors choose a random effects model for pooling of results because of heterogeneity of results within some of the subsets of studies)	Yes; yes in the meta-analyses of vitamins during pregnancy, i.e. I^2 42.6% (in the other 4 meta-analyses no heterogeneity, i.e. I^2 0%)
Results as presented in article	*Maternal use of mind-altering drugs (mostly marijuana) during or in the year before the pregnancy:* **OR 11.0 (95% CI 1.42-85.20)** *Paternal marijuana use:* OR 1.47 (95% CI not provided; p=0.32)	*Exposure to tobacco smoke from mother during pregnancy:* ALL: No pooling of results; descriptive results of individual studies: 1) Maternal smoking 1-9 cpd RR 1.0 (95% CI 0.6-1.5); maternal smoking >=10 cpd RR 0.9 (95% CI 0.7-1.1) 2) Maternal smoking 1-9 cpd RR 1.3 (95% CI 0.7-2.6); maternal smoking >=10 cpd **RR 3.4 (95% CI 2.1-5.7)**	*Vitamins with folate versus no folate during pregnancy:* OR 1.06 (95% CI 0.77-1.46; 2 studies) *Vitamins with folate versus no vitamins during pregnancy:* OR 1.02 (95% CI 0.86-1.21; 2 studies) *Vitamins before pregnancy:*

		The interpretation was limited due to the selection of children with diabetes as controls. 3) Maternal smoking any RR 0.7 (95% CI 0.5-1.1) 4) Maternal smoking any: RR 1.9 (95% CI 0.9-4.1) 5) Maternal smoking 1-10 cpd RR 0.8 (95% CI 0.5-1.3); maternal smoking 11-20 cpd RR 0.8 (95% CI 0.4-1.4); maternal smoking >= 21 cpd: RR 0.5 (95% CI 0.1-1.9) 6) Maternal smoking any: RR 1.2 (95% CI 1.0-1.5) AML: 1) Maternal smoking any: RR 2.0 (95% CI 0.8-4.8) 2) Maternal smoking 1-10 cpd: RR 0.5 (95% CI 0.2-1.3); maternal smoking 11-20 cpd RR 0.4 (95% CI 0.1-1.1); maternal smoking >= 21 cpd: RR 0.7 (95% CI 0.1-5.8) *Exposure to maternal tobacco smoke before pregnancy:* ALL: No pooling; descriptive results of individual study: OR 2.1 (95% CI 1.0-4.3) *Exposure to paternal tobacco smoke:* ALL: 4 studies were pooled (individual results not presented; 3 studies paternal smoking any, 1 study paternal smoking 1-10 cpd, 11-20 cpd	OR 0.95 (95% CI 0.95-1.18; 2 studies) *Vitamins only before pregnancy:* OR 1.05 (95% CI 0.55-2.01; 2 studies) *Vitamins during pregnancy:* **OR 0.83 (95% CI 0.73-0.94**; 5 studies) *Maternal folate supplementation in month preceding pregnancy:* OR 1.63 (95% CI 0.55-4.82; 1 study)

		and >=21 cpd): RR=1.17 (95% CI 0.96-1.42) 1 study: a trend in risk was suggested for ALL (no further information provided) 1 study: a significant dose response was found among pack years of cigarettes smoked before conception and risk of ALL Additional information: In 1 study data were provided on paternal smoking before birth in absence of maternal smoking: a weak association was identified (no further information provided) In 1 study evaluating a dose response relationship no clear evidence of a dose response relationship was found (no further information provided). Analysis of pack years smoked by the father after the index birth was associated with a non-significantly increasing trend of ALL. AML: 1) paternal smoking any: RR 0.9 (95% CI 0.3-2.1) 2) paternal smoking 1-10 cpd: RR 0.4 (95% CI 0.1-1.9); paternal smoking 11-20 cpd RR 0.7 (95% CI 0.3-1.9); paternal smoking >= 21 cpd: RR 1.3 (95% CI 0.4-3.7) I.e. no clear evidence of a dose response relationship. 3) In 1 study evaluating a dose response relationship a non-significant increasing trend was found for AML (no further information provided). Analysis of pack years smoked by the father after the index	

		birth was not associated with the risk of AML.	
Conclusion of article	Sufficient studies are not available to adequately evaluate marijuana impact on AML risk. The identified study had several limitations (such as small number of exposed cased, possible publication and recall bias, confounding by other drugs such as tobacco use). Dose response relations were not assessed.	Results for maternal or paternal tobacco smoke before, during and after pregnancy were too sparse to suggest an association with childhood ALL or AML. No clear evidence of dose response was present in the studies that addressed this issue. Bias and confounding cannot be ruled out. Further studies are needed to confirm the hypothesis that parental tobacco smoke is a risk factor for childhood AML or ALL.	The results do not support the hypothesis that maternal use of folate supplements during pregnancy protects against the risk of childhood ALL. It suggests that vitamin supplementation in general during pregnancy may protect against childhood ALL, but, on present evidence, this effect is unlikely to be large or, if real, due specifically to folate.
Notes	In this review also studies which did not present results on AML and ALL separately were included, but those studies were not eligible for our publication; in total 2 studies reporting on leukaemia only were included, of which 1 (also) presented results on AML separately.	In this review also studies which did not present results on AML and ALL separately were included, but those studies were not eligible for our publication; for maternal smoke during pregnancy in total 11 studies reporting on leukaemia only were included, of which 6 (also) presented results on AML and/or ALL separately; for maternal smoke before pregnancy in total 3 studies reporting on leukaemia only were included, of which 1 (also) presented results on ALL separately; for paternal smoke in total 7 studies reporting on leukaemia only were included, of which 4 (also) presented results on AML and/or ALL separately.	-

Table 1 Study characteristics and results of included systematic reviews (continued)

Description of aetiological factor [reference]	**Different types of allergy** [16]	**Birth weight** [2]	**Breast feeding** [17]
Type of acute leukaemia evaluated	ALL and AML	ALL and AML	ALL and AML
Number of included studies	ALL: n=8 AML: n=3	ALL: n=24 AML: n=14	ALL: n=19 AML: n=10
Design(s) of included studies	ALL: all case-control studies (6 population-based; 2 hospital-based) AML: all case-control studies (unclear if hospital- or population-based)	ALL: n=20 case-control studies (unclear if population- or hospital based); n=4 cohort studies AML: n=12 case-control studies (unclear if population- or hospital based); n=2 cohort studies	ALL: n=18 case-control studies (n=13 population-based, n=4 hospital-based and n=1 unclear) ; n=1 historical cohort AML: n=10 case-control studies (n=7 population-based, n=2 hospital-based and n=1 unclear)
Number of included children	ALL: unclear (at least 4522 cases) AML: unclear (at least 327 cases) There were 9619 controls in total, but it was unclear if those were used for ALL or AML.	ALL: 10974 cases[#]; controls unclear AML: 1832 cases[#]; controls unclear	ALL: 7842 cases; controls unclear AML: 1286 cases; controls unclear
Age included children	ALL and AML: < 16 years	ALL and AML: < 30 years (when one study including patients < 30 years was excluded the age limit was < 20 years)	ALL and AML: 0-17 years
Gender of included children	Unclear	Unclear	Unclear

Description of literature search (i.e. sources, dates, search strategy provided yes/no, additional information)	PubMed (no dates provided, studies published before November 2008 included; EMBASE (no dates provided; studies published before November 2008 included); reference lists of identified publications/reviews; manual search on author name of persons known to be active in the field of childhood cancer epidemiology. Search strategy provided No language restrictions	Medline (dates not provided; articles published before September 1st 2008 were included); EMBASE (dates not provided; articles published before September 1st 2008 were included); cross-referencing using a validated snowballing technique. Search strategy provided	Medline (from inception up to June 2004 and updates until April 2005); reference lists of eligible studies, reviews and meta-analyses Search strategy provided
Meta-analysis performed?; If yes: heterogeneity present?	Yes; see results below	Yes; see results below	Yes; see results below
Results as presented in article	ALL: *Overall allergy:* OR 0.67 (95% CI 0.54-0.82); 8 studies; I^2 not mentioned *Asthma:* OR 0.82 (95% CI 0.63-1.10); 6 studies; I^2 43% *Hay fever:* OR 0.53 (95% CI 0.43-0.65); 5 studies; I^2 28% *Eczema:* OR 0.68 (95% CI 0.56-0.83); 5 studies; I^2 29% 1 study compared relationship between allergies and age at diagnosis leukaemia: no	*High birth weight compared to normal birth weight (no definitions provided):* ALL: **OR 1.24 (95% CI 1.18-1.33)**[$]; 23 studies; no heterogeneity AML: **OR 1.24 (95% CI 1.16-1.32)**[$]; 9 studies; no heterogeneity *Low birth weight (no definition provided):* ALL: OR 0.97 (95% CI 0.81-1.16); 10 studies; no heterogeneity AML: **OR 1.50 (95% CI 1.05-2.13)**[$]; 9 studies; heterogeneity of borderline significance (p=0.05)	*Breast feeding:* ALL **OR 0.91 (95% CI 0.84-0.98)**; 17 studies; I^2 16% AML: OR 0.88 (95% CI 0.76-1.02); 9 studies; I^2 0% *Duration of breast feeding < 6 months:* ALL: OR 0.93 (95% CI 0.86-1.00); 12 studies; I^2 0% AML: OR 0.97 (95% CI 0.81-1.17); 8 studies; I^2 0%

	interaction AML: *Allergies:* 3 studies were based on sparse data and showed a statistically non-significant inverse association (data were not pooled; no further information available).	 *Per kilogram increase in birth weight:* ALL: **OR 1.18 (95% CI 1.12-1.23)**; 16 studies; no heterogeneity	*Duration of breast feeding > 6 months:* ALL: **OR 0.81 (95% CI 0.72-0.91)**; 13 studies; I^2 18% AML: **OR 0.72 (95% CI 0.57-0.91)**; 9 studies; I^2 0%
Conclusion of article	It is unlikely that the strong statistical inverse association presented in the ALL analyses is solely based on methodological bias or chance.	The combined available evidence from observational studies suggests that high birth weight is associated with an increased risk of ALL. For AML the risk may be elevated at both high and low extremes of birth weight, suggesting a U-shaped association. A dose-response relationship for every kg increase in birth weight discovered positive associations for ALL.	Ever having been breast-fed is inversely associated with ALL (i.e. lower risk), but non-causal explanations are possible. A dose response relationship remains unclear. Even if causal, the public health importance of these associations may be small. Our estimates suggest that increasing breast-feeding from 50% to 100% would prevent at most 5% of cases of childhood acute leukaemia and lymphoma.
Notes	-	In this review also studies which did not present results on AML and ALL separately were included, but those studies were not eligible for our publication; in total 32 studies reporting on leukaemia only were included, of which 26 (also) presented results on AML and/or ALL separately.	-

Table 1 Study characteristics and results of included systematic reviews (continued)

Description of aetiological factor [reference]	**Day-care attendance and other early social contacts** [18]	**Different infectious exposures** [4]	**Socioeconomic status** [19]
Type of acute leukaemia evaluated	ALL	ALL and AML	ALL and AML
Number of included studies	n=11 (in 7 studies common ALL patients were included)	ALL: n=12 (in 1 study common ALL patients were included) AML: n=1 (recent studies only, no data on studies up to 1997 available; see notes)	ALL: n=10 AML: n=2
Design(s) of included studies	Case-control studies n=1 hospital based, n=8 population based; n=1 part hospital based, part population based; n=1 unclear	ALL: n=11 case-control studies and n=1 cohort study AML: n=1 case-control study ALL and AML: unclear if population- or hospital based	ALL: n=8 case-control studies (n=1 unclear if population- or hospital based; n=7 population-based[‡]), n=1 cohort study and n=1 ecological study AML: n=2 case-control studies; both unclear if population- or hospital based
Number of included children	5924 cases (including 2824 common ALL cases); 19135 controls	Unclear (for recent studies only, no data on studies up to 1997 available; see notes)	ALL: 4016 cases; number of controls unclear AML: 721 cases; number of controls unclear
Age included children	0-15 years	Unclear (for recent studies only, no data on studies up to 1997 available; see notes)	ALL and AML: unclear (inclusion criterion for review was 0-24 years)
Gender of included children	Unclear	Unclear (for recent studies only, no data on studies up to 1997 available; see notes)	ALL and AML: unclear

Description of literature search (i.e. sources, dates, search strategy provided yes/no, additional information)	PubMed (January 1966 to October 2008); reference lists of review articles and included studies. Search strategy provided Published in English	PubMed (from 1970 to date, but not mentioned which date); earlier review (published in 1999) for earlier references and for references up to and including 1997. Search strategy not provided	PubMed (January 1st 1965 to August 31st 2002); PsychInfo (January 1st 1960 to August 31st 2002); Eric (January 1st 1966 to August 31st 2002); manual search of Index Medicus (1945-1964); additional relevant reports referenced in these articles were collected. Search strategy provided Published in English
Meta-analysis performed?; If yes: heterogeneity present?	Yes; see results below	No	No
Results as presented in article	ALL: Individual study results; no pooling: *Preschool playgroup (yes/no) in the year before diagnosis (for ≥ 3 months):* OR 0.6 (95% CI 0.2-1.8) *Regular contact with other children from outside home at < 12 months (yes/no; age < 15 months excluded):* OR 0.65 (95% CI 0.36-1.17) *Day-care attendance by age at entry:* *- entry ≤ 2 years old versus no:* **OR 0.49 (95% CI 0.31-0.77)** *- entry > 2 years old versus no:* OR 0.67 (95% CI 0.45-1.01)	*Maternal infections:* ALL: No pooling, individual study results: Recent studies: *Epstein Barr virus in mother*: **OR 2.9 (95% CI 1.5-5.8)** *Recurrent maternal infections:* OR 1.09 (95% CI 0.65-1.84) *Any infection in pregnancy:* OR 1.44 (95% CI 0.81-2.55) From the earlier review: *Non-specific viral infection:* OR 4.0 (95% CI not mentioned; no significant difference) *Non-specific maternal infection:* **OR 1.5 (95% CI not mentioned, p<0.05**; precursor B-cell ALL)	*Family income:* ALL: Association direction* (p-value) in 4 case-control studies: + (0.90); + (0.92); - (0.00001); - (0.0013); no pooled estimate. AML: Association direction (p-value) in 1 case-control study: - (0.00002) *Mother's education:* ALL: Association direction (p-value) in 6 case-control studies: + (0.030); - (0.11); - (0.10); - (0.03); - 0.70); - (0.00024); no pooled

	Day-care attendance (age < 1 year excluded): - *yes versus no:* OR 0.96 (95% CI 0.82-1.12) - *day care before age 2 years versus no:* OR 0.99 (95% CI 0.84-1.17) *Total duration of out-of-home care duration versus > 36 months):* - *stay home:* OR 1.32 (95% CI 0.70-2.52) - *1-18 months:* OR 1.74 (95% CI 0.89-3.42) - *19-36 months:* OR 1.32 (95% CI 0.70-2.52) *Day-care attendance (age < 1 year excluded):* - *ever versus never:* OR 0.70 (95% CI 0.60-1.0) - *started at age < 3 months versus never*: **OR 0.60 (95% CI 0.40-0.80)** *Social activity in first year of life (age < 2 years excluded):* - *any versus no social activity:* **OR 0.66 (95% CI 0.56-0.77)** - *age started versus no day care:* ***< 3 months*: OR 0.71 (95% CI 0.60-0.85)** ***3-5 months*: OR 0.71 (95% CI 0.56-0.90)** ***6-11 months*: OR 0.76 (95% CI 0.63-0.92)** *Child-hours of exposure at day-care (age < 1 year excluded):* - *≥ 5000 child hours (first year) versus 0˜*: *Hispanic*: OR 2.10 (95% CI 0.70-6.34) *White*: OR 0.42 (95% CI 0.18-0.99)	*Influenza during pregnancy:* No significantly raised OR (no further data reported) *Childhood infections:* ALL: No pooling, individual study results: Recent studies: *Early infections*: OR 0.8 (95% CI 0.6-1.0) *Roseola/fever and rash in first year of life*: **OR 0.33 (95% CI 0.16-0.68)** *Tonsillitis 3/12 months before diagnosis*: OR 2.56 (95% CI 1.22-5.38) *Increasing number of ear infections*: P-value for trend = 0.03 (protective effect) *Neonatal infections*: **OR 0.49 (95% CI 0.26-0.95)** *Vaccinations:* ALL: No pooling, individual study results: Recent studies: *Conjugate Haemophilus influenza type B*: **OR 0.57 (95% CI 0.36-0.89)** *Measles or measles vaccination*: RR 0.2 (95% CI 0.1-0.7) *Measles, mumps, rubella vaccination:* OR 1.7 (95% CI not mentioned; p<0.01; in common ALL) *Individual social mixing:* *Birth order:* Recent studies:	estimate. Maternal education ≥ 16 years versus ≤ 12 years (1 case-control study): OR 0.78 AML: Association direction (p-value) in 1 case-control study: - (0.25) Maternal education ≥ 16 years versus ≤ 12 years (1 case-control study): OR 0.65 *Father's education:* ALL: Association direction (p-value) in 4 case-control studies: - (0.89); - (0.94); - (0.78); - (<0.001); no pooled estimate. AML: Association direction (p-value) in 2 case-control studies: - (0.72); - (0.048); no pooled estimate. *Father's occupational class:* ALL: Association direction (p-value) in 1 case-control and 1 cohort study: + (0.95); + (0.057); no pooled estimate.

	Childcare attendance in children during first 2 years of life (yes/no): **OR 0.68 (95% CI 0.48-0.95)** *Timing of day-care attendance:* *Day-care any time:* OR 0.96 (95% CI 0.82-1.12) OR 0.76 (95% CI 0.70-2.52) OR 0.70 (95% CI 0.60-1.0) OR 0.75 (95% CI 0.38-1.45): White OR 1.09 (95% CI 0.62-1.90): Hispanic *Day-care at age ≤ 2:* OR 0.91 (95% CI 0.90-1.30) OR 0.65 (95% CI 0.36-1.17) OR 0.49 (95% CI 0.31-0.77) OR 0.99 (95% CI 0.84-1.17) OR 0.96 (95% CI 0.70-1.32) **OR 0.66 (95% CI 0.56-0.77)** OR 0.77 (95% CI 0.43-1.40): White OR 1.92 (95% CI 0.89-4.13): Hispanic OR 0.68 (95% CI 0.48-0.95) Common ALL: Meta-analysis of association day-care attendance and risk of common ALL (7 studies; different definitions of day care attendance; p-value heterogeneity 0.044): **OR 0.83 (95% CI 0.70-0.98)**	ALL: No pooling, individual study results: 1: OR 1 (reference) 2: OR 0.9 (95% CI 0.7-1.2) 3: OR 1.1 (95% CI 0.8-1.7) 4+: OR 2.0 (95% CI 1.1-3.7) 1: OR 1 (reference) 2: OR 0.98 (95% CI 0.71-1.36) 1: OR 1 (reference) 2: OR 1.3 (95% CI 1.1-1.6) 3: OR 1.5 (95% CI 1.2-2.0) 4+: OR 2.0 (95% CI 1.3-3.0) 1: OR 1 (reference) 2: OR 1.08 (95% CI 0.93-1.26) 3+: OR 1.05 (95% CI 0.88-1.26) Having older siblings at time of diagnosis in children aged < 4 years: OR 4.54 (95% CI 2.27-9.07) Having older siblings in first year of life in children aged ≥ 4 years: OR 0.46 (95% CI 0.22-0.97) AML: No pooling, individual study results: In 0-2 year olds 3+: **OR 1.59 (95% CI 1-2.53)**	AML: Not evaluated *Household density (i.e. persons per room, no cut-off value provided) :* ALL: Association direction (p-value) in 1 cohort study: + (0.58) AML: Not evaluated *Derived measure (i.e. combining father's education and occupation):* ALL: Association direction (p-value) in 1 case-control study: - (0.13) AML: Not evaluated *Ecological measures:* Association direction (p-value) in 1 ecological study: Both education and occupational class + (<0.01) AML: Not evaluated

	Individual studies, no pooling: *Day-care attendance (age < 1 year excluded):* - *yes/no*: OR 0.96 (95% CI 0.75-1.24) - *started at age < 3 months versus never:* OR 0.6 (95% CI 0.4-0.9) *Child-hours of exposure at day-care (age < 1 year excluded):* - *≥ 5000 child hours (first year) versus 0*$^{-}$: *Hispanic*: OR 2.53 (95% CI 0.60-10.7) *White*: OR 0.33 (95% CI 0.11-1.01)	From the earlier review: ALL: Non-significant trend for decreasing risk with *increasing birth order* for cases of ALL aged 0-4 years. *Parental occupational contact levels (i.e. number of social contact with father whilst at work):* ALL: No pooling, individual study results: *Father's occupational contact very high; aged 2-5 years*: OR 1.5 (95% CI 1.1-2.1)	*Highest parental education:* ALL: ≥ 16 years versus < 12 years (1 case-control study): OR 1.34 AML: ≥ 16 years versus < 12 years (1 case-control study): OR 1.24
Conclusion of article	This review provides strong support for an association between exposure to common infections in early childhood (during day-care attendance) and a reduced risk of ALL. Implications of a 'hygiene'-related aetiology suggest that some form of prophylactic intervention in infancy may be possible.	It is difficult to draw any firm conclusions from these data, but there is a suggestion that maternal infection during pregnancy may be linked with an increased risk of ALL development. However, the results of childhood infection, vaccination and social mixing are inconclusive.	Case–control studies almost all consistently report inverse (negative) associations of ALL and AML with individual-level measures of family income, mother's education, and father's education. In contrast, associations have been consistently positive with father's occupational class and with average occupational class in ecological studies. Connections of SES measures to childhood leukaemia are likely to vary with place and time. Validation studies are needed to estimate SES-related selection and participation in case–control studies.

Notes	In this review also studies which did not present results on AML and ALL separately were included, but those studies were not eligible for our publication; in total 14 studies reporting on leukaemia only were included, of which 11 (also) presented results on ALL separately. In this review it was stated that in the studies that did not distinguish between specific leukaemia subtypes it was assumed that ALL was the primary subtype. However, for our study we only included results of studies in which the diagnosis of ALL was sure.	In this review also studies which did not present results on AML and ALL separately were included, but those studies were not eligible for our publication; in total 30 studies reporting on leukaemia only were included, of which 13 (also) presented results on AML and/or ALL separately. This review reports in detail on references from 1998 to date, but only sites selected references that show marked results from the earlier period (we did not assess the number of studies evaluating leukaemia only). Evidence from descriptive epidemiology was not included in our results. Day-care attendance and breastfeeding were also presented in this review, but not included in our results; these etiologic factors have been analysed more extensively in other reviews [17, 18].	In this review also studies which did not present results on AML and ALL separately were included, but those studies were not eligible for our publication; in total 44 studies reporting on leukaemia only were included, of which 12 (also) presented results on AML and/or ALL separately.

Table 1 Study characteristics and results of included systematic reviews (continued)

Description of aetiological factor [reference]	**Extremely low-frequency (ELF) electric and magnetic fields** [66]	**Extremely low frequency fields** [67]
Type of acute leukaemia evaluated	ALL	ALL and AML
Number of included studies	Unclear (at least 4 studies (4 publications on one study); unclear how many studies included in the presented pooled analysis)	ALL: n=1 AML: n=1
Design(s) of included studies	Unclear (at least 1 descriptive study and 3 case-controls studies (population-based); unclear which designs are included in the presented pooled analysis, at least 1 case-control (population-based))	ALL and AML: case-control study (unclear if hospital- or population based)
Number of included children	Unclear (in 3 case-control studies 1803 cases and 2572 controls; in presented pooled analysis 2704 cases, controls unclear; unclear in descriptive study)	ALL: 251 cases and 495 controls AML: 61 cases and 108 controls
Age included children	Unclear (in 2 case-controls studies < 15 years; unclear in descriptive study and presented pooled analysis)	≤ 15 years
Gender of included children	Not mentioned	Not mentioned

Description of literature search (i.e. sources, dates, search strategy provided yes/no, additional information)	Medline and Toxline (among others; dates not provided) Search strategy not provided	Databases such as Medline and PubMed (dates not provided, but search for studies published after the IARC publication [66]); IARC and ICNIRP reviews. Search strategy not provided.
Meta-analysis performed?; If yes: heterogeneity present?	An earlier published meta-analysis was included in this publication; unclear if heterogeneity was present.	Not applicable
Results as presented in article	*Residential exposure:* Individual study data: Descriptive study: Peak incidence of ALL appeared to have developed earlier in those states in which more homes were connected earlier to electricity supply Case-control study: ORs were only altered slightly when the analyses were restricted to residentially stable children. The association was strongest for children aged 4 years or younger *Median magnetic fields (24-hour bedroom measurement):* < 0.1 µT (baseline): OR 1 0.1-<0.2 µT: OR 1.2 (95% CI 0.73-1.8) 0.2-<0.4 µT: OR 1.2 (95% CI 0.43-3.1)	*ALL:* Exposed to magnetic fields 0.4 µT (as compared to <0.1 µT): OR 4.73 (95% CI 1.14-19.7) *AML:* Exposed to magnetic fields 0.4 µT (as compared to <0.1 µT): risk not increased (no cases in highest category; no further information provided)

	≥ 0.4 μT: OR 5.8 (95% CI 0.78-43) ≥ 0.2 μT: OR 1.6 (95% CI 0.65-3.7) ≥ 0.2 μT excluding 2 cases of Down syndrome: OR 1.3 (95% CI 0.49-3.2) *Night-time magnetic fields:* < 0.1 μT (baseline): OR 1 0.1-<0.2 μT: OR 1.4 (95% CI 0.90-2.2) 0.2-<0.4 μT: OR 2.5 (95% CI 0.86-7.5) **≥ 0.4 μT: OR 5.5 (95% CI 1.2-27)** ≥ 0.2 μT: **OR 3.2 (95% CI 1.3-7.8)** ≥ 0.2 μT excluding 2 cases of Down syndrome: **OR 2.8 (95% CI 1.1-7.0)** Case-control study: *Time-weighted average (24-hour bedroom measurement plus spot measurements in two rooms):* *Unmatched:* < 0.065 μT (baseline): OR 1 0.065-0.099 μT: OR 1.1 (95% CI 0.81-1.5) 0.1-0.199 μT: OR 1.1 (95% CI 0.83-1.5) ≥ 0.200 μT: OR 1.2 (95% CI 0.86-1.8) *Matched:* < 0.065 μT (baseline): OR 1 0.065-0.099 μT: OR 0.96 (95% CI 0.65-1.4) 0.1-0.199 μT: OR 1.2 (95% CI 0.79-1.7) ≥ 0.200 μT: OR 1.5 (95% CI 0.91-2.6) ≥ 0.3 μT: **OR 1.7 (95% CI 1.0-2.9)**◊ (unclear if unmatched or matched analysis)	

	When partial participants (i.e. did not allow in-home measurements or interviews) were excluded: **OR 1.9 (95% CI 1.1-3.3)** ≥ 0.5 μT: OR near unity in matched analysis (no further data presented) No significantly elevated risks when exposure during pregnancy was considered. 90th% versus < 50th%: 24-hour measurements: OR 1.4 (95% CI 0.87-2.2) night-time measurements: **OR 1.7 (95% CI 1.1-2.7)** Little evidence for any association with peak exposure, thresholds or variability was found As presented in pooled analysis: 0.1-<0.2 μT: RR 1.1 (95% CI 0.81-1.5) 0.2-<0.4 μT: RR 1.0 (95% CI 0.65-1.6) ≥ 0.4 μT: **RR 3.4 (95% CI 1.2-9.5)** Continuous analysis: **RR 1.3 (95% CI 1-1.7)** *Wire code:* Matched: UG/VLCC (baseline): OR 1 OLCC: OR 1.1 (95% CI 0.74-1.5) OHCC: OR 0.99 (95% CI 0.67-1.5) VHCC: OR 0.88 (95% CI 0.48-1.6)◊ When partial participants (i.e. did not allow in-home measurements or interviews):	

	VHCC: OR 1.2 (95% CI 0.74-2.0) *Distance and relative load for high voltage and three-phase primary power lines:* Living within 14 meter of a potentially high-exposure line: OR 0.79 (95% CI 0.46-1.3) Highest category of the exposure index (mean magnetic field in homes 0.213 µT): OR 0.98 (95% CI 0.59-1.6) Pooled analysis (number of studies unclear): 0.1–< 0.2 µT: RR 1.1 (95% CI 0.88-1.3) 0.2–< 0.4 µT: RR 1.1 (95% CI 0.84-1.5) ≥ 0.4 µT: **RR 2.1 (95% CI 1.3–3.3)** *Exposure from electrical appliances:* Individual study data: *Electric blankets:* Prenatal use: **OR 1.6 (95% CI 1.1-2.3)** Postnatal use: **OR 2.8 (95% CI 1.5-5.0)**, but the highest risk was found for the shortest duration of use in years (**OR for < 1 year of use 5.5 (95% CI 1.1-26)**) *Sewing machines:* Prenatal use: OR 0.76 (95% CI 0.59-0.98) *Television:* *< 4 feet versus ≥ 6 feet [1.2 versus ≥ 1.8 meter] from TV:* Prenatal use: OR 1.9 (95% CI 0.79-4.5) Postnatal use: **OR 1.6 (95% CI 1.1-2.4)** *≥ 6 hours versus < 2 hours/day:*	

	Postnatal use: **OR 2.4 (95% CI 1.5-3.8)** (Regardless of the reported distance that the child sat from the television) *Hair dryer:* Postnatal use: **OR 1.6 (95% CI 1.2-2.1)**, but the highest risk was for children who had used one hair dryer for less than one year **(OR 2.5 (95% CI 1.3-4.9)** *Bed-heating pads:* Prenatal use: **OR 1.5 (95% CI 1.0-2.1)** *Humidifiers:* Prenatal use: OR 1.4 (95% CI 1.0-2.0) *Video arcade games:* **OR 1.7 (95% CI 1.2-2.3)** *Video games connected to televisions:* **OR 1.9 (95% CI 1.4-2.7)** *Use of a personal computer:* OR 1.2 (95% CI 0.83-1.7) No evidence of a dose-response effect	
Conclusion of article	There is limited evidence in humans for the carcinogenicity of extremely low frequency magnetic fields in relation to childhood ALL	Results are limited by small sample size leading to a broad range of uncertainty. Observed association for ALL can be due to chance, selection bias, misclassification and other confounding factors, or can be a true causal relationship

Notes	In this review also studies which did not present results on AML and ALL separately were included, but those studies were not eligible for our publication; in total 23 original studies reporting on leukaemia only and 1 review were included (it was unclear how many of those reported AML and/or ALL separately). In this review only data considered relevant by the working group is included.	In this review also studies which did not present results on AML and ALL separately were included, but those studies were not eligible for our publication; in total 2 studies reporting on leukaemia only were included, of which 1 (also) presented results on AML and/or ALL separately. A summary of the IARC publication [66] was presented, but in our publication only data published after the IARC publication were included. In this publication not all available data is included.

ALL: acute lymphoblastic leukaemia; AML: acute myeloid leukaemia; n: number; OR: odds ratio; CI: confidence interval; cpd: cigarettes per day; RR: relative risk; IARC: International Agency for Research on Cancer; ICNIRP: International Commission on non-ionizing radiation protection; UG/VLCC: underground wires/very low current configuration; OLCC: ordinary low current configuration; OHCC: ordinary high current configuration; VHCC: very high current configuration.

[@] After completion of this report, online supplemental material of this review became available; slight discrepancies exist between data reported in the supplemental material and in the review; for ALL the review included 10 case-control and 1 cohort study and for AML 6 case-control and 1 cohort study; for the ALL studies the number of included subjects was at least 3415 cases and 3810 controls,and for the AML studies at least 999 cases and 1183 controls; the age of the included subjects in the ALL studies was <18 years and unspeciifed in 2 studies and unclear in 4 studies, for the AML studies this was <18 years and unclear in 3 studies; the overall OR for paternal exposure for AML, based on 4 studies, was 1.13 (95% CI: 0.59-2.14), for maternal exposure, based on 6 studies it was 2.64 (95% CI: 1.47-4.74).

^ This we assumed, it was not completely clear from the information provided in the review.

[¥] Based on information provided in table A4 and A5 of this review.

[†] For 1 study results were not clearly presented and could thus not be included here; the same is true for alcohol consumption in the year before pregnancy.

[#] Based on text, in the table different numbers were presented.

[$] Based on information provided in the figures, in the text slightly different results were stated.

[~] Based on information in table 1, in another table different numbers are presented.

[‡] We assumed that these studies were population-based, they were stated to be registry, while others (not eligible for this overview) were reported as hospital-based.

* Negative direction=higher rates associated with lower SES levels; positive direction: higher rates associated with higher SES levels.

[◊] In another publication of this study a slightly different OR and 95% CI were presented (i.e. OR 1.6 (95% CI 0.98-2.6) for measured fields and OR 1.0 (95% CI 0.62-1.6) for wire-code). This was due to small differences in study populations included and to differences in the variables adjusted for).

Table 2 Methodological quality of included systematic reviews

	Description / aetiological factor [reference]	**Parental occupational pesticide exposure [9]**	**Residential pesticide use [5]**	**Arsenic exposure in drinking water [10]**	**Nuclear facilities/power plant [6]**	**Diagnostic X-rays [11]**
1	Was an 'a priori' design provided?	Yes	Yes	Can't answer	Can't answer	Yes
2	Was there duplicate study selection and data extraction?	Can't answer	Yes	Can't answer	Can't answer	Can't answer
3	Was a comprehensive literature search performed?	Yes	Yes	No	Can't answer	Yes
4	Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Can't answer	Can't answer	Can't answer	Can't answer	Yes
5	Was a list of studies (included and excluded) provided?	No	No	No	No	Yes
6	Were the characteristics of the included studies provided?	Can't answer	No	No	No	No
7	Was the scientific quality of the included studies assessed and documented?	Yes	Yes	No	Can't answer	Yes
8	Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	Yes	No	Yes	Yes
9	Were the methods used to combine the findings of studies appropriate?	Yes	Yes	NA	NA	NA
10	Was the likelihood of publication bias assessed?	NA	NA	NA	NA	NA
11	Was the conflict of interest stated?	No	No	No	No	No
	Total number of criteria scored as yes out of applicable criteria (%)	**5/10 (50%)**	**6/10 (60%)**	**0/9 (0%)**	**1/9 (11%)**	**6/9 (67%)**

Table 2 Methodological quality of included reviews (continued)

	Description / aetiological factor [reference]	**Parental alcohol consumption [12]**	**Marijuana (cannabis) smoking by parents [13]**	**Exposure to passive smoking from the parents [14]**	**Maternal folate and vitamin supplementation [15]**	**Different types of allergy [16]**
1	Was an 'a priori' design provided?	Can't answer	Can't answer	Can't answer	Can't answer	Can't answer
2	Was there duplicate study selection and data extraction?	Can't answer	Can't answer	Can't answer	Can't answer	Can't answer
3	Was a comprehensive literature search performed?	No	No	Can't answer	No	Yes
4	Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Can't answer	Can't answer	Can't answer	Can't answer	Yes
5	Was a list of studies (included and excluded) provided?	No	No	No	No	Can't answer
6	Were the characteristics of the included studies provided?	No	No	No	No	No
7	Was the scientific quality of the included studies assessed and documented?	No	No	No	No	Can't answer
8	Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	Yes	Yes	Yes	Yes
9	Were the methods used to combine the findings of studies appropriate?	NA	NA	Can't answer	No	Yes
10	Was the likelihood of publication bias assessed?	Can't answer	NA	Yes	No	Yes
11	Was the conflict of interest stated?	No	No	No	No	No
	Total number of criteria scored as yes out of applicable criteria (%)	**1/10 (10%)**	**1/9 (11%)**	**2/11 (18%)**	**1/11 (9%)**	**5/11 (45%)**

Table 2 Methodological quality of included reviews (continued)

	Description / aetiological factor [reference]	**Birth weight [2]**	**Breast feeding [17]**	**Day-care attendance and other early social contacts [18]**	**Different infectious exposures [4]**	**Socioeconomic status [19]**
1	Was an 'a priori' design provided?	Can't answer	Can't answer	Can't answer	Can't answer	Can't answer
2	Was there duplicate study selection and data extraction?	Can't answer	No	Can't answer	Can't answer	Can't answer
3	Was a comprehensive literature search performed?	No	No	No	No	Yes
4	Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Yes	Yes	Can't answer	Can't answer	Can't answer
5	Was a list of studies (included and excluded) provided?	No	Yes	Yes	No	No
6	Were the characteristics of the included studies provided?	No	No	No	No	No
7	Was the scientific quality of the included studies assessed and documented?	No	Yes	No	No	No
8	Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	Yes	Yes	No	Yes
9	Were the methods used to combine the findings of studies appropriate?	No	Yes	Yes	NA	NA
10	Was the likelihood of publication bias assessed?	Can't answer	Yes	Yes	NA	NA
11	Was the conflict of interest stated?	No	No	No	No	No
	Total number of criteria scored as yes out of applicable criteria (%)	**2/11 (18%)**	**6/11 (55%)**	**4/11 (36%)**	**0/9 (0%)**	**2/9 (22%)**

Table 2 Methodological quality of included reviews (continued)

	Description / aetiological factor [reference]	**Extremely low-frequency (ELF) electric and magnetic fields [66]**	**Extremely low frequency fields [67]**
1	Was an ‘a priori’ design provided?	Can’t answer	Can’t answer
2	Was there duplicate study selection and data extraction?	Can’t answer	Can’t answer
3	Was a comprehensive literature search performed?	No	No
4	Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Can’t answer	Can’t answer
5	Was a list of studies (included and excluded) provided?	No	No
6	Were the characteristics of the included studies provided?	No	No
7	Was the scientific quality of the included studies assessed and documented?	Can’t answer	Can’t answer
8	Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	Yes
9	Were the methods used to combine the findings of studies appropriate?	Can’t answer	NA
10	Was the likelihood of publication bias assessed?	NA	NA
11	Was the conflict of interest stated?	No	No
	Total number of criteria scored as yes out of applicable criteria (%)	**1/10 (10%)**	**1/9 (11%)**

NA: not applicable

Table 3 Short summary of main results (for more detailed information see table 1)

Aetiological factor [reference]	**Type of leukaemia**	**Number of studies; pooling or individual study results**	**Results**	**Methodological quality of systematic review/meta-analysis, i.e. total number of criteria scored as yes out of applicable criteria**
Parental occupational pesticide exposure [9]				
Paternal	ALL	8 pooled	Non-significantly higher risk	5/10 (50%)
	AML	4 pooled	Non-significantly higher risk	
Maternal	ALL	5 pooled	**Significantly higher risk**	
	AML	4 pooled	**Significantly higher risk**	
Residential pesticide use [5]				
Unspecified during pregnancy	ALL	5 pooled	**Significantly higher risk**	6/10 (60%)
	AML	3 pooled	Non-significantly higher risk	
Unspecified during childhood	ALL	4 pooled	Non-significantly higher risk	
	AML	2 pooled	Non-significantly higher risk	
Residential insecticides during pregnancy	ALL	4 pooled	**Significantly higher risk**	
	AML	2 pooled	**Significantly higher risk**	
Residential insecticides during childhood	ALL	3 pooled	Non-significantly higher risk	
Residential herbicides during pregnancy	ALL	4 pooled	**Significantly higher risk**	
Residential herbicides during childhood	ALL	3 pooled	Non-significantly lower risk	
Arsenic exposure in drinking water [10]				
Prenatal	ALL	1 individual	Non-significantly lower risk	0/9 (0%)
Postnatal	ALL	1 individual	Non-significantly higher risk	
Nuclear facilities/power plant [6]				
Closer to nuclear power plant	ALL	1 individual	Higher risk (significance level not stated)	1/9 (11%)
Pre-and postnatal diagnostic X-rays [11]				
Prenatal	ALL	1 individual	Non-significantly lower risk	6/9 (67%)
	AML	1 individual	Non-significantly higher risk	
Postnatal	ALL	1 individual	**Significantly higher risk**	
Parental alcohol consumption [12]				
Maternal alcohol consumption:				1/10 (10%)

Year before pregnancy	ALL	1 individual	Non-significantly higher risk	
Month prior to pregnancy	ALL	2 individual	Inconsistent risk	
	AML	1 individual	Non-significantly higher risk	
During pregnancy; several subgroups	ALL	> 2 individual	Inconsistent risk	
	AML	> 2 individual	Inconsistent risk	
During breast feeding	ALL	2 individual	Inconsistent risk	
	AML	1 individual	Non-significantly lower risk	
Paternal alcohol consumption:				
Month prior to conception; several subgroups	ALL	> 2 individual	Inconsistent risk	
	AML	> 2 individual	Inconsistent risk	
Exposure period not stated	ALL	1 individual	Non-significantly higher risk	
One year prior to conception	AML	1 individual	Non-significantly higher risk	
Marijuana (cannabis) smoking by parents [13]				
Maternal use during or in the year before pregnancy	AML	1 individual	**Significantly higher risk**	1/9 (11%)
Paternal use	AML	1 individual	Non-significantly higher risk	
Exposure to passive smoking from parents [14]				
From mother during pregnancy; several subgroups	ALL	6 individual	Inconsistent risk	2/11 (18%)
	AML	2 individual	Inconsistent risk	
From mother before pregnancy; several subgroups	ALL	1 individual	Non-significantly higher risk	
From father; several subgroups	ALL	4 pooled	Non-significantly higher risk	
	AML	3 individual	Inconsistent risk	
Maternal folate and vitamin supplementation [15]				
Vitamins with folate versus no folate during pregnancy	ALL	2 pooled	Non-significantly higher risk	1/11 (9%)
Vitamins with folate versus no vitamins during pregnancy	ALL	2 pooled	Non-significantly higher risk	
Vitamins before pregnancy	ALL	2 pooled	Non-significantly lower risk	
Vitamins only before pregnancy	ALL	2 pooled	Non-significantly higher risk	
Vitamins during pregnancy	ALL	5 pooled	**Significantly lower risk**	
Folate preceding pregnancy	ALL	1 individual	Non-significantly higher risk	
Different types of allergy [16]				
Overall allergy	ALL	8 pooled	**Significantly lower risk**	5/11 (45%)

	AML	3 individual	Non-significantly lower risk	
Asthma	ALL	6 pooled	Non-significantly lower risk	
Hay fever	ALL	5 pooled	**Significantly lower risk**	
Eczema	ALL	5 pooled	**Significantly lower risk**	
Birth weight [2]				
High birth weight compared to normal birth weight	ALL	23 pooled	**Significantly higher risk**	2/11 (18%)
	AML	9 pooled	**Significantly higher risk**	
Low birth weight	ALL	10 pooled	Non-significantly lower risk	
Per kilogram increase in birth weight	AML	9 pooled	**Significantly higher risk**	
	ALL	16 pooled	**Significantly higher risk**	
Breast feeding [17]				
Breast feeding	ALL	17 pooled	**Significantly lower risk**	6/11 (55%)
	AML	9 pooled	Non-significantly lower risk	
Duration of breast feeding < 6 months	ALL	12 pooled	Non-significantly lower risk	
	AML	8 pooled	Non-significantly lower risk	
Duration of breast feeding > 6 months	ALL	13 pooled	**Significantly lower risk**	
	AML	9 pooled	**Significantly lower risk**	
Day-care attendance and other early social contacts [18]				
Day-care attendance/social contacts; different definitions and subgroups	ALL	> 2 individual	Mostly non-significantly lower risk	4/11 (36%)
	Common ALL	7 pooled	**Significantly lower risk**	
		> 2 individual	Mostly non-significantly lower risk	
Different infectious exposures [4]				
Different maternal infections	ALL	> 2 individual	(Non-)significantly higher risk	0/9 (0%)
Different childhood infections	ALL	> 2 individual	Inconsistent risk	
Different vaccinations	ALL	> 2 individual	Inconsistent risk	
Individual social mixing birth order; several subgroups	ALL	> 2 individual	Inconsistent risk	
	AML	1 individual	Non-significantly higher risk	
Parental occupational contact levels	ALL	1 individual	**Significantly higher risk**	
Socioeconomic status [19]				
Family income	ALL	4 individual	Inconsistent risk	2/9 (22%)

	AML	1 individual	**Higher AML rates significantly associated with a lower socioeconomic status**	
Mother's education	ALL	6 individual	Inconsistent risk	
	AML	1 individual	Higher AML rates non-significantly associated with a lower socioeconomic status	
Father's education	ALL	4 individual	Higher ALL rates (non-) significantly associated with a higher socioeconomic status	
	AML	2 individual	Higher AML rates (non-) significantly associated with a lower socioeconomic status	
Father's occupational class	ALL	2 individual	Higher ALL rates non-significantly associated with a higher socioeconomic status	
Household density	ALL	1 individual	Higher ALL rates non-significantly associated with a higher socioeconomic status	
Derived measure (i.e. combining father's education and occupation)	ALL	1 individual	Higher ALL rates non-significantly associated with a lower socioeconomic status	
Ecological measures (i.e. both education and occupational class)	ALL	1 individual	**Higher ALL rates significantly associated with a higher socioeconomic status**	
Extremely low-frequency (ELF) electric and magnetic fields [66]				
Magnetic fields; different definitions and subgroups	ALL	> 2 individual	Mostly non-significantly higher risk*	1/10 (10%)
		Unclear, pooled	Non-significantly higher risk*[#]	
Electric blankets (postnatal and prenatal use)	ALL	1 individual	**Significantly higher risk**	
Sewing machines (prenatal use)	ALL	1 individual	**Significantly lower risk**	

Television; different definitions (prenatal and/or postnatal)	ALL	1 individual	**Significantly higher risk postnatal;** non-significantly higher risk prenatal	
Hair dryer (postnatal use)	ALL	1 individual	**Significantly higher risk**	
Bed-heating pads (prenatal use)	ALL	1 individual	Non-significantly higher risk	
Video games; different definitions	ALL	1 individual	**Significantly higher risk**	
Personal computer	ALL	1 individual	Non-significantly higher risk	
Humidifiers	ALL	1 individual	Non-significantly higher risk	
Extremely low frequency fields [67]				
Exposed to magnetic fields 0.4 μT (as compared to <0.1 μT)	ALL	1 individual	**Significantly higher risk**	1/9 (11%)
	AML	1 individual	Risk not increased (no further information available)	

ALL: acute lymphoblastic leukaemia; AML: acute myeloid leukaemia

* Mostly (non-)significant higher risk, especially with doses ≥ 0.4 μT.

[#] For different subgroups, no overall estimate presented.