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THE ARCTIC UNIVERSITY OF NORWAY

Faculty of health sciences / Department of community medicine

Parental exposure and risk factors for leukemia in offspring

- *A systematic review*

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HEL-3950 Master's thesis in Public Health
Dec 2018

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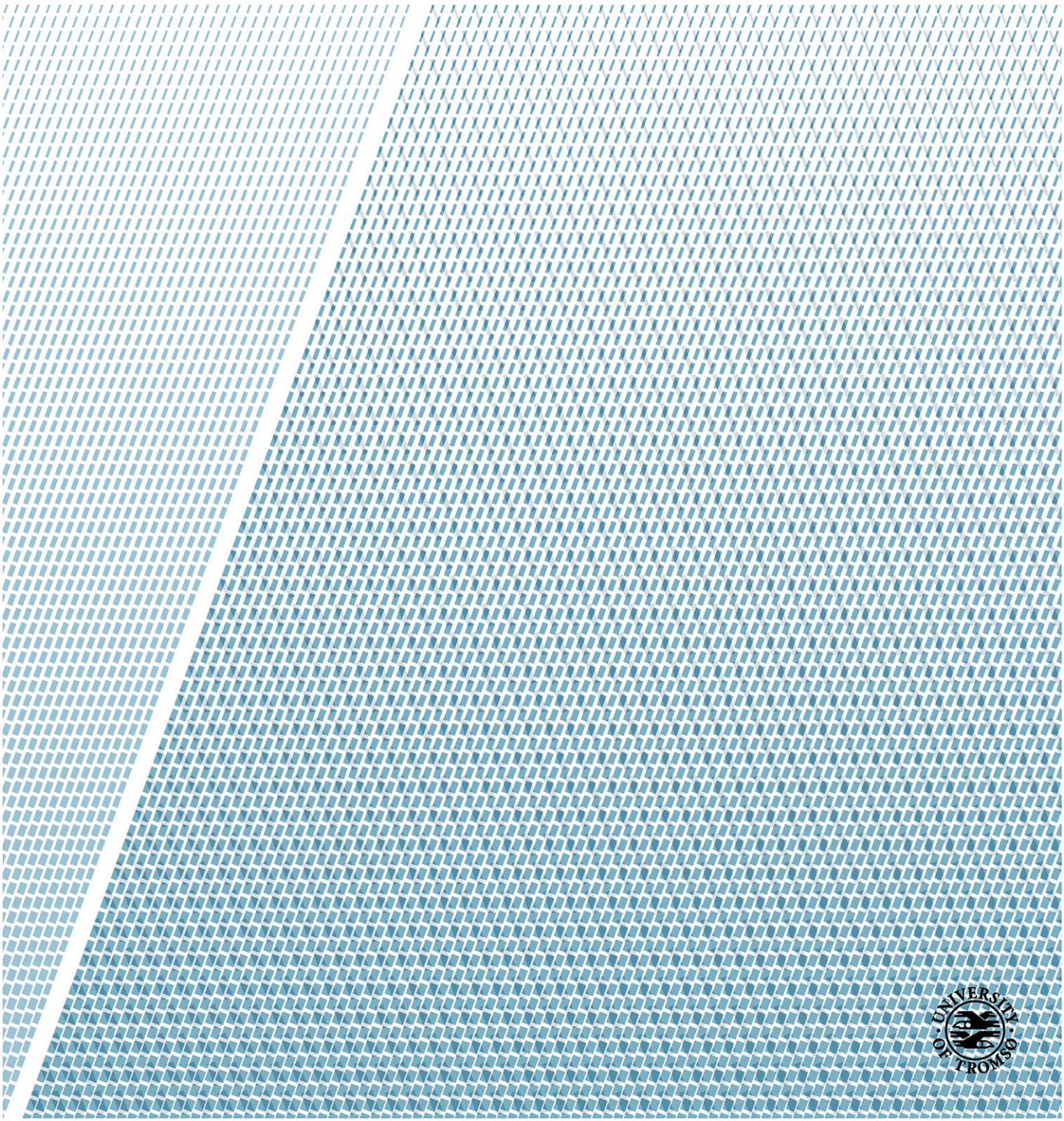

Abstract

Objective: The purpose of this thesis is to identify and investigate risk factors associated with childhood leukemia, formulated by the research question: Which risk factors are associated with parental exposure and childhood leukemia in the offspring?

Methods: A systematic literature search was performed in the three databases Embase, Medline and Cochrane. The articles found were selected and read by the author and included when related to the research question. All articles were evaluated for risk of bias and level of evidence using the quality assessment system Grading of Recommendation, Assessment, Development and Evaluation (GRADE). The exposures were divided into several categories, all relevant to parental exposure: air pollution, use of alcohol and medications, occupational exposure, pesticides, socio-economic status (SES) and smoking.

Results/Discussion: 27 articles were found and included in the systematic review.
Exposure to petroleum and hydrocarbons as well as pesticides appears to increase the risk of childhood leukemia. A high risk of bias was found in several of the studies and GRADE level varied from very low to medium with no studies in the high category. Heterogeneity was high between the studies, both in way of exposure measurement and in exposure category. The lack of differentiation in the outcome between different subtypes of leukemia in childhood was problematic and new research must consider this.

Conclusion: There is not enough evidence to support that smoking, use of alcohol or medications and SES are risk factors for childhood leukemia. What we can determine is that pesticides, solvents and petroleum-derivates can be considered as potential risk factors and that timing of exposure is crucial for the development of childhood cancer. However, we cannot conclude that there is any causality between the risk factors and childhood leukemia, nor any of its subtypes. Register-based cohorts with global cooperation, with focus on subgroups, should be performed to better understand the impact of parental exposure and risk of childhood leukemia.

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1.0 Background

In 2012 there were an estimated 14.1 million cancer cases globally. Of these, 7.4 million cases were in men and 6.7 million in women (1). There are many known risk factors for cancer in adults, such as smoking, alcohol consumption and asbestos (2-4), but few have been proved to be clear risk factors for cancer in children (5). Cancer is a medical diagnosis defined by international classifications in ICD-10 as neoplasms. There are 137 main categories of neoplasms and several subtypes (6). One of these categories is leukemia, and according to ICD- 10 there are seven main categories of leukemia and several subtypes (6).

Cancer in adults and children is different. The most prevalent cancers in children are leukemia, cancer in the central nervous system and lymphomas (7). The most prevalent cancers are prostate, lung and bronchi and colorectal for male adults, and breast, lung and bronchi and colorectal cancers for female adults (7). Pesola et al (8) described the incidence of cancer in English children from 1989-2013. They found an increasing incidence for all cancers in children under 15 years of age, with an age-standardized rate (ASR) for boys from 3,5 per million in 1989 to 24,5 per million in 2009. The statistics for girls were 19,4 and 20,1 respectively (8), indicating that more boys than girls develop cancer.

There is also a geographic difference. The Nordic Cancer Registry (9) collects data from all the national cancer registers in the Nordic countries: Norway, Sweden, Denmark, Finland, Iceland, the Faroe Islands and Greenland. Current data is available up until 2015. The registry gives an age standardized rate (ASR) compared to the world-standard population (ASR (w)). An ASR is a weighted average of the age-specific rate, in this case compared to the world ASR. It shows that the highest incidence of cancer in general in the period 1989-2014 for males aged 0-14, was in Greenland- ASR(w): 18,7 per 100.000 and the lowest incidence was for females in the Faroe Islands- ASR(w): 5,7. The Nordic countries have a quite similar

Country	ASR (w) Males	ASR (w) Females
Denmark	18, 2	15, 7
Faroe- Island	12, 1	5, 7
Finland	17, 6	15, 9
Greenland	18, 7	9, 6
Iceland	15, 9	12, 9
Norway	17, 4	15, 9
Sweden	17, 7	15, 9

Table 1: Age standardized rate per 100.000 for all cancers in the Nordic region in the period 1989-2014 according the Nordic Cancer registry (9)

demography, economy and living environment, however, there still appears to be a difference in cancer incidence in children.

Several risk factors for leukemia have been suggested. Socio-economic status (SES) has been studied as a risk factor for leukemia. Children living under poorer conditions are found to have an increased risk (10). Other suggested risk factors include oil combustion (11), other types of air pollution (12), in vitro fertilization (13), ultra violet sun exposure (14) and radon (15). Stiller (5) has made an overview of some previously found risk factors, such as viruses and hormone treatment but concluded that more research is needed. He claims that this is due to poor evidence or biased publications (5).

One known risk factor is the atomic bombing of Japan during the Second World War, where both adults and children who survived developed cancer in general at a much higher rate than those not exposed to the atomic bomb (16). Similar increases have been observed after the Chernobyl disaster in 1986 (17, 18). The similarity of these incidences has led scientists to believe that x-rays could be a risk factor as they include ionizing radiation. Today there is an agreement that prenatal x-rays should be considered as a risk factor for childhood cancer, despite the risk being low (19-21).

Greaves (22) introduced the Hit theory in an attempt to explain why there has not been found any clear risk factors for childhood leukemia. The genetic translocation of the chromosomes involved in childhood leukemia happens in utero but is then called a pre-leukemic cell. These cells do not directly evolve to cancer but need several impacts to become leukemic. The cells' autoprotective systems are supposed to fix broken gene-copies and the cell should also

normally be able to kill itself. If this does not happen, the genetic material is exposed to other "hits", the pre-leukemic cell can develop into a leukemic cell. Such "hits" can consist of all the previously mentioned risk factors: air pollution, pesticides, smoking among others (22).

Twin studies and new-born blood spots have been used to investigate this theory (22). The main findings were that even though some are born with the gene defect of pre-leukemic cells, not all develop into leukemia, but those who had cancer were most likely born with the pre-disposing gene translocation. About 1 % of the newborns investigated had this translocation, but only one in 2.000 developed into a malignancy. Greaves underlines that the second "hit" could appear in utero or in childhood, for example in the form an infection (22). This "hits" also happens in adulthood, with the examples of smoking and alcohol.

According to Greaves (22) there are two theories on how the immune system is related to the development of leukemia: the delayed infection theory and the population mixing theory (22). The delayed infection theory claims that the child is not exposed to early childhood infections and the immune system overreacts towards viruses or bacteria so that the pre-leukemic cells divide in such a way that it causes cancer. The population mixing theory discusses the idea that when people move or commute, they meet infectious agents that are not normal for them, and since the immune system does not know how to react, it gives the pre-leukemic cells the opportunity to develop into leukemia (22).

Lightfoot (23) further developed Greaves' theory, and suggests that one side of the second "hit" is the repair mechanism. The child and the mother have the mechanisms to detoxify the hazardous agent, so it is not only the question of *when* the exposure happens, but the *ability to metabolize* it. Some hazardous agents change rapidly, while others take time to change and metabolize. This means that an exposure could be a risk factor in small dosages because it takes a long time to metabolize, while other agents are only a risk factor when the dosage is high. The aspect of timing is crucial in view of how the subject metabolizes the dangerous

agent, which could be different from person to person and between age-groups to some degree.

Lightfoot further discusses that it is not just the child or the mother that must be exposed, the ovaries of the mother are already produced in the grandmother's womb, and cell damage could happen years before the cancerous child is born (23). It is possible that if the grandmother is exposed, it could also be a risk factor for leukemia in the grandchildren. Many studies find a link between paternal exposure, but not maternal. This could be due to the rapid gametes maturing in fathers, which is different from in mothers (23).

Globally, the proportion of leukemia in adult cancer is about 2 %, while in children it is about 33% of all cancer cases. It is expected that in 2018 there will be 371.922 new leukemia cases in adults and 65.111 new childhood leukemia cases worldwide (24). As leukemia is the most common cancer for children, and it is hypothesized that the development of cancer happens already in utero, the parental exposure to risk factors is of importance to investigate. Lack of evidence in this field calls for more research. The main goal for this thesis, therefore, was to investigate the literature and identify parental risk factors for leukemia in children.

1.1 Objectives

1.1.1 Primary objective

The purpose of this thesis is to identify and investigate risk factors associated with childhood leukemia. Only exposure to the parents will be investigated, and those exposures include occupational risk, smoking, diet during pregnancy and household-exposures. Studies that investigate the exact genetic mutations will not be included. If there is a link between parental exposure and childhood leukemia, there must be a genetic mutation due to the nature of cancer, but what kind of genetic mutation this is, will not be discussed in this thesis.

1.1.2 Research question

What risk factors through exposure in parents are associated with childhood leukemia in offspring?

2.0 Methodology

This thesis is a systematic review of the available papers in three databases; Medline, Embase, and Cochrane.

2.1 PICO

The population of interest for this project was children of both sexes who developed leukemia in their childhood (aged 0-18). The exposures to investigate are mainly separated in two categories: environmental and lifestyle factors. The comparison was exposed and non-exposed parents and the outcome of interest was leukemia, C90-C96 according to ICD- 10 (6) or previous versions. Only studies that are either meta-analysis, systematic reviews, cohorts or case-controls were included.

2.2 Data-collection

Data was collected from January 2018 to February 2018 through the databases previously mentioned. The searches were constructed using Medical Subjected Headings (MeSH) terms or Embase Subjected Headings. These labels the studies provided by the database to find and compare similar published articles. Different databases use different labels and have a slightly different usage. For example: the database Medline has an option that is called exploding. This means that when using the Subject Heading there are several subcategories, and by exploding them the search will find all relevant articles also in the subcategory.

The search was done systematically using the same search terms in all databases. Below is a scheme for the search strategy: words in the boxes were combined using OR and boxes were combined with AND, except for the last box which was combined with NOT. All the search words are subject headings used in the databases, except dietary exposure, which is not used in Embase, (for extended explanation, see appendix 1).

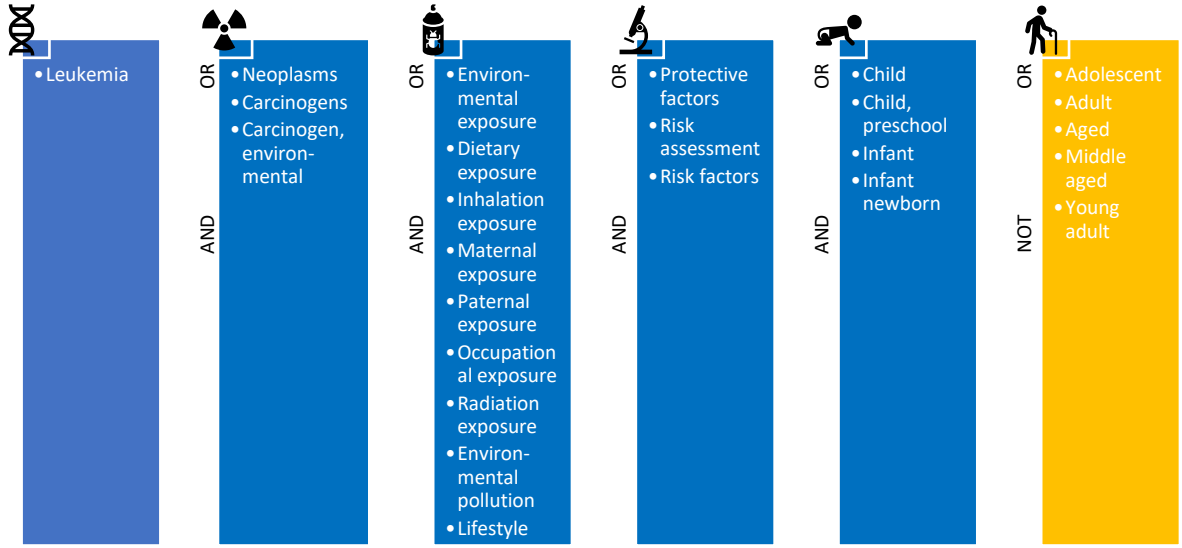

Figure 1: Search strategy. This is an illustration of the systematic search performed: ((Leukemia) and (exp Neoplasms/ or exp carcinogens/ or exp carcinogens, environmental/) and (exp environmental exposure/ or exp dietary exposure/ or exp inhalation exposure/ or exp maternal exposure/ or exp occupational exposure/ or exp paternal exposure/ or exp radiation exposure/ or exp lifestyle) and (exp protective factors/ or exp risk assessment/ or exp risk factors/) and (exp child/ or exp child, preschool/ or exp infant/ or exp infant, newborn/) not (exp adolescent/ or exp adult/ or exp aged/ or exp middle aged/ or exp young adult/).

Due to the low number of meta-analysis found in Cochrane (only eight, of which none were relevant), an additional search was conducted with the search frame: “risk factors for childhood leukemia” (the British writing leukaemia was also tried). No relevant studies were found. The studies included are shown in the PRISMA principle in fig 2.

Genetics was not a part of this study, and because both the Chernobyl disaster and medical x-rays are considered known risk factors (17-21), studies covering these topics were also excluded.

2.3 Quality assessment of included studies

Articles were selected where the title, topic and summary appeared to be of relevance. The articles included were evaluated using Grading of Recommendation, Assessment, Development and Evaluation (GRADE) (25). GRADE (25) uses a classification of bias:

selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias. The risk of bias gives an overall understanding of the trust in evidence and is important in grading an article. There is no cut off point, but the scale is based on the reviewer's subjective opinion.

To determine the overall trust in evidence, GRADE uses a scale. This is based on the study design and significance of bias. The scale has four levels, from very low to high, upgrading only if there is no risk of bias, and downgrading if the risk of bias is high. Based on the study design and evaluation of bias the articles achieved a level of evidence, randomized control trials (RCT) start at medium level, while other study designs start at low level (25). The *selection bias* is an evaluation of how the cases/controls or studies were included, whether they are handpicked (high risk of bias) or randomly selected from the population (low risk of bias). For the reviews, selection bias is how the investigator chose to include the studies (25).

Performance bias is the evaluation of risk in the way the study was performed. If participants are blinded or there is an accurate measurement of exposure, the risk of bias will be low. In the event when participants with the disease are aware of the hypothesis, or if they answer a questionnaire about their exposures, the bias will be high. In reviews, performance is how the studies were found; the systematic search. *Detection bias* is whether the differentiation between sick vs healthy, or positive/negative outcome has a clear definition or not; in this thesis "leukemia" or "not leukemia". This type of bias arises in reviews if the researcher has not found all of the studies through the search (25).

Attrition bias is the follow up of cases and controls: whether the groups were similar, whether the follow up was different, or how many respondents declined to participate. Attrition bias is not relevant for reviews. *Reporting bias* is whether the researchers held information back so that the findings are more plausible, both for single studies and reviews. If, for example,

research has been done that does not support the researchers' hypotheses, the researchers can hold back this information (25).

Finally, *other bias* is any other risk that can influence the degree of evidence in a negative way, for example if the researchers are funded by the tobacco industry and declare that smoking is not harmful. A high risk of bias does not mean that the findings are not legitimate, but the level of trust in the evidence is low. Larger studies and studies with a cohort design are more likely to have a low risk of bias than smaller studies or case-control studies (25).

2.4 Inclusion and exclusion criteria for articles

Table 2. Inclusion and exclusion criteria

Inclusion criteria:	**Exclusion criteria:**
Study exploring Leukemia, according to ICD-10 (6)	Benign neoplasms or other childhood cancer
Describing parental exposure as risk factors associated with leukemia	Genes as risk factor
Studies including children 0-18 years	Medical radiation
Articles from research done on human beings only	Chernobyl disaster
English language	Second malignancies
Study design as cohort, case-controls or reviews	Animal studies
Access to full text article through the University of Tromsø (UiT) server	Articles that are defined as letters, summaries of conferences etc.
No restriction on year of publication	Case reports or case series
	Articles not available in full text
	Articles in other languages than English
	Articles that study exposure to the child

3.0 Result

In this systematic literature search a total of 439 studies were obtained through search in 3 different databases (Figure 2). After removal of duplicates (n=59) and studies not relevant based on title and/or abstract (n= 315) the remaining 65 studies were read. The exclusion criteria sorted out 38 articles (N= 38 (2 letters) (1 news-article) (11 full text not available) (2 workshop presentations) (3 genetic) (5 study design) (1 animal model) (7 not leukemia specific) (6 not parental specific) and the final number of included studies was 27.

After the search, all the included studies were sorted into a main category [risk factor] and subcategories [study design]. The main categories were air pollution, maternal intake, occupation, pesticides, SES and smoking. Many of the studies investigated several risk factors and are therefore referred to in several of the categories. Table 4 summarizes the findings and the GRADE evaluation.

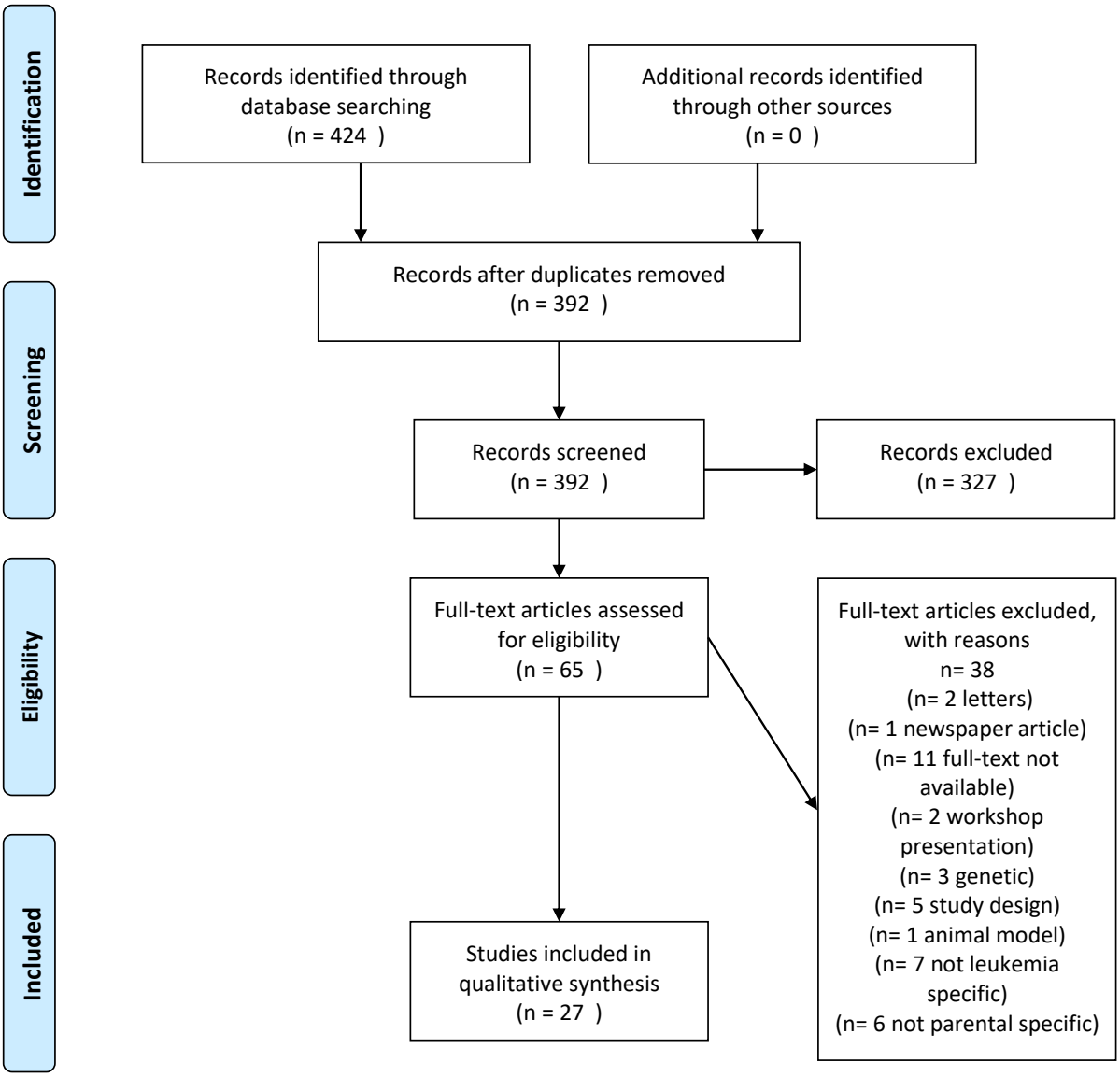

Figure 2: PRISMA search result (26).

3.1.1 Parental exposure to air pollution

The systematic search found 2 reviews (27, 28) and 4 single studies (29-32) on the topic air pollution. All of the included studies are shown in table 4. Pyatt et al (27) investigated the relationship of benzene, hydrocarbons, atmospheric contamination, traffic density and proximity to refineries and leukemia. Based on 106 studies, reviews as well as cohorts and case- control studies, they concluded that there is not enough evidence to say that there is an

association. The data collected in the studies was *"extremely inconsistent"* (27); in the way it was collected, the way exposure was measured, and also in the results. The heterogeneity was described as high between studies, but no statistical tests were done. Heterogeneity is a measure of comparableness between studies (33).

Zhou et al (28) compared 28 studies, 27 case-control studies and one cohort, and investigated if maternal benzene exposure was associated with leukemia. The studies included a total of 16.695 cases and 1.472.786 controls. Through a meta-analysis they concluded that the risk of acute lymphoblastic leukemia (ALL) was increased if the mother was exposed to solvents (Odds Ratio (OR) = 1.25 (95% Confidence Interval (CI) = 1.09–1.45)), paint (OR= 1.42 (95% CI 1.10–1.84)) or petroleum (OR= 1.23 (95% CI=1.02–1.47)) during pregnancy. The included studies showed heterogeneity solely in the studies on paint (I^2 =47.6%, P= 0.076). This is explained by the lack of questions asking whether the mother was exposed to paint domestically, resulting in a falsely low exposure level. On the contrary, occupational exposure was consistently high and was linked to an increased risk of leukemia (28).

When looking at the single studies, there were exclusively case-control study designs (29-32). Bailey et al (31) did a national population-based case-control study in Australia. They enrolled 416 cases and 1.361 controls aged under 15 years. The cases were recruited from oncology centers throughout Australia, 10 in total, and controls were recruited through random digit dialing (RDD). RDD is a procedure where telephone numbers are used to contact potential subjects. Through telephone interviews, the parents were to answer a questionnaire about potential exposures from one year prior to the pregnancy of the sick or control child. The researchers had two main research questions: do the parental refueling of vehicles or the use of wood burners in the home increase risk of leukemia in the offspring? Their conclusion was that refueling had no association to leukemia, but the use of wood

burners could be associated to leukemia if a closed burner was used to heat the house during pregnancy, OR =1.41 (95% CI 1.02- 1.94).

Heck et al (32) did their case-control study on Californian residents under six years of age during a 17 year period. Cases were enrolled through the California Cancer Registry and data was collected from birth certificates. They also used birth certificates to find control-children. By using the address stated on the certificate, all houses were geocoded and mapped. The map was compared to a statewide register for monitored air toxins executed by the Californian state government. This system was used as a proxy for maternal exposure during the third trimester.

Separate estimates were done for ALL and Acute Myeloid Leukemia (AML); analyses of ALL included 69 cases and 2.994 controls who lived within 2 km of an air pollution monitor, and analyses of AML included 46 cases and 19.209 controls living within 6 km of an air pollution monitor. Their conclusion was that the risk of ALL was increased if the mother was exposed to polyaromatic hydrocarbons (PAHs), 1,3 butadiene, benzene, meta/para-xylene, arsenic and lead. The risk of AML increased if the mother was exposed to benzene, toluene, meta/para-xylene and chloroform (32). (See table 4 for exact OR)

Reynolds et al (29) also use the California Cancer Registry for their case-control study. During the years 1983-94, all children born in San Diego county that developed leukemia, were the population of interest; a total of 90 cases under the age of 5. Controls were selected from birth registers and were selected if they were born on the same day as the case; a total of 349 controls were used for the analysis. The address from the birth register was geocoded and compared with a geocoded map of traffic density, delivered by the Californian Transportation Authority. A radius of 165 m around each subject's house was compared to the average traffic in that zone. They concluded that traffic was not associated with the risk of leukemia.

Steffen et al (30) did a hospital-based case-control study on children under 15 years. In total, they had 280 cases and 287 controls. The cases were newly diagnosed and were in hospital for that reason, and controls were hospitalized because of acute orthopedic trauma or disease. Maternal interviews were conducted if the mother was available during opening hours of the interviewer at the hospital. The study investigated whether living close to a petrol station or repair garage or living near high traffic roads during pregnancy could increase the risk of leukemia. They found that traffic was unrelated but living close to a garage or petrol station could increase the risk of childhood leukemia, though not significantly: OR= 2.2 (95% CI 0.9-5.7).

3.1.2 Evaluation of bias according to air pollution

Both of the reviews above (27, 28) have clearly stated their search strategy and how they treated their findings. Pyatt et al (27) found major heterogeneity. The studies were small, had an inaccuracy in measurement, they showed different exposure measurement and confounding factors to other chemicals. The study carried out by Zhou et al (28) had a low level of heterogeneity, but the level was moderate for paint exposure due to the use of different paints, and the lack of explaining this in the included studies. The heterogeneity could lead to impreciseness in the conclusion, but all in all there is a low risk of bias in the reviews. Table 3 shows a summary of risk of bias in evidence using GRADE (25).

The single studies all have medium to high risk of bias, and the main concern is the variation of exposure measurement, in particular Reynolds et al, Heck et al and Steffen et al (29, 30, 32). All used an estimated distance from source of exposure to the child's home, either at birth or at the time of diagnosis. The estimates are connected to spots of emission and are quite rough and consequently increase the risk of bias due to performance. Bailey et al (31)

used parental questionnaires to explore the level of exposure which could lead to differences from the true exposure as mothers of diseased children tend to overestimate the exposure, especially if it is believed to be a risk factor for the disease in question. Doing parental interviews after the child has developed the disease could lead to a false conclusion about the risk.

Two of the single studies had attrition issues; Steffen et al and Baileys et al (30, 31). There were differences in the study groups, and the loss of follow up difference was about 20 %. As so many controls were lost to follow up, the association of exposure and disease could shift to parity.

3.2.1 Parental oral dietary intake and medicine use

One of the studies performed a meta-analysis on the dietary intake; Karalexi et al (34). Through a search in PubMed a total of 39 studies that were included; all were case-controls. Studies were divided into the following categories: non-specific leukemia, ALL specific or AML specific and after maternal or paternal intake. There was a total of 8.117 ALL, 1.683 AML and 6.598 total leukemia cases for the maternal intake group, and 1.859 ALL, 270 AML and 1.684 total leukemia cases in the paternal intake group (34).

The exposure investigated was alcohol consumption, either pre-conception for both maternal and paternal, or during pregnancy for maternal only. Self-reported paternal alcohol consumption was not associated with either outcome group. Self-reported maternal alcohol consumption was not associated with total leukemia or ALL, but with AML a moderate intake compared to none alcohol showed OR= 1.64 (95% CI 1.23–2.17). For a high intake versus none there was a non-linear relation OR= 2.36 (95% CI 1.60–3.49. When restricted to the type of alcohol, only wine was associated with increased risks. Studies carried out on paternal

alcohol consumption were small and heterogeneous, while those on maternal consumption were considered not heterogeneous (34).

Three of the single studies investigated alcohol consumption; Menegaux et al (35), Perèz-Saldivar et al (36) and Soldin et al (37). Menegaux et al (35) conducted a hospital-based case-control study in children under 15 years of age. The cases had newly been diagnosed with acute leukemia, ALL or Acute Non-Lymphoid Leukemia (ANLL), and a total of 280 cases were included in the study. The controls were hospitalized due to diseases other than cancer and birth defects, and there was a total of 288 controls. All subject-mothers were interviewed face-to-face. The researchers found that maternal alcohol consumption increased the risk of both ALL, OR = 2.0 (95% CI 1.4–3.0), and ANLL, OR = 2.6 (95% CI 1.2–5.8). Cola (all kinds of cola, no specific brands) and tea intake were also studied and showed no relation to the risk of any leukemia. Coffee consumption during pregnancy, on the other hand, increased the risk of ALL; 4-8 cups of coffee per day- OR= 2.4 (95% CI 1.3– 4.7), but not significantly for ANLL; OR= 2.8 (95% CI 0.7-10.4) (35).

Perèz-Saldivar et al (36) also performed a hospital-based case-control. Their study was done in Mexico City between 1998 and 2013 and included a total number of 195 cases of children aged below 2 years recently diagnosed. For comparison, 369 control children, also in hospital, but for other reasons, were included. In-person interviews were done for each of the parents, and their occupational history was assessed.

Exposure was separated into four time periods: pre-conception, during pregnancy, during breastfeeding and post-breastfeeding for both parents. The only exposure found to be relevant for leukemia risk was paternal alcohol consumption pre-conception; OR = 2.06 (95% CI 1.23-3.47). Maternal alcohol intake was not associated with leukemia, neither before nor during pregnancy (36).

Soldin et al (37) also performed a hospital-based case-control study. Their cases were younger than 18 years and had been diagnosed with leukemia within the last six months, 41 cases in total. The controls were healthy and were at the clinic to receive a vaccination or for minor ailments. The subject-mothers were to answer a questionnaire, and biological samples were collected from both subject and mother. Soldin et al (37) found no statistical difference between cases and control in relation to alcohol consumption prenatally, and neither maternal, p=0.58, nor paternal, p=0.82, with no risk estimate calculated. They concluded that parental alcohol consumption was not associated with leukemia (37).

The two remaining studies on parental intake were Ross (38) and Ross et al (39), who investigated the maternal intake of topoisomerase 2-inhibitor and the use of medicine in relation to the risk of leukemia. Ross (38) re-interviewed cases and controls from previous studies conducted during the past 10 years. All had been diagnosed before the age of 18. A total of 84 cases and 84 control-mothers were included. The mothers were asked to answer a telephone interview that covered medicinal use and oral intake of topoisomerase 2-inhibitors, such as fruit, vegetables, soy, beans, coffee, tea, cocoa and wine. Two outcomes were measured: ALL and AML. No correlation was found for the use of medicine and any type of leukemia, nor was there any association between diet and ALL. There was however an association between dietary intake of topoisomerase 2-inhibitors during pregnancy and AML, with a higher risk when eating more, p trend = 0.04, risk estimate not calculated (38).

Ross et al (39) performed a case-control study covering USA and Canada, using the Children Cancer Group as a source for cases. The cases were under 18 months at the time of the diagnosis and 243 were included. There were 393 controls recruited through random digit dialing. The mother was asked to give the name of all the physicians they had used from one year prior to the pregnancy, and medical records were gained from the physician and all prescription medicine use was recorded. Acetaminophen (a pain killer) and other non-

prescriptive drugs were not included as not all of them were registered by the physician. A total of 27 drugs were analyzed and overall there was no association found between maternal use of drugs during pregnancy and the risk of leukemia. There was one exception: Cotrimoxazole (an antibiotic) - which none of the control-mothers had received, and 5 of the ALL case-mothers had. Based on this the estimated OR was 11.18 (95% CI 1.51- ∞). The possible increased risk for ALL and the use of this drug could be based on chance, and the researchers concluded that prescription drug use during pregnancy was not associated with either ALL, or AML (39).

3.2.2 Evaluation of bias according to dietary intake and medicines

The meta-analysis and systematic review by Karalexi et al (34) did not found any publication bias or reporting bias. It is therefore likely that their conclusion is based on all the evidence that exists. This increases the reproducibility and the risk of bias is small. There is some heterogeneity for the specific drink types; both on the size of studies and the prevalence of drinking patterns. However, in their main conclusion the heterogeneity is low (I^2 = 59.4%, p-0.001) and gives trust that the evidence found is correct.

As for the single studies, there were some issues with the selection of case and controls. Ross (39) used random digit dialing for controls which could lead to selection bias as phone numbers are often built up as a system whereby the random selection can retrieve neighboring controls. Digit dialing excludes all of those who do not have a telephone, both cases and controls.

Ross et al (38) have not described the process of case-control selection, as this was a re-interview of a previous study. Another issue with Ross et al (38) is the recall bias. Mothers were asked to remember 16 years back on what their habits were during pregnancy. The

search for something to blame in a situation where your child is recently diagnosed with severe leukemia could lead mothers to increase their claimed exposure. These remarks make the evidence less reliable, and the study is degraded to a low level of trust.

Menegaux et al (35) also performed interviews with the mothers and introduced a high risk of recall bias. In addition to the recall bias, mothers were asked to give information on behalf of the fathers which could lead to wrong classification of the exposure. Perèz-Saldivar (36) reduces this risk of bias by limiting the age to 2 years so that it is easier to remember.

Attrition bias could be an issue for three of the studies (35, 36, 38) where the number of cases and controls excluded varies by about 20%. When such high numbers of controls are either excluded or denied participation, the risk of wrong risk estimate calculation is considerable.

3.3.1 Parental occupational exposure

This category focuses on exposure in an occupational setting, as opposed to domestic exposure. Therefore, some exposures may be found in another category, but this category is specific to occupation exposure. Seven studies investigated the relationship between parental occupational exposure and leukemia; one review (40) and six case- control studies (36, 41-45). No cohorts were found.

Bailey et al (40) conducted a review on studies executed by the Childhood Leukemia International Consortium. In the 13 included studies, there were a total of 8.835 ALL cases and 1.357 AML cases. There were 15.486 controls for the ALL cases and 12.443 for the AML cases. All studies had included children under the age of 15, with one exception that included children under 18. The exposure of interest was the parental occupational exposure to paint prior to and during pregnancy. No association was found for ALL, AML or maternal or paternal exposure. They reported low heterogeneity throughout the studies, for paternal

exposure the AML and ALL cases were divided, I^2 = 0,0 %, p- 0,607 and I^2 =0,0%, p- 0,708 respectively. Heterogeneity was combined for maternal exposure and AML/ALL, I^2 = 0,0%, p- 0,803 (40).

Miligi et al (43) investigated the occupational exposure to hydrocarbons, exhaust, minerals and heavy metals. They did a case-control study with children under the age of 10 in the time-period 1998-2001. 683 leukemia cases were enrolled from oncology centers and local controls were selected randomly from the National Health Service records, where 1.044 controls were eligible for inclusion. The subjects' parents were interviewed to establish exposure levels. There were several exposures that were related to increased risk of leukemia: maternal exposure to aromatic hydrocarbon, both prior to and during pregnancy, and paternal exposure to diesel exhaust, mineral oils and lead. See table 4 for details.

The study of Perèz-Saldivar et al has been described previously (p.16) (36). In the same study they also investigate the association of workplace carcinogens and risk of leukemia. Work exposure was calculated by an occupational hygienist in addition to the parents' self-reported use of protective equipment and intake of food. In neither of the exposure windows were maternal nor paternal occupational exposure associated with risk of leukemia.

Infante-Rivard et al (42) investigated the association between maternal exposure to occupational electromagnetic fields (EMF) through a case-control study. Cases were inhabitants of Quebec province, Canada, and were hospitalized in oncology specialist centers; 491 cases in total. Controls were found through family allowance files, a mandatory register for all families with children in Canada, and a total of 491 controls were included in the analysis. Interviews were done with the parents, and occupational history was collected from two years prior to pregnancy. Occupation was then coded accordingly to governmental registers and EMF exposure was estimated based on this. Both high exposure and those with

maximum exposure to EMF were associated with increased risk of leukemia; high: OR= 1.6 (95% CI 1.0–2.7), and maximum: OR= 2.5 (95% CI 1.3–5.0) (42).

Shu et al (45) did a case-control study on what type of occupation the parent had. Cases were enrolled through the Cancer Institute of Shanghai and were under the age of 15 years, where in total 309 were eligible. These controls were selected from the Shanghai district. District committees were randomly selected, and they randomly selected house groups which again gave the contact information for the case family. The parents were interviewed in person about their occupation. ALL and ANLL were combined in the analysis. Paternal occupation during pregnancy showed no association to risk of leukemia. Maternal occupational exposure during pregnancy, on the other hand, showed that if the mother worked in the chemical industry (OR = 3.3 (95% CI 1.6-6.8)), or was a physician (OR= 5.7 (95% CI = 1.3-24.5)) or pharmacist (OR= 19.7 (95% CI = 2.3-169.6)), the risk was increased.

Two of the studies investigated whether parental occupation at a nuclear power plant could increase the risk in offspring (41, 44). The disaster at Chernobyl is already excluded as a risk factor, but these two studies are included here because a nuclear power plant is an occupational risk for the many employees working there, and Chernobyl was a disaster and an accident that spread radioactive matter all over Europe. Being employed at a nuclear power plant, where safety is not at immediate risk, is normal for many parents across the globe and in this situation is included as a normal occupation.

Gardner et al (41) included patients under 25 years of age in their nested case-control study, using data from a larger cohort study. 52 cases that were found to live within West-Cumbria health administration district and diagnosed in the period 1950-1985, were included in the study. Controls were found through birth registers conducted by the government. In total 564 controls were included. Whereas some were local controls, others were district-controls, and some were both. Parents were to fill in questionnaires to evaluate exposure. The exposure was

divided in two parts: those employed at Sellafield nuclear power plant, and those employed and monitored for radiation while working at Sellafield. Paternal employment at the time of conception and at birth were both associated with an increased risk of leukemia; Relative Risk (RR)= 2.79 (95% CI 1.04-7.52) and RR= 2.82 (95% CI 1.07-7.40), respectively. Employment before conception did not increase the risk significantly, RR= 1.97 (95% CI 0.82-4.78). Paternal monitoring for radiation was found to be associated with increased risk; RR= 3.07 (95 % CI 1.09-8.65)(41).

Roman et al (44) used a case-control study-design to explore the relation between parental occupation at a nuclear power plant and the risk of leukemia. They had several sources for the cases to ensure they covered everyone who had been diagnosed in the period 1972-1989 and was under the age of 5 at the time. They had 54 cases and 324 controls. The controls were found through the National Birth Register of England and through delivery wards in the same hospital as the case. Information about the children and their parents came from four sources: the child's birth certificate, a personal interview with the parents, the mother's medical delivery records, and employment and health records made by the nuclear industry. Maternal employment, either before or during pregnancy was found to have no association to leukemia in the offspring. Paternal employment was also not associated, neither before nor after conception. However, if the father had been monitored for radiation before conception, the risk of leukemia in the offspring was increased; OR= 9.0 (95% CI 1.0- 107.8) (44).

3.3.2 Evaluating bias according to occupation

The review by Bailey et al (40) did not carry out a systematic review but used chosen studies from a research group. By excluding all other studies done on the same topic, this could lead to detection bias.

For the single studies there were minor issues with possible selection bias; Infante-Rivard et al (42) narrowed their selection of cases to one year in the entire study period of ten years, and also excluded those who were not diagnosed in the Quebec area, thus reducing the total population to about 60% of the original. This could influence the risk estimate and the true risk could be inflicted.

Roman et al (44) inform that some of the controls were selected by cancer register staff, but they fail to explain the process in which this happened and if it was randomly or consciously performed. Shu et al (45) also had selection of controls. They used so-called neighborhood committees. It is described how these committees chose the controls, but it is possible that the committee knew the children in their area of administration and chose the healthier or best choices for the controls.

As for performance bias, all the single studies had issues. Gardner et al (41) used GPS points up to an accuracy of 100 meters and only considered the distance to Sellafield, not other emission points or other confounders. Infante-Rivard et al (42) carried out maternal interviews which included recall bias and the exposure was not measured directly but calculated due to what kind of occupation the mother had. Misclassification is a risk with this method. The same problem occurred in Shu et al (45). Roman et al (44) used several sources of information including parental interview, but confirmed this information to the other sources, thus reducing risk of bias. For the rest of the single studies, recall bias over a 10-15 year span was the main issue (36, 43).

Attrition bias was an issue for most of the case-control studies included (36, 41-43) with large differences between participating cases and controls.

3.4.1 Parental exposure to pesticides

Five studies investigated parental exposure to pesticides and the risk of childhood leukemia; three reviews (46-48) and two case-controls (37, 49). No cohort studies were included.

Bailey et al (46) did a review on studies done by the Childhood Leukemia International Consortium, in all 12 studies with 7.956 ALL cases and 14.494 ALL controls, as well as 740 AML cases and 10.847 AML controls. The studies were quite similar, but heterogeneity was found concerning the term "prevalence of use" (46). Regardless of this, the data was pooled. The term "use" could mean sprayed, applied, exposed to, and the prevalence varied from "ever used" to "spraying indoors every day" (46). Increased risk was found for both ALL and AML if the parents had been exposed to pesticides 1-3 months preconceptionally; ALL: OR= 1.39 (95% CI 1.25- 1.55), AML: OR= 1.49 (95% CI 1.02, 2.16). Increased risk was also found for both ALL, OR= 1.43 (95% CI 1.32, 1.54) and AML, OR= 1.55 (95% CI 1.21, 1.99) if pesticides were used during pregnancy.

Schuz et al (47) included 38 studies in their review, but did not describe their search procedure. They did not conclude that domestic parental use of pesticides does increase the risk of childhood leukemia. There are indications that paternal use of pesticide preconceptionally could increase the risk of ALL, and that maternal use of pesticide during pregnancy could increase the risk of AML (47).

Van Maele-Fabry et al (48) conducted a search in PubMed to find studies for their review, which included 13 case-control studies. There was strong heterogeneity (all studies, I^2 = 73,1%) and the data was modified to better fit the timing of exposure. They separately analyzed the studies done on exposure before and after pregnancy, and where the exposure took place (outside, inside). When heterogeneity was reduced, they carried out a meta-analysis. They concluded that domestic use of pesticides during pregnancy increased the risk of leukemia in the offspring; RR: 2.19 (95% CI 1.92–2.50) (48).

Rudant et al (49) did a case-control study on domestic use of pesticides and the risk of leukemia in children under the age of 15. Cases were enrolled through French oncology centers as well as the National Cancer Registry. Controls were selected through a quota sampling method. 60.000 addresses were selected randomly covering the entirety of France. The addresses were collected from a telephone register. They then added quotas so that cases and controls were matched by sex and age amongst other features. In the end they had 764 leukemia cases and 1.681 controls. The mother of the subject was interviewed on the topics of pesticide use. Their conclusion was that maternal use of pesticides during pregnancy increased the risk of leukemia; OR= 2.2 (95% CI 1.8–2.6). Maternal use of herbicide also increased the risk; OR= 1.5 (95% CI 1.0–2.2). Paternal use of any pesticide also increased the risk of leukemia; OR =1.4 (95% CI 1.2–1.7) (49).

Soldin et al (37) has previously been described (p.16). With their 41 cases and 41 controls they found a difference in case-mothers and control-mothers regarding the question of domestic pesticide use, p=0.02, with more case-mothers exposed. There was no difference in paternal use of pesticides, p= 0.99.

3.4.2 Evaluation of bias according to Pesticide

Schuz et al (47) included 38 studies in their review. Their methods were not described but they claimed heterogeneity was a major concern, I^2 not available. This is due to the different use of the word pesticide, from general to specific brands, the way exposure is measured, the age population studied and the way questions in questionnaires were asked. This results in the risk of bias being high. Van Maele-Fabry et al (48) on the other hand gave a very precise description and the risk of bias is low in their review. They had a high level of heterogeneity,

and so their data is stratified by comparable studies to reduce heterogeneity, thus reducing the risk of misclassification and consequently reducing the risk of bias.

Rudant et al (49) used telephone directories as the source of controls, which excludes those without a landline-based telephone. This could potentially lead to wrong estimates based on richer controls and possibly a lesser use of domestic pesticides. Performance bias is a greater issue for this study. Maternal interviews were carried out where the mother was to answer on behalf of the father and remember 15 years back. This could lead to a misclassification bias as well as a recall bias which reduces the trust in this evidence. No major bias issues were found for Soldin et al (37).

3.5.1 Parental socioeconomic status (SES)

There were four studies that investigated parental economic status (50), one cohort study (10) and two case-control studies (29, 30). Adam et al (50) conducted a literature search in PubMed and excluded studies from developing countries as the authors claim that SES has a different meaning in developed and developing countries. They included seven studies in their analysis, but due to major heterogeneity as they describe it (I^2 not estimated) even when they only compared the most similar studies, they could not conclude that SES is a risk factor for leukemia in children.

Del Risco Kollerud (10) carried out a cohort study and included all live births in Oslo between 1967-2009; 712.674 children were registered in the National Birth Registry, 437 of these developed leukemia before the age of 16 years. An individual social security number for all Norwegian citizens made it possible to link all the registered cancer cases in the cancer registry to the birth registry. The same identification number was used to extract family taxable income and education level from Statistics Norway, consequently linking birth

certificates and family SES. They found a correlation between family income in the first two years of life and risk of ALL; OR=1.72 (95% CI= 1.11–2.64). There was found no association for the disease later in life.

The study by Reynolds et al (29) has been previously described (p. 13), and with their 90 cases and 349 controls they could not find any correlation between SES at birth and childhood leukemia. Steffen et al (30) is also previously described (page 14), and with 280 cases and 287 controls they could not establish a correlation between SES during pregnancy and leukemia in the offspring.

3.5.2 Evaluation of bias according to SES

Adam et (50) al completed a detailed search and gave clear information on excluded studies, but the heterogeneity is large, making the conclusion uncertain.

The use of birth registry linked to cancer registry in the study by Kollerud et al (10) reduces the risk of bias and the study is upgraded due to high trust in evidence. As for the other two single studies there are some issues with the way the data was collected as previously stated (p.13-14) Reynolds et al (29) and Steffen et al (30).

3.6.1 Parental smoking

The largest group within parental exposure was that of smoking. The systematic search found nine studies, whereby four were reviews (27, 28, 47, 51) and five were case-control studies (35-37, 52, 53). No cohort studies were found on this exposure category.

Bruin et al (51) conducted a review on nicotine replacement therapy and the risk of nicotine itself. They have not described their methods, nor how many articles they used, nor do they

claim anything about heterogeneity. They do, however, conclude that nicotine could be harmful for the oncoming generation, as well as for the second generation to the nicotine-using mother. They do not show any risk estimates but claim there is a possible correlation.

The study by Pyatt et al (27) is earlier described (p.12), and with their 106 included studies they conclude that there is likely to be no correlation between paternal smoking and leukemia in the offspring. The included studies on smoking are as heterogeneous as they were for air pollution.

Schuz et al (47) is also described previously (p.23) and with their 38 included studies they concluded that for ALL and AML combined there is an increased risk if the father smoked preconceptionally, OR not stated. There was no correlation between maternal smoking and ALL and AML combined.

Zhou et al (28) did a systematic search through several databases on English studies only. They included 29 single studies, whereby one of which was a cohort and the rest case-control designs. They investigated the correlation between maternal smoking during pregnancy and the risk of leukemia in the offspring and concluded that there was no correlation.

Farioli et al (52) did a case control study in Italy in the period 1998-2003. Due to the Italian Registry of Cancer, they were certain to find most cases there. The cases were under the age of 10 at the time of diagnosis and they were diagnosed with ALL, in total 557 cases and 855 controls were used in the analysis. Controls were randomly selected from the health authority registers. Subjects' parents were to answer a questionnaire about exposures in the time frame of up to six months prior to pregnancy and onwards. Neither paternal nor maternal smoking prior to or during pregnancy were found to have a correlation to offspring leukemia.

Mattioli et al (53) also executed a case-control study in Italy between 1998-2003 and they included 82 cases of ANLL below the age of 10. They had controls drawn at random from the

health care authority, with a total of 1.044 controls. Parents were interviewed in person. The conclusion was that paternal smoking prior to conception does increase the risk of childhood leukemia in the offspring: heavy smoker versus non-smoker, OR= 1.90 (95% CI 1.14-3-17). The correlation between leukemia and moderate smoking was not significant. This was also the case for maternal smoking during pregnancy (53).

Menegaux et al (35) has been described previously (p.16) and with their 280 cases and 288 controls under the age of 15, they conclude that there is no correlation between paternal or maternal smoking during pregnancy, neither to ALL, nor ANLL.

Perèz-Saldivar et al (36) have been earlier mentioned (p. 12), and with their 196 cases and 369 controls under 2 years of age, they could not find any relation between either paternal smoking prior to or during pregnancy, or maternal smoking in the same period, as well as the risk of childhood leukemia.

Soldin et al (37) has also been previously described (p. 16), and they could not find any differences between cases and the control-group when it came to parental smoking; paternal smoking, p= 0.33, maternal smoking, p = 0.88.

3.6.2 Evaluation of bias according to smoking

As for the risk of bias in the review of Bruin et al (51), there is no information on the included /excluded studies, nor how they were found. The risk of selection and performance bias is therefore high, and the study's level of evidence is low. All other studies are previously explained, except in the studies by Farioli et (52) and Matioli et al (53). Both these studies used the same approach for including cases, and they both state that they include most cases of leukemia. It is, however, not clear who the excluded cases are and what they could have contributed to the risk estimate. The main issue in the last two studies is the use of interview,

where parents are supposed to remember many years back how much they smoked during pregnancy, resulting in a large risk of recall bias therefore being introduced. Mattioli et al (53) also have some issues with attrition bias; 30 % of controls refused to participate, whereas only 8 % of cases refused.

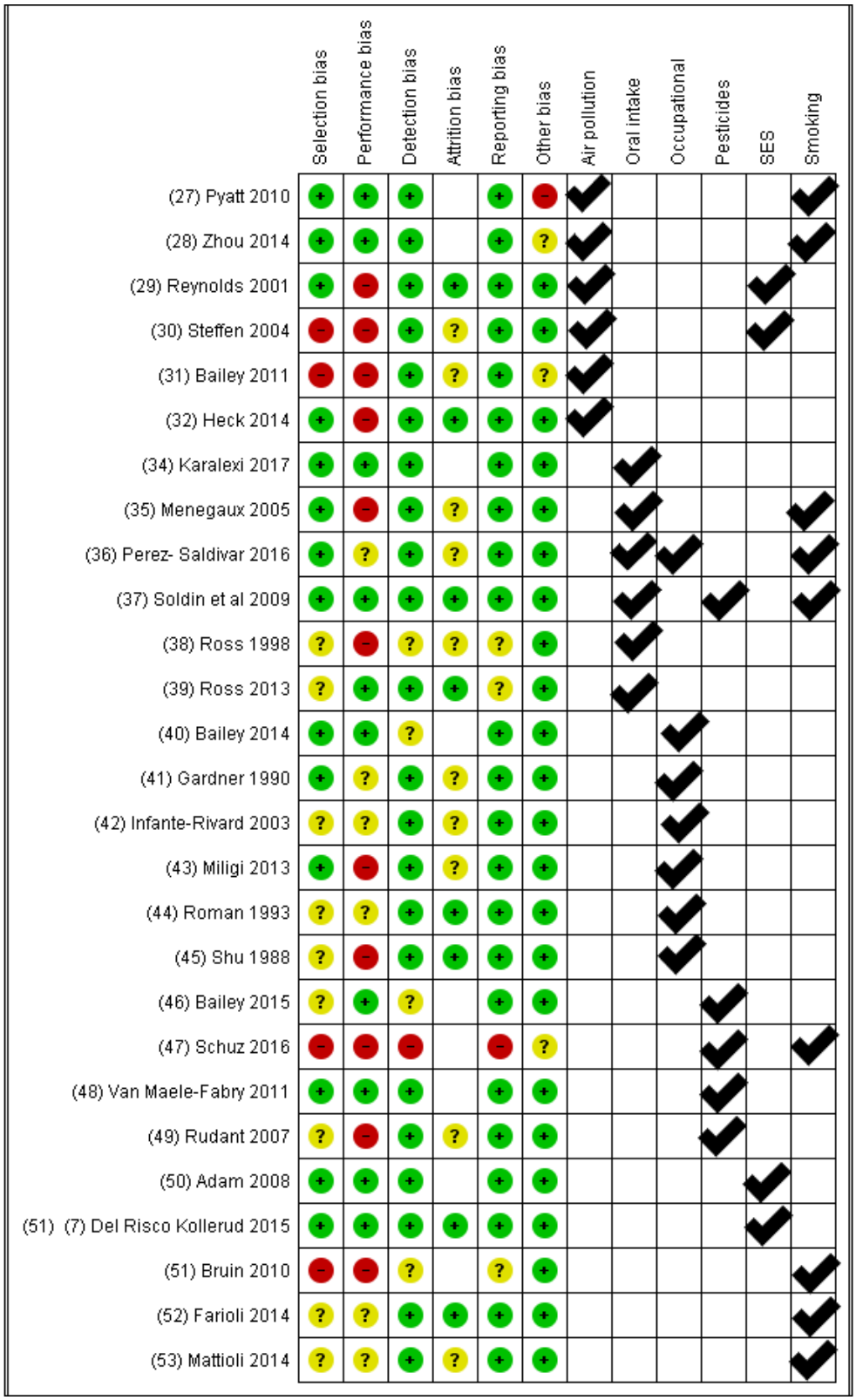

Table 3: The author's risk of bias assessment in three levels;
+ No risk of bias suspected.
? There could be some possible risk of bias.
- The risk of bias is high

An overview of categories for each article

Table 4A, Summary of findings air pollution. Significant findings in bold text, the summary of trust in evidence based on risk of bias and study design is graded to the far right.

Reference	Number of studies or cases	Exposure	Outcome	Risk estimate	GRADE
Pyatt 2010 (27), Review	106 studies	Benzene, Hydrocarbon, Atmospheric contaminants, Traffic density and Proximity to refineries	Leukemia: ALL, AML	Probably not an increased risk. Inconclusive due to lack of evidence	⊕⊕⊕◯
Zhou 2014 (28), Review	29 studies	**Maternal exposure to solvent during pregnancy** **Maternal exposure to petroleum during pregnancy** **Maternal exposure to paint during pregnancy**	Leukemia	**OR= 1.25 (95% CI 1.09–1.45)** **OR= 1.42 (95% CI 1.10–1.84)** **OR= 1.23 (95% CI 1.02–1.47)**	⊕⊕⊕◯
Bailey 2011 (31), Case-control, <15 years	416 cases and 1361 controls	Paternal/ maternal refueling of vehicles one year prior to and during pregnancy Using wood-burner for heating home one year prior to and during pregnancy a. Open burner **b. Closed burner**	Leukemia	$OR_{paternal}$= 1.56 (95% CI 0.65- 3.77) $OR_{maternal}$= 0.82 (95% CI 0.57- 1.20) a. OR = 1.20 (95% CI 0.51- 2.84) **b. OR = 1.41 (95% CI 1.02- 1.94)**	⊕◯◯◯
Heck 2014 (32), Case- control, < 6 years	69 cases with ALL and 2,994 controls 46 cases with AML and 19,209 controls	Maternal exposure to air toxins during 3rd trimester and risk of ALL: **1. Polyaromatic hydrocarbons (PAHs)** **2. 1,3 butadiene** **3. Benzene** **4. Meta/para-xylene** **5. Arsenic** **6. Lead** 7. Toluene 8. Cholorform Maternal exposure to air toxins during 3rd trimester and risk of AML: 1. PAHs 2. 1,3 butadiene **3. Benzene** **4. Meta/para-xylene** 5. Arsenic 6. Lead **7. Toluene** **8. Cholorform**	Leukemia: ALL AML	**1 OR= 1.16 (95% CI 1.04- 1.29)** **2 OR= 1.54 (95% CI 1.19- 1.99)** **3 OR= 1.50 (95% CI 1.08- 2.09)** **4 OR= 1.33 (95% CI1.05- 1.69)** **5 OR= 1.33 (95% CI 1.02- 1.73)** **6 OR= 1.42 (95% CI 1.02- 1.96)** *7 OR= 1.22 (95% CI 0.90- 1.65)* *8 OR= 1.00 (95% CI 0.78- 1.28)* *1 OR= 1.13 (95% CI 0.93- 1.36)* *2 OR=1.45(95% CI 0.99- 2.15)* **3 OR= 1.75 (95% CI 1.04- 2.93)** **4 OR= 1.37 (95% CI 1.01- 1.85)** *5 OR= No value* *6 OR= 1.09 (95% CI 0.61- 1.92)* **7 OR= 1.50 (95% CI 1.04- 2.16)** **8 OR= 1.30 (95% CI 1.00- 1.69)**	⊕⊕◯◯
Reynolds 2001 (29), Case-control,	90 cases and 349 controls	Traffic density near home during pregnancy	Leukemia	OR=1.10 (95% CI 0.56- 2.15)	⊕◯◯◯
Steffen 2004 (30), Case-control, < 15 years	280 cases and 287 controls	Neighboring a garage or petrol station during pregnancy Living near high traffic road during pregnancy	Leukemia	OR= 2.2 (95% CI 0.9- 5.7) OR= 1.3 (95% CI 0.5- 3.2)	⊕◯◯◯

Table 4B, Summary of findings parental oral intake and medication use. Significant findings in bold text, the summary of trust in evidence based on risk of bias and study design is graded to the far right.

Reference	Number of studies or cases	Exposure	Outcome	Risk estimate	GRADE
Karalexi 2017 (34), Meta -analysis	39 studies	Maternal alcohol consumption during pregnancy and total leukemia Maternal alcohol consumption during pregnancy and risk of ALL, any consumption **Maternal alcohol consumption during pregnancy and risk of AML** **a. High versus none** **b. Moderate versus none** Paternal alcohol consumption and total leukemia Paternal alcohol consumption and risk of ALL Paternal alcohol consumption and risk of AML	Leukemia: ALL AML	OR= 0.98 (0.95 % CI 84–1.14) OR= 0.97 (95% CI 0.85–1.11) **a OR= 2.36 (95% CI 1.60–3.49)** **b OR= 1.64 (95% CI 1.23–2.17)** OR= 1.05 (95 % CI 0.91–1.22) OR= 1.10 (95% CI 0.93–1.30) OR= 1.23 (95% CI 0.83–1.82)	⨁⨁⨁◯
Menegaux 2005 (35), Case- control, < 15 years	280 cases and 288 controls	Risk of ALL: **Maternal coffee consumption during pregnancy** **a. ≤ 3 cups/day** **b. 4-8 cups /day** **c. > 8 cups /day** Maternal tea consumption during pregnancy **Maternal alcohol consumption during pregnancy** Risk of ANLL: Maternal coffee consumption during pregnancy a. ≤ 3 cups/day b. 4-8 cups /day c. > 8 cups /day Maternal tea consumption during pregnancy **Maternal alcohol consumption during pregnancy**	Leukemia ALL ANLL	 **a OR= 1.1 (95% CI 0.7–1.8)** **b OR= 2.4 (95% CI 1.3– 4.7)** **c OR= 3.1 (95% CI 1.0–9.5)** OR= 1.2 (95% CI 0.6–2.6) **OR = 2.0 (95% CI 1.4–3.0)** a OR= 1.6 (95% CI 0.6-4.3) b OR= 2.8 (95% CI 0.7-10.4) c OR= 3.0 (95% CI 0.3-35.1) OR= 0.6 (95% CI 0.3–1.4) **OR = 2.6 (95% CI 1.2–5.8)**	⨁◯◯◯
Perèz-Saldivar 2016 (36), Case- control, < 2 years	195 cases and 369 controls	**Paternal alcohol consumption preconceptionally** Maternal alcohol consumption preconceptionally Maternal alcohol during pregnancy	Leukemia	**OR = 2.06 (95% CI 1.23-3.47)** OR= 1.43 (95% CI 0.92-2.23) OR= 1.08 (95% CI 0.51-2.30)	⨁⨁◯◯
Ross 1998 (38), Case-control	84 cases and 84 controls	Maternal medical use during pregnancy and risk of ALL Maternal medical use during pregnancy and risk of AML Maternal dietary intake of topo 2 inhibitors during pregnancy and risk of ALL **Maternal dietary intake of topo 2 inhibitors during pregnancy and risk of AML**	Leukemia ALL AML	Risk estimate not provided Risk estimate not provided Risk estimate not provided **Increase with higher intake, trend p value= 0.04**	⨁◯◯◯
Ross 2013 (39), Case-control, < 1,5 years	243 cases and 393 controls	Maternal prescription medicine usage during pregnancy	Leukemia	No associations found	⨁⨁◯◯

Soldin 2009 (37), Case-control, < 18 years	41 cases and controls	Maternal alcohol consumption prenatally Paternal alcohol consumption prenatally	Leukemia, ALL	Risk not calculated, only differences between cases and controls: No difference, p=0.58 No difference, p=0.82	⊕⊕◯◯

Table 4C, Summary of findings parental occupational exposure. Significant findings in bold text, the summary of trust in evidence based on risk of bias and study design is graded to the far right.

Reference	Number of studies or cases	Exposure	Outcome	Risk estimate	GRADE
Bailey 2014 (40), Review	13 studies	Paternal occupational exposure to paint prior to and during pregnancy and risk of ALL Maternal occupational exposure to paint prior to and during pregnancy and risk of ALL Paternal occupational exposure to paint prior to and during pregnancy and risk of AML Maternal occupational exposure to paint prior to and during pregnancy and risk of AML	Leukemia: ALL, AML	OR= 0.93 (95% CI 0.76- 1.14) OR= 0.81 (95% CI 0.39- 1.68) OR= 0.96 (95% CI 0.65- 1.41) OR= 1.31 (95% CI 0.38- 4.47)	⨁⨁◯◯
Gardner 1990 (41), nested Case- control, < 25 years	52 cases and 564 controls	Paternal employment at Sellafield Nuclear Power plant preconceptionally **Paternal employment at Sellafield Nuclear Power plant at conception** **Paternal employment at Sellafield Nuclear Power plant birth** **Paternal monitoring of radiation while employed at Sellafield preconceptionally**	Leukemia	RR= 1.97 (95% CI 0.82-4.78) **RR= 2.79 (95% CI 1.04-7.52)** **RR= 2.82 (95% CI 1.07-7.40)** **RR= 3.07 (95 % CI 1.09-8.65)**	⨁⨁◯◯
Infante Rivard 2003 (42), Case-control, < 9 years	491 cases and 491 controls	**Maternal occupational EMF exposure during pregnancy** **Maximum exposure** **High exposure**	Leukemia	 **OR= 2.5 (95% CI 1.3–5.0)** **OR= 1.6 (95% CI 1.0–2.7)**	⨁⨁◯◯
Miligi 2013 (43), Case-control, < 10 years	683 cases 1044 controls	**Maternal occupational exposure to aromatic hydrocarbon preconceptionally** **Maternal occupational exposure to aliphatic hydrocarbon preconceptionally** **Maternal occupational exposure to aromatic hydrocarbon during pregnancy** **Maternal occupational exposure to aliphatic hydrocarbon during pregnancy** Paternal occupational exposure to aromatic hydrocarbon Paternal occupational exposure to aliphatic hydrocarbon **Paternal occupational exposure to diesel exhaust fumes** **Paternal occupational exposure to mineral oils** **Paternal occupational exposure to lead**	Leukemia; ALL and ANLL combined	**OR= 3.8 (95 % CI 1.6 - 9.2)** **OR= 4.3 (95% CI 1.8 - 10.4)** **OR= 1.8 (95% CI 1.0 - 3.4)** **OR= 2.4 (95% CI 1.0 - 2.7)** OR= 1.1 (95% CI 0.8-1.6) OR= 0.9 (95% CI 0.6- 1.4) **OR= 1.5 (95% CI 1.2 - 2.0)** **OR= 1.5 (95% CI 1.1 - 2.0)** **OR= 1.7 (95% CI 1.1 - 2.7)**	⨁⨁◯◯
PerèsSaldivar 2016 (36), Case- control, < 2 years	195 cases and 369 controls	Paternal occupational exposure to carcinogens preconceptionally Maternal occupational exposure to carcinogens preconceptionally Paternal occupational exposure to carcinogens during pregnancy	Leukemia	OR= 0.96 (95% CI 0.53-1.72) OR= 1.01 (95% CI 0.37-2.73) OR= 1.01 (95% CI 0.51-1.99)	⨁⨁◯◯

		Maternal occupational exposure to carcinogens during pregnancy		OR= 1.2 (95% CI 0.23-6.28)	
Roman 1993 (44), Case- control, < 5 years	54 cases and 324 controls	Paternal employment in nuclear powerplant preconceptionally Paternal employment in nuclear powerplant after conception **Paternal monitoring for radiation while employed preconceptionally** Paternal monitoring for radiation while employed after conception Maternal employment in nuclear powerplant preconceptionally Maternal employment in nuclear powerplant after conception	Leukemia	RR= 2.8 (95% CI 0.6- 10.5) RR= 1.2 (95% CI 0.1- 10.7) **RR= 9.0 (95% CI 1.0- 107.8)** RR= 6.0 (95% CI 0.1- 471.0) RR= 0.0 (95% CI 0.0- 5.1) RR= 3.0 (95% CI 0.1-57.6)	
Shu 1998 (45), Case-control, < 15 years	309 cases and 618 controls	Paternal occupation during pregnancy **Maternal occupation in chemical industry during pregnancy** Maternal occupation in agriculture during pregnancy Maternal occupation in metal refining during pregnancy **Maternal occupation as physician during pregnancy** **Maternal occupation as pharmacist during pregnancy**	Leukemia Combined ALL and ANLL	OR= 0.8 (95% CI 0.5-1.2) **OR = 3.3 (95% CI 1.6-6.8)** OR= 2.3 (95% CI 0.9-6.3) OR= 2.6 (95% CI = 0.9-7.7) **OR= 5.7 (95% CI = 1.3-24.5)** **OR= 19.7 (95% CI = 2.3-169.6)**	

Table 4D, Summary of findings parental exposure to pesticides. Significant findings in bold text, the summary of trust in evidence based on risk of bias and study design is graded to the far right.

Reference	Number of studies or cases	Exposure	Outcome	Risk estimate	GRADE
Bailey 2015 (46), Review	12 studies	**Parental exposure to pesticides 1- 3 months prior to pregnancy and risk of ALL** **Parental exposure to pesticides 1- 3 months prior to pregnancy and risk of AML** **Parental exposure to pesticides during pregnancy and risk of ALL** **Parental exposure to pesticides during pregnancy and risk of AML**	Leukemia: 1. ALL 2. AML	**OR= 1.39 (95% CI 1.25- 1.55)** **OR= 1.49 (95% CI 1.02, 2.16)** **OR= 1.43 (95% CI 1.32, 1.54)** **OR= 1.55 (95% CI 1.21, 1.99)**	⊕⊕◯◯
Schuz 2016 (47), Review	38 studies	ALL: Paternal use of pesticide preconceptionally Maternal use of pesticide during pregnancy AML: Paternal use of pesticide preconceptionally Maternal use of pesticide during pregnancy	Leukemia: ALL AML	 Increased risk OR not stated No association No association Increased risk OR not stated	⊕◯◯◯
Van Maele-Fabry 2011 (48), Review	13 studies	Domestic pesticide usage during pregnancy	Leukemia	**RR= 2.19 (95% CI 1.92–2.50)**	⊕⊕⊕◯
Rudant 2007 (49), Case- control, < 15 years	1460 cases and 1681 controls	**Maternal use of domestic pesticides during pregnancy** **Maternal use of domestic herbicides during pregnancy** **Paternal domestic use of pesticide**	Leukemia	**OR= 2.2 (95% CI 1.8–2.6)** **OR= 1.5 (95% CI 1.0–2.2)** **OR =1.4 (95% CI 1.2–1.7)**	⊕◯◯◯
Soldin 2009 (37), Case-control, < 18 years	41 cases and controls	**Maternal use of pesticide prenatally** Paternal use of pesticide prenatally	Leukemia, ALL	Risk not calculated, only differences between cases and controls: **More case mothers used, p=0.02** No difference, p=0.99	⊕⊕◯◯

Table 4E, Summary of findings Socioeconomic status. Significant findings in bold text, the summary of trust in evidence based on risk of bias and study design is graded to the far right.

Reference	Number of studies or cases	Exposure	Outcome	Risk estimate	GRADE
Adam 2008 (50), Review	7 studies	Low SES at birth	Leukemia	OR= 0.89 (95% CI 0.47–1.70)	⨁⨁⨁◯
Del Risco Kollerud 2015 (10), Cohort, < 16 years	864 cases 712 674 live births	**Low family income first two years of life and risk off ALL** Low family income later and risk of ALL Low family income first two years of life and risk off AML Low family income later and risk of AML	Leukemia: ALL AML	**OR=1.72 (95% CI 1.11–2.64)** Hazard ratio (HR)= 1.36 (95% CI 0.95–1.96) OR= 0.59 (95% CI 0.22–1.56) HR= 0.81 (95% CI 0.40–1.61)	⨁⨁⨁◯
Reynolds 2001 (29), Case-control	90 cases and 349 controls	Low SES at birth	Leukemia	OR= 0.86 (95% CI 0.31- 2.38)	⨁◯◯◯
Steffen 2004 (30), Case-control, < 15 years	280 cases and 287 controls	Low SES during pregnancy	Leukemia	P >0.05	⨁◯◯◯

Table 4F, Summary of findings smoking. Significant findings in bold text, the summary of trust in evidence based on risk of bias and study design is graded to the far right.

Reference	Number of studies or cases	Exposure	Outcome	Risk estimate	GRADE
Bruin 2010 (51), Review	Not declared	Nicotine replacement therapy during pregnancy	Leukemia	Possible association, NO risk estimate	⨁◯◯◯
Pyatt 2010 (27), Review	106 studies	Maternal smoking Paternal smoking	Leukemia: ALL, AML	Probably not an increased risk. Inconclusive due to lack of evidence	⨁⨁⨁◯
Schuz 2016 (47), Review	38 studies	 Paternal smoking preconceptionally Maternal smoking during pregnancy	Leukemia: 1. ALL 2. AML	ALL and AML combined: Increased risk, OR not stated No association	⨁◯◯◯
Zhou 2014 (28), Review	29 studies	Maternal smoking during pregnancy	Leukemia	OR= 0.99 (95% CI 0.93-1.06)	⨁⨁⨁◯
Farioli 2014 (52), case-control, < 10 years	557 cases of ALL and 855 controls	Paternal smoking prior to pregnancy and risk of ALL Paternal smoking during pregnancy and risk of ALL Maternal smoking during pregnancy and risk of ALL	Leukemia, ALL	OR= 0.93 (95% CI 0.69–1.27) OR= 1.01 (95% CI 0.74–1.39) OR= 1.64 (95% CI 0.67–4.03)	⨁⨁◯◯
Mattioli 2014 (53), Case- control, < 10 years	82 cases 1044 controls	Paternal preconceptionally **a. Heavy smoker** b. Moderate smoker Maternal smoker during pregnancy	Leukemia: ANLL	 a **OR= 1.90 (95% CI 1.14-3-17)** b OR= 1.74 (95% CI 0.87-3.78) OR= 1.35 (95% CI 0.68–2.66)	⨁◯◯◯
Menegaux 2005 (35), Case- control, < 15 years	280 cases and 288 controls	Maternal smoking during pregnancy and ALL Maternal smoking during pregnancy and ANLL Paternal smoking preconceptionally and ALL/ ANLL combined	Leukemia 1. ALL 2. ANLL	OR= 0.9 (95% CI 0.6–1.4) OR= 1.0 (95% CI 0.4–2.3) OR = 0.9 (95% CI 0.6–1.3)	⨁◯◯◯
Perès Saldivar 2016 (36), Case- control, < 2 years	195 cases and 369 controls	Paternal smoking preconceptionally Maternal smoking preconceptionally Paternal smoking during pregnancy Maternal smoking during pregnancy	Leukemia	OR= 0.86 (95% CI 0.52-1.43) OR= 0.5 (95% CI 0.27-0.94) OR= 0.78 (95% CI 0.46-1.30) OR= 0.35 (95% CI 0.07-1.51)	⨁⨁◯◯
Soldin 2009 (37), Case-control, < 18 years	41 cases and controls	 Maternal smoking prenatally Paternal smoking prenatally	Leukemia, ALL	Risk not calculated, only differences between cases and controls: No difference, p=0.88 No difference, p=0.33	⨁⨁◯◯

4.0 Discussion

4.1 Level of evidence

There are no clear risk factors for childhood leukemia found in this systematic review. The risk of bias is high in most studies and some are graded as very low trust in evidence found. Some evidence, however, points to an increased risk of any childhood leukemia in parental exposure to pesticides, hydrocarbons, solvents and petroleum products or petroleum exhaust.

The evidence in the included studies was evaluated by GRADE, and varies from “very low”, to “medium”, with no studies showing high trust in evidence. An RCT will be upgraded to high quality if performed with accuracy and a low level of bias. Carrying out an RCT to find a cause for childhood leukemia will be ethically condemnable as this would include exposing parents to “known” carcinogenic substances, and deliberately causing harm. Therefore, meta-analysis of previously observational studies is the second-best option. In the studies of Schuz et al (47) and Bruin et al (51), failing to describe methods used gives weaker evidence. To summarize the evidence, it is crucial to weigh the GRADE in different studies; a study that has a medium trust in evidence is worth more than one with a very low trust in evidence. The final conclusions are based on the overall grading of the evidence.

The results showed that the strength of the associations in general were low. This means that if there is any true risk, the association is small or that researchers cannot find the true association. Ioannidis (54) has written an article on false conclusions in research and points to many reasons why research on epidemiology is false: small sample sizes, small effect-sizes, a great number of comparisons but a low number of calculations of relationship, great flexibility and outcome in the studies, financial interest, as well as many study groups carrying out the same research (54). These points are important in the evaluation of the findings in this systematic review.

Most of the statistically significant risk-estimates lie between 1- 1.5 and the CI's are generally broad (28, 31, 32, 35, 37, 38, 41, 43-46). This could be due to a low number of cases, a lack of true effect or a small effect, and must be considered when discussing the results (54).

4.2 Pesticide

The risk-estimates found in studies of pesticides exposure were consistently associated with a higher risk of leukemia in children. The study by Bailey et al (46) showed the lowest risk estimate, (OR= 1.39 (95% CI 1.25- 1.55)) in their meta-analysis of pesticides exposure 1- 3 months prior to pregnancy and risk of ALL. The risk-estimate is considered as more precise and comprised a high number of cases in the meta-analysis. The highest risk estimate (OR= 2.2 (95% CI 1.8–2.6) was found in the study by Rudant et al (49) on maternal use of domestic pesticides during pregnancy.

The study by Rudant et al (49) shows some serious bias and its level of trust in the evidence is low. However, the findings are supported by other studies with a high trust in evidence (48). With both a high level of trust in evidence, and a relatively high increased risk, they conclude that domestic use of pesticides during pregnancy increased the risk of leukemia; RR= 2.19 (95% CI 1.92–2.50) (48).

4.3 Hydrocarbons

Furthermore, there is evidence for hydrocarbons and petroleum products are associated with an increased risk of leukemia. However, due to heterogeneity in exposure measures it is difficult to compare results between studies. Some studies have looked at petroleum, like Zhou et al (28), and some have investigated the different substances found in exhaust, like

Heck et al (32). Yet other studies have looked at proxies for hydrocarbons, such as distance to the nearest petrol station or garage, like Steffen et al (30). In Steffen et al (30) the findings were not statistically significant and could possibly be due to the imprecise way the exposure was measured, recall bias or a lack of true effect on the risk of childhood leukemia. Nevertheless, despite the different ways of measuring exposure and different levels of accuracy in their studies, the collected evidence points in the same direction; that hydrocarbon exposure prior to and during pregnancy is associated with an increased risk of leukemia.

4.4 Oral intake

A summary of the evidence of alcohol intake, conclude that there is no agreement. Perèz-Saldivar et al (36) found no increased risk if the mother drank alcohol during pregnancy, while Menegaux et al (35) found an association for ALL and ANLL if the mother reported alcohol intake during pregnancy. Karalexi et al (34) found no increased risk if the mother drank during pregnancy and the risk of ALL, OR= 0.97 (95% CI 0.85–1.11), but there was a large increase in the risk of AML, OR= 2.36 (95% CI 1.60–3.49). Indirect measure, the number of cases and controls and recall bias gives heterogeneity between studies and cannot be compared directly.

Medicines do not seem to increase the risk of leukemia in offspring, except for Cotrimoxazole, but only one study had investigated this antibiotic and only 5 case-mothers had used it. Therefore we cannot conclude that this association is true (39).

4.5 Nuclear powerplant

Paternal employment at a nuclear powerplant at conception was claimed to be a risk factor for childhood leukemia, RR= 2.79 (95% CI 1.04-7.52) (41). The risk-estimate is quite strong, but the confidence interval is, however, wide and therefore imprecise. This means that the true population risk-estimate may be far away from the sample risk-estimate calculated (55). The population risk-estimate is unknown, and we cannot know if the sample is a good representation of the population. The risk-estimate is also close to 1, meaning that the population risk could be close to unity. Both Gardner et al (41) and Roman et al (44) found an increased risk if the parent was monitored for radiation at the time of conception, respectively RR= 3.07 (95 % CI 1.09-8.65) and RR= 9.0 (95% CI 1.0- 107.8). The parents were monitored for radiation because it was feared they were exposed to harmful ionizing radiation. A plausible explanation for the increased risk was that the levels that were considered safe were in fact harmful for the gonadal cells.

Other studies point to some residual confounding factors that could be the plausible explanation for the increased risk if parents work in a nuclear powerplant (56, 57): actual radiation not discovered or population mixing. Population mixing is described as a high turnover of workers or people in a community, and these people bring in new microbes that the immune system is not adapted to. This causes the immune system to overreact and could be a plausible risk factor for childhood leukemia. A combination of the two factors of radiation and population mixing could partly explain the increased risk (56, 57).

4.6 Other risk factors

As for SES, smoking and occupational hazards, there seems to be no association to the risk of leukemia. There is however one exception: the exposure to hydrocarbons and solvents, as mentioned previously (part 4.3).

4.7 Confounders

Confounders is associated with both the exposure and the outcome and must be included in the statistical calculations so that the exposure is the measured variable and not the confounding factors (33). Confounding by several factors is a problem in these kinds of studies. Such factors include the background radiation, health and lifestyle of the child and parents, and diet of the child and parents, to mention a few. SES could be a confounder. The income of the family is usually defined by the occupation the parents has, so it could be occupational exposure and not the SES itself. Poorer SES is also a marker for poorer housing and living conditions, with a higher risk of exposure to pollution (58). Furthermore, poorer housing and a poorer diet could lead to increased sickness, which could impact the immune system, as referred to in the Hit theory (23). The causal pathway is unclear for childhood leukemia, and therefore the factors possibly associated with this cancer are also unknown. There could be confounding factors not yet discovered in the association between parental exposure and childhood leukemia and if RCT's cannot be carried out to completely control the exposures, residual confounding factors in general can potentially never be excluded.

The risk of leukemia can be partly explained by impacts on the immune system according to the Hit theory. The immune system is overactive or under-stimulated so that cell division gets out of control (22).

Several of the included studies tested whether the time of exposure had a correlation to childhood leukemia, and some found that fathers' exposure before pregnancy was more

strongly associated than the mothers' exposure (32, 36, 43, 44, 53). This is possibly due to the short life of sperm and the long life of oocytes; the oocytes are generated already in the womb, but sperm are produced throughout life and are therefore more sensitive to exposure (59). However, this could imply that the maternal exposure is not a risk for the first generation, but the second (22, 60). The timing of exposure is very difficult to estimate and relate to leukemia, and the study design chosen is therefore important for the correct assumption (61). The child needs several "hits" in the genome before cancer is a fact, and it most likely requires a combination of exposure and critical timing of exposure to develop leukemia. It is likely that immune system mechanisms, population mixing, and chemical and radiation risk factors could cause diseases if they are introduced at the right time, at the right amount, in the right order and with enough critical "hits" on the child; especially if the repair mechanisms or other protective measures are not working properly.

4.8 Study design

Case-control studies have a weakness in that the outcome is known and the investigation is retrospective to find the exposure. This leads to recall bias and a lot of the included studies present this issue (33). Cohort studies will in this view be more trustworthy as the outcome is not known in advance, but it is then often difficult to achieve precise exposure estimates. The exposure of investigation may vary through time both in concentration and the amount of exposure, and during a cohort study the estimate can be unprecise (33).

The use of questionnaires is less reliable as direct measures (62). Responders may lie, either subconsciously or with intention. Individuals could lie because it is not socially accepted to drink during pregnancy, and they do not want to be judged. This could lead to misclassifications and can be a problem that leads to a false risk-estimate (62). Many of the

included studies used different questionnaires, each validated, and some even asked the subjects to recall many years back, up to 15 years. This is an imprecise way of measuring exposure and could affect the risk estimates. There is a need for standardized questionnaires that are validated, and different studies must use the same questionnaire to be able to directly compare the association with an outcome. Even though questionnaires are a quick and cheap way of exposure measurement, it is not good enough for estimate exposure precisely. Newer studies, however, has an advantage if they use internet-based questionnaires. The researchers can then reach a greater number of people with a larger geographical scope. Different research teams could also be using the same questionnaire to compare directly the data found in different studies.

To compare further, other kind of data collection should be as standardized as possible, such as the measure of air pollution in relation to the children. Newer data programs with simulation of weather and topography could be useful for air-born pollution, but the most precise way would be direct measurements, which would be expensive (63). It could be that in epidemiological studies one needs to settle with the second best, but in that case, all researchers should do so likewise.

Hospital-based controls could be another challenge with epidemiological studies. The population at risk is much greater than the hospitalized population, and the hospital controls are mostly not healthy and therefore could be more susceptible to catching other diseases that could lead to the disease in question (64). When using hospital-based controls, it should be ascertained that all cases will be directed to that hospital, and that the general population is also referred to the same hospital in all cases. To do this there must not be competing hospitals nearby and other medical practitioners must all refer to that one hospital. This is impractical and, in most cases, impossible.

Another problem in studying childhood leukemia is the rarity of the disease. The incidence is extremely low, compared to adult leukemia. There could be communities where no leukemia cases have been registered for years and making conclusions based on an extremely low number of cases is challenging. Some of the included studies have extremely low numbers of included cases and lack statistical power; Soldin et al (37) have only 41 cases and controls in their study, compared to Karalexi et al (34), who include more than 8.000 cases. The conclusions made in the different studies are diverting in trust despite the low risk of bias found.

Due to the low number of cases in some of the studies, it is likely that reviews find a more precise risk estimate than single studies, if they perform a meta-analysis. However, the reviews do not come to the same conclusions either. An example of this can be found in the studies by Bailey et al (46) and Schuz et al (47) where Bailey finds an increased risk with the use of pesticides and Schuz does not. Bailey et al (46) included 24 references and Schuz et al (47) had 53, only 3 of the studies overlapped. This could be due to selection bias; the reviewers could select the studies that support their hypothesis. The risk of bias can be reduced by declaring the search strategy, but also by clear inclusion and exclusion criteria. At the same time, the inclusion criteria must not be so narrow that the only studies found will support the research hypothesis.

The studies with the lowest degree of bias are those that are based on registers: medical-, birth- and cancer registers. These kinds of registries are extremely important as they exclude the recall bias of parents. On the other hand, there is no exact measure of the exposures and exposure levels can vary within a stratum. Therefore, even studies based entirely on registers can have misclassification mistakes, and the risk calculated could contain errors.

The cancer registers contain data from the 1940's, but the technology of diagnosing and treating different kinds of cancers, is rapidly changing. Cancer is detected and diagnosed by

doctors using the ICD-10 (6) since 1992. The coding system has changed over time and now includes more diagnoses than previously (65). This means that what was considered one type of cancer previously could be classified as several cancers today.

Smoking habits were in the study by Mattioli et al (53) found to be related to the risk of ANLL if the parent was a heavy smoker. On the contrary, Farioli et al (52) could not find any association between smoking and ALL. One of the main issues in the studies on risk factors for leukemia is how the outcome is classified. There are different subtypes of leukemia. Some studies investigate all leukemia (28-31, 36, 39, 41, 42, 44, 48-51), while some divide leukemia into the subtypes AML or ANLL and ALL (10, 27, 32, 34, 35, 37, 38, 40, 43, 45-47, 52, 53). Different sub types could possibly have different risk factors. A global research effort on collaboration could provide more cases and statistical power to investigate subtypes.

Heck et al (32) did separate AML and ALL analyses and found that the two different classifications had different risk factors; PAHs and 1,3-butadiene, arsenic and lead exposure in the third trimester were risk factors for ALL, but not for AML. On the other hand, toluene and chloroform were risk factors for AML, but not ALL. Benzene was found to be a risk factor for both ALL and AML (32). This illuminates the importance of subtype classification of leukemia and should be taking into account in oncoming studies to reduce heterogeneity and increase the accuracy of the evidence.

Another challenge with registry data is that the doctors can report wrongly or inaccurate to the registry according to diagnose and other factors. This also implies for cancer registers. There could be imprecisions and flaws throughout the registers, either from the time of diagnosis, the use of coding or wrong input. All of this could lead to some bias that is impossible to detect. Even though there has been strict double-checking in the registers, different nations have used ICD-10 in various forms and there could be global differences in registration (65).

There are several studies done on the validity of registers, and most of them find high quality data (66-68), but there are some with poorer quality (69) which must be considered.

4.9 Limitations

4.9.1 Selection bias

One considerable limitation with this study is that the main author did the systematic search alone and evaluated and decided which studies to include. Even though the search strategy was developed with guiding from a librarian, the search could have limitations. One limitation could be that the MeSH terms were incomplete, both in the search and in the databases. The MeSH terms included should cover all relevant articles, but part of the problem is that Embase and Medline define the terms differently and that not all articles are tagged by the search term. Another limitation could be that the combined search-phrases excluded some relevant studies; that the MeSH search terms were combined wrongly. The systematic search done for this thesis found some articles that were not included in other systematic reviews, therefore, the search strategy did not reveal all published studies. The risk of selection bias of studies included in this thesis could be considered as high.

On this basis, a manual search in the reference lists of the included studies showed that 62 studies were not found in the systematic search, a major limit in this thesis. Appendix 4 shows extended information on non-accessible articles and the relevant articles found referred to in other studies, but not included in this thesis. 12 of the studies referred to elsewhere were not accessible through the UiT server and could not be assessed. Open access could have reduced this limitation and the amount of selection bias. Most of the single studies was evaluated in the systematic reviews and meta-analyses and does not change the overall conclusion in this thesis. However, 7 of the single studies found referenced in the articles was not accorded for

elsewhere and was not previously mentioned in this systematic review. Therefore, a short summary of their conclusions will follow below to investigate if the inclusion of these studies could have changed the conclusion of this thesis.

Kroll et al (70) included 11.940 cases and found that SES could be associated with increased risk of childhood leukemia, but in affluent communities (RR: 0.97, 95% CI 0.96–0.98). Another study also investigated SES, Borugian et al (71). They included 5240 cases and concluded that there was a slightly lower risk of childhood leukemia if the index child was in the poorest group compared to the rich (RR: 0.87, 95% CI 0.80–0.95). This is not consistent with the other findings in in this review as the main conclusion was that SES is not associated with childhood leukemia.

As for pesticide exposure, three study were found that has not previously been discussed. Monge et al (72) included 334 cases with leukemia and concluded that Maternal exposure to pesticide preconceptionally (OR: 2.4, 95% CI 1.0–5.9) or during pregnancy (OR: 4.5, 95% CI 1.4–14.7) increased risk of childhood leukemia. There was also an association between paternal exposure and the second trimester (OR: 1.5, 95% CI 1.0–2.3). As there is no biological explanation for this and that the CI starts at 1, they concluded that this finding had occurred buy chance (72). Wigle et al (73) did a systematic review and included 31 single-study articles and excluded reviews. They concluded that there was no overall association between childhood leukemia and any paternal occupational pesticide exposure (OR = 1.09; 95% CI, 0.88–1.34). Maternal exposure however, was associated with prenatal occupational pesticide exposure (OR = 2.09; 95% CI, 1.51–2.88). Merhi et al (74) did a meta-analysis on 13 case-control studies and concluded that occupational exposure to pesticides of the parent increased the risk of leukemia in offspring (OR: 2.18 95% CI = 1.43–3.35).

The next study was McKinney et al (75) had 234 cases in their dataset and the onsly association they could find between parental exposure and leukemia in offspring was the use

of narcotic analgesics during pregnancy (RR: 8,3 95 % CI 2,2- 30,7). The last study was Urquhart (76). In their study of 14 cases they cannot find any association to parental occupation at a nuclear powerplant and leukemia in offspring.

With several studies not found by the systematic search the search itself must be considered a limitation. However, most of the studies not found was included in the meta-analysis and the remaining studies would not change the conclusion in this thesis.

4.9.2 Language

The exclusion criteria of studies published in other languages except English is a limitation of this study. This led to an exclusion of 41 articles or about 8 % of the total number of articles. No attempts have been made to translate the remaining articles, so it is not known what kind of information was lost. As English is the international research language and articles that were included derive from all over the world, there are no indications that the remaining articles would change the outcome significantly. Had the foreign language studies been included, the conclusion of this thesis would probably not have been different.

Even though studies were found from all around the world, the findings are not necessarily globally valid. This is due to the extremely different situations around the world, most people do not live in cities, and the burden of pollution is harder in developing countries. It could be that some risk factors are true risk factors for childhood leukemia in some parts of the world where the impact of the risk factor is higher.

4.9.3 Other limitations

Heterogeneity in the included studies is also a limitation to this systematic review study; studies included had very different definitions of exposures, exposure measurement, way of follow-up, way of treating confounders and outcome; Overall leukemia, ALL, ANLL or AML. Some of the studies also had subclassification of leukemia types and the evidence is inconclusive if some exposures lead to a specific cancer type. Some exposure, in some circumstances, could increase the risk of some subgroups of leukemia in parts of the population.

The evaluation of risk of bias in the included studies was based solely on one author's opinion. It could be that others would have evaluated the risk of bias differently and thereby weighted the studies differently and concluded differently. Another limitation with this study is that the etiology of childhood leukemia is not fully known. Therefore, not all risk factors have yet been studied.

5.0 Conclusion

This systematic review included 27 articles published on the topic of risk factors for childhood leukemia. The articles included identified several potential risk factors: air pollution, magnetic fields, nuclear powerplants, parental circumstances, pesticides and tobacco exposure. There is not sufficient evidence to support that smoking, use of alcohol or medications and SES are risk factors for childhood leukemia. Due to a high risk of bias in several of the included studies, not all can be determined as clear risk factors. Pesticides, solvents and petroleum-derivates can be considered as potential risk factors and the timing of exposure is crucial for the development of childhood leukemia. However, we cannot conclude that there is any causality between the risk factors and either overall leukemia, or subclassifications of childhood leukemia.

There is evidence that parental exposure to risk factors up until a year before pregnancy is associated with an increased risk of childhood leukemia, but it is not likely that this is a causal factor to leukemia.

It is not unlikely that some of the investigated risk factors play a role in the development of childhood leukemia. However, more good quality research is needed, and the research must be trustworthy.

In the meantime, pregnant women and couples who are trying to get pregnant, could be warned against the potential hazards of solvents and pesticides. The UK National Health Services guidelines to pregnancy claims that pregnant women should avoid smoking, coffee consumption, vitamin A and fish liver supplements (77). The US center for disease control and prevention encourage women who are planning on becoming pregnant to stop smoking, using “street drugs”, drinking excessive amounts of alcohol and to avoid toxic substances such as: synthetic chemicals, metals, fertilizer, bug spray, and cat or rodent feces (78). And

the Norwegian Labour Inspection Authority warns female employers about ionizing radiation, too warm environment, chemical substances such as pesticides, medications, metals and carcinogenic substances, and difficult working hours (79). It seems that of these, only the Norwegian governmental policy is to protect the child from cancer, while the others are more general protection of the mother and child, but not directed towards cancer in specific.

It is better to use the precautionary principle than not, in case there is a true risk. Due to the lack of complete evidence of risk factors for childhood leukemia we cannot change health care protocols. There is too much we do not know about the etiology of childhood leukemia and the risk factors associated to parental exposure to make significant conclusions.

6.0 Funding

No funding was received for this thesis.

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Appendix 1

Explanation of MeSH, according to PubMed, National Center for Biotechnology Information, U.S. National Library of Medicine

Leukemia: A progressive, malignant disease of the blood-forming organs, characterized by distorted proliferation and development of leukocytes and their precursors in the blood and bone marrow.

Neoplasms: New abnormal growth of tissue. Malignant neoplasms show a greater degree of anaplasia and have the properties of invasion and metastasis, compared to benign neoplasms.

Carcinogens: Substances that increase the risk of neoplasms in humans or animals. Both genotoxic chemicals, which affect DNA directly, and nongenotoxic chemicals, which induce neoplasms by other mechanism, are included.

Carcinogens, environmental: Carcinogenic substances that are found in the environment.

Environmental exposure: The exposure to potentially harmful chemical, physical, or biological agents in the environment or to environmental factors that may include ionizing radiation, pathogenic organisms, or toxic chemicals.

Dietary exposure: The exposure to potentially harmful factors such as trace heavy metals, chemicals, radiation, or toxins due to food contamination including drinking water contamination.

Inhalation exposure: The exposure to potentially harmful chemical, physical, or biological agents by inhaling them.

Maternal exposure: Exposure of the female parent, human or animal, to potentially harmful chemical, physical, or biological agents in the environment or to environmental factors that may include ionizing radiation, pathogenic organisms, or toxic chemicals that may affect offspring. It includes pre-conception maternal exposure.

Occupational exposure: The exposure to potentially harmful chemical, physical, or biological agents that occurs as a result of one's occupation.

Paternal exposure: Exposure of the male parent, human or animal, to potentially harmful chemical, physical, or biological agents in the environment or to environmental factors that may include ionizing radiation, pathogenic organisms, or toxic chemicals that may affect offspring.

Radiation exposure: Phenomenon in which organisms are subjected to radiation.

Lifestyle: Typical way of life or manner of living characteristic of an individual or group.

Protective factors: An aspect of personal behavior or lifestyle, environmental exposure, or inborn or inherited characteristic, which, on the basis of epidemiologic evidence, is known to be associated with prevention or mitigation of a health-related condition considered important to prevent.

Risk assessment: The qualitative or quantitative estimation of the likelihood of adverse effects that may result from exposure to specified health hazards or from the absence of beneficial influences.

Risk factors: An aspect of personal behavior or lifestyle, environmental exposure, inborn or inherited characteristic, which, on the basis of epidemiological evidence, is known to be associated with a health-related condition considered important to prevent.

Child: A person 6 to 12 years of age.

Child, preschool: An individual 2 to 5 years old

Infant: A child between 1 and 23 months of age.

Infant, newborn: An infant during the first 28 days after birth.

Adolescent: A person 13 to 18 years of age.

Adult: A person having attained full growth or maturity. Adults are of 19 through 44 years of age.

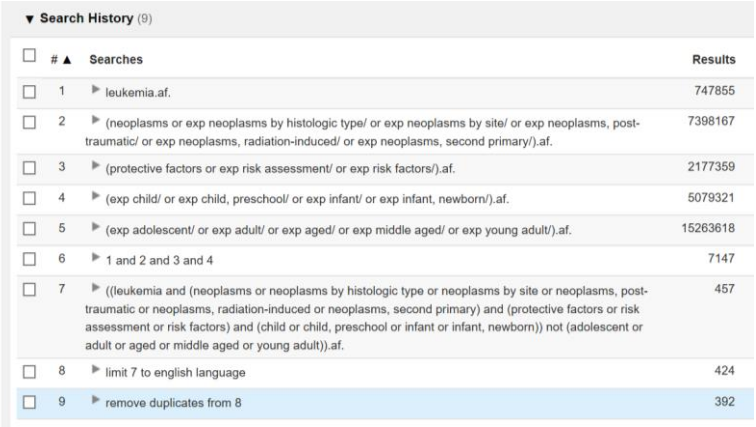
Aged: A person 65 through 79 years of age.

Middle aged: A person age 44 to 64

Young adult: A person between 19 and 24 years of age.

Appendix 2

Search history Embase/Medline

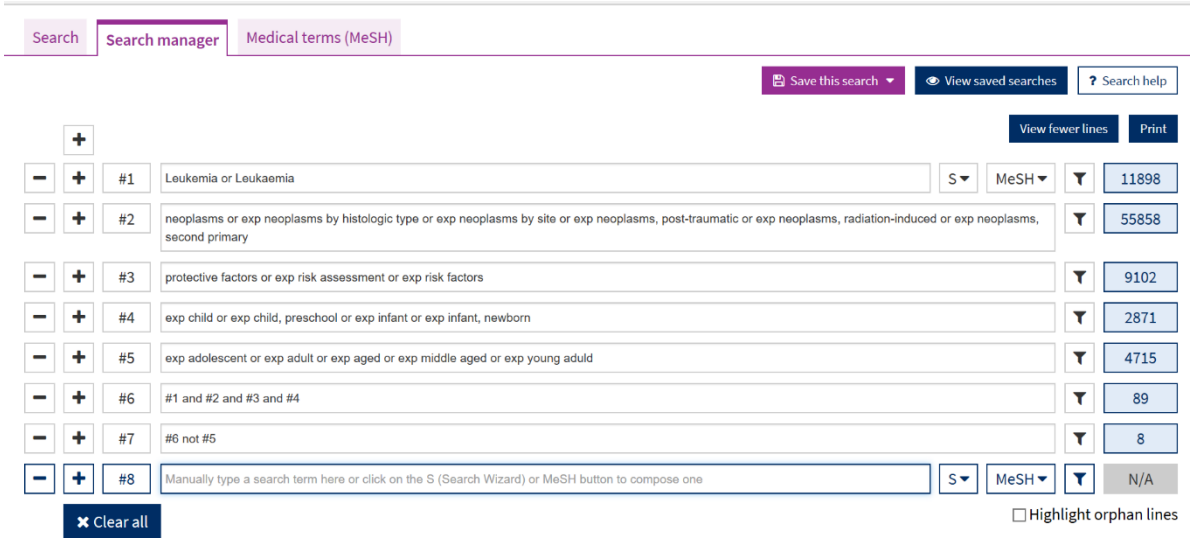


▼ Search History (9)

	# ▲	Searches	Results
☐	1	▶ leukemia.af.	747855
☐	2	▶ (neoplasms or exp neoplasms by histologic type/ or exp neoplasms by site/ or exp neoplasms, post-traumatic/ or exp neoplasms, radiation-induced/ or exp neoplasms, second primary/).af.	7398167
☐	3	▶ (protective factors or exp risk assessment/ or exp risk factors/).af.	2177359
☐	4	▶ (exp child/ or exp child, preschool/ or exp infant/ or exp infant, newborn/).af.	5079321
☐	5	▶ (exp adolescent/ or exp adult/ or exp aged/ or exp middle aged/ or exp young adult/).af.	15263618
☐	6	▶ 1 and 2 and 3 and 4	7147
☐	7	▶ ((leukemia and (neoplasms or neoplasms by histologic type or neoplasms by site or neoplasms, post-traumatic or neoplasms, radiation-induced or neoplasms, second primary) and (protective factors or risk assessment or risk factors) and (child or child, preschool or infant or infant, newborn)) not (adolescent or adult or aged or middle aged or young adult)).af.	457
☐	8	▶ limit 7 to english language	424
☐	9	▶ remove duplicates from 8	392

Appendix 3

Search history Cochrane library, none was relevant.



Appendix 4

List of articles referred to in included studies, but not found for this systematic search:

- Relevant articles from other studies:

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