

Childhood leukaemia

Chemical and Infectious Exposure

All the references (Author year) in this article are listed alphabetically by author in "Childhood Leukaemia Articles References". Where the [year](#) is in blue, and underlined, it is a hyperlink to the pubmed entry.

1. Chemical exposure

Pollution in air, food and water, etc.

Air pollution

The majority of exposure to air pollution arises from vehicle exhausts, especially from the polycyclic aromatic hydrocarbons (PAHs), such as benzo[*a*]pyrene (Reynolds [2003](#)). Modern cars with catalytic converters emit particles mainly in the form of ultra-fine or nano-aerosols. Such very small particles can travel considerable distances from their source, and can go deeply into the bloodstream. As such the exposure of children to air pollution in the UK is essentially ubiquitous and therefore how it may influence the risk of leukaemia is extremely difficult to determine. It has been suggested that 30-80% of childhood leukaemia and other cancers in the UK could be linked to traffic pollution *in utero* and in early infancy.

Other epidemiological evidence supports the suggestion that air pollution may feature in the causes of childhood leukaemia and other cancers (Knox [2005a](#), [2005b](#)). Knox ([2006](#)) found the risk of childhood cancer doubled if the mother (during pregnancy) or the newly born child, lived within 100 metres of bus or railway stations, ferries, railways and A or B roads. A UKCCS study by McKinney ([2003](#)) and Fabia & Thuy ([1974](#)) found that paternal exposure to vehicle related exhaust fumes and/or inhaled hydrocarbons, just before or just after his partner became pregnant, was associated with a small increase in risk. Brosselin ([2009](#)) found that acute childhood leukaemia was significantly associated with living next to a petrol garage. The association that Knox found with birth address suggests the importance of early and *in utero* exposure through inhalation by the mother and transplacental transfer.

Children whose homes were exposed to significant amounts of road traffic emissions (Crosignani [2004](#)) using nitrogen dioxide as an indicator of exposure (Weng [2008](#), [2008](#)) were more likely to develop leukaemia. Reynolds ([2001](#)) found no link between leukaemia and any of the measures of traffic density used, though Bräuner ([2010](#)) found that air pollution from traffic could enhance the effect of radon on the risk of childhood leukaemia. It is unlikely that this confounder would have been considered in many studies and may therefore explain some of the different findings.

Some intriguing experiments on the heritable effects of exposure to ambient air pollution levels have been carried out in Ontario. Yauk & Quinn ([1996](#)) found 2-3 times the rate of heritable genetic mutations in herring gulls nesting in an urban industrialised site compared with a rural site 30 kilometres away. Somers ([2002](#)) exposed mice 1 km downwind of two steel mills in Ontario. 1.5 to 2.0-fold increased heritable mutations via the paternal germline were found compared with control mice placed 30 km away in a rural location. Somers ([2004](#)) further exposed mice 1 km downwind from the above steel mills, alongside control mice who breathed air filtered from particulates down to 0.1 mm. A 2.8-fold increased rate of heritable mutations in "exposed" mice was observed.

Other chemical exposure (including hydrocarbons)

The incidence of AML has been linked to chemical, especially petrochemical exposure, of both parents and children (Buckley [1989](#)). Pyatt & Hays ([2010](#)) in a literature review, concluded that exposure to environmental levels of benzene is not related to an increased risk of childhood leukaemia. They did point out that there had been no work done on exposure of children to high levels of benzene, comparable to occupational levels, as such exposure is likely to be extremely rare. European White Spirit can contain up to 10 parts per million of benzene which is known to cause myeloid leukaemia. White spirit can be detected in the bloodstream for up to 3 days after physical exposure (e.g. by inhalation or by skin contamination) and will pass into the foetus – albeit at very low concentration levels. There is no published direct link between white spirit exposure and childhood leukaemia, though there are with a variety of other serious birth defects. There are published papers showing a statistical association between maternal exposure to solvent chemicals, especially petrol, with about a 50% increase in leukaemia incidence.

Paternal occupational exposure to aniline, benzene and petroleum/coke pitch/tar was associated with an increased risk of ALL (Feingold [1992](#)).

In studies on occupational exposure, including a review of 7 different papers on parental exposure by Savitz and Chen ([1990](#)), maternal/paternal or parental exposure (van Steensel-Moll [1985](#), Lowengart [1987](#), Cocco ([1996](#)), Colt & Blair [1998](#), Shu [1999](#), [2004](#), Schüz [2000](#), Sung [2008](#), McKinney [2008](#)) to solvents, thinners, and paint, during the pre-conception period and during pregnancy, were related to an increased risk of ALL, AML or both. It has been suggested that the chemicals may have been brought into the house on the clothing worn by the parent in question. The authors concluded that the effect of parental occupational exposure to hydrocarbons on offspring may depend on the type of hydrocarbon, the timing of the exposure, and the age of onset of the disease. Freedman ([2001](#)) found that exposure to solvents through hobbies or frequent internal house painting increased the risk of ALL, although how much participation there was by the children was not clear. Scélo ([2009](#)) concluded that the association of ALL risk with paint exposure was strong, as did Bailey ([2010](#)), and AML with solvent exposure. Shu ([2004](#)) also found that paternal exposure to plastic materials before, and maternal exposure during and after pregnancy were related to RAS mutations found in children who develop ALL. Exposures to oil and coal products and other hydrocarbons were also linked to such changes. Buffler (2008) suggested that some genetic translocations were more vulnerable to paint and petroleum products.

Badham & Winn ([2010](#)) suggests a mechanism by which maternal exposure to benzene during pregnancy could produce a disruption in blood cell signalling that could lead to leukaemia in the foetus.

Pesticides

Children are exposed to pesticides from a number of sources, including residential and agricultural applications. Parental exposure is also of concern, due to possible germline effects for fathers and exposure of foetuses due to cross placental transfer from mother to baby during pregnancy. As more is known about genetic predisposition to DNA changes, it is clear that these will become an important confounder in future studies and may well change associations made between cancer and pesticide exposures in previous studies when this knowledge was not available (Infante-Rivard & Weichenthal [2007](#)). Windows of vulnerability have not always been examined in studies especially where the authors believed that parental recall bias could render data unreliable. Rull ([2009](#)) found that moderate lifetime (child's) exposure, but not high exposure, to certain categories of pesticides, were linked to increased leukaemia risk.

Despite these caveats, associations have been reported between childhood leukaemia (ALL or AML) and exposure to pesticides for either parent (Lowengart [1987](#), Buckley [1989](#), Daniels [1997](#), Infante-Rivard [1999](#), Meinert [2000](#)), especially maternal occupational exposure (Van Maele-Fabry [2010](#)).

Various authors (Zahm & Ward [1998](#), Ma [2002](#), Monge [2007](#), Lafiura [2007](#), Rudant [2007](#), Wigle [2009](#), Turner [2010](#)) found that insecticide and pesticide exposures early in life appear to be more significant than later exposures, and the highest risk was observed for exposure during pregnancy, or pre-pregnancy (Hernández-Morales [2009](#)). Additionally, more frequent exposure to insecticides was associated with a higher risk. The study by Emerenciano ([2007](#)) found that infant acute leukaemia specifically was linked with maternal exposure to pesticides.

Exposure to home pesticides and insecticides, used outdoors or indoors (Grossman [1995](#), Menegaux [2006](#)) has been associated with an increased risk. Children exposed to professional pest control services at any time 1 year before birth to 3 years after, were found to have an increased risk of leukaemia (Ma [2002](#)). However, Urayama ([2007](#)) found that certain specific genetic subtypes seemed to be less susceptible to the leukemogenic effects of indoor insecticide exposures. Alderton ([2006](#)) found positive associations between pesticides, professional pest exterminations and any chemical in children with Down syndrome with ALL.

Childhood leukaemia (Meinert [2000](#), Reynolds [2002](#), [2005](#)) especially AML (Carozza [2008](#)) has been associated with the use of agricultural pesticides.

Chemicals found in head-lice treatments can be quite toxic, and small quantities are absorbed through the skin. Menegaux ([2006](#)) found an association between childhood leukaemia and pyrethroid-based shampoos. It may be worth looking for natural remedies that do not contain organophosphates.

Lu ([2008](#)) looked at the exposure of young children to organophosphorus pesticides in their diet and discovered by switching them to an organic diet for a brief period of time and measuring urinary metabolites, that a standard (non-organic) diet was the chief contributor to pesticide exposure. It seems that eating a largely organic diet, when possible, may help to eliminate children's exposure to these potential carcinogens.

Jurewicz & Hanke concluded after a literature review ([2006](#)) that *"In the light of existing, although still limited evidence of adverse effects of pesticide exposure, it is necessary to reduce exposure to pesticides. The literature review suggests a great need to increase awareness among people occupationally or environmentally exposed to pesticides about their potential negative influence on health of their children."*

Carpet dust was collected and residues of PCBs were obtained from it. There was an increased risk of childhood leukaemia in homes where there were high levels of PCBs, especially among non-Hispanic white children (Ward [2009](#)).

Smoking

Epidemiological evidence to support a link between parental smoking and childhood leukaemia is inconsistent, possibly because of genetic susceptibilities.

Three studies (John [1991](#), Cocco [1996](#), Hernández-Morales [2009](#)) found an increased risk for ALL. Rudant ([2008](#)) found that paternal, but not maternal, smoking was associated with an increased risk of ALL and AML. The risk increased with the number of cigarettes smoked.

Maternal smoking

Maternal smoking, especially 10 or more cigarettes per day was associated with an increased risk of AML (Cnattingius [1995](#), Mucci [2004](#)) but not ALL (Mucci [2004](#)), and De la Chica ([2005](#)) found chromosomal abnormalities in foetuses of smoking mothers. No association has been found between maternal smoking and ALL. Clavel ([2005](#)) suggested that maternal smoking may be a risk factor for leukaemia in children who carry CYP1A1 or GSTM1 genotypes.

Paternal smoking

There does seem to be some evidence for paternal preconception smoking and subsequent childhood leukaemia (Sorahan [1995](#), [1997](#), Ji [1997](#)).

Prescription drugs (pre-natal exposure)

One study has reported an association between childhood ALL and maternal use of antihistamines and allergy remedies (Wen [2002](#)). Robison ([1989](#)) reported a link between maternal use of anti-emetic medication and AML and Cocco ([1996](#)) found a link with ALL.

Other drugs (pre-natal exposure)

Parental use of amphetamines or diet pills and mind-altering drugs before and during the pregnancy was related to an increased risk of childhood ALL (Wen [2002](#), Shu [2004](#)), particularly among children where both parents reported using these drugs. If the mother used both mind-altering drugs, and antihistamines or allergy remedies the risk for infant ALL was strongly increased.

Parental alcohol consumption

Metabolites of alcohol are likely carcinogens, which is why this has been the subject of several papers looking at potential links to childhood leukaemia of parental alcohol consumption. A review of 33 studies by Infante-Rivard & El-Zein ([2007](#)) found mixed results, with maternal alcohol consumption being linked most frequently, though there was some evidence of modest consumption having a protective effect. A small number reported a link to paternal alcohol consumption (Cocco [1996](#)). The authors suggested that genetic susceptibility and cancer subtypes may be responsible for the different findings. Individual studies have found some evidence for a possible link between maternal alcohol consumption and AML (van Duijn [1994](#), Latino-Martel [2010](#)) especially in very young children (Severson [1993](#), Shu [1996](#)) though the evidence for ALL risk is uncertain. Some studies have found such a risk (Menegaux [2005](#), [2007](#), Macarthur [2008](#)) whilst others did not (Little 1999). Paternal alcohol consumption before conception did not appear to increase risk (Shu [1996](#), Macarthur [2008](#)).

Recreational drugs (pre-natal and pre-conceptual exposure)

Maternal use of marijuana has been reported to increase the risk of childhood ALL (Wen [2002](#)), and in one study was associated with a 10-fold increased risk of AML when used just before or during pregnancy (Robison [1989](#)). However, Trivers ([2006](#)) found an inverse relationship between maternal marijuana use just before and during pregnancy and AML risk. There is evidence that the risk may be higher when both parents use the drug.

Fluoridated water

An American study found an increase in osteosarcoma in young boys (not girls) drinking water which contained fluoride (Bassin [2006](#)). Ramesh ([2001](#)) had found a correlation between high

fluoride content in the bone and osteosarcoma. Half of all fluoride ingested is stored in the body, accumulating in calcifying tissue such as teeth and bones (more than 90%). Although no research has looked at leukaemia, the fact that the risk increase is age-specific and that fluoride changes bone chemistry may be important.

Watershed

An increased risk of ALL was found where mothers had lived on watersheds in Texas. It was hypothesised that the maternal consumption of waterborne toxins had affected the foetus (Thompson [2010](#)).

Paternal military exposure

A study by Wen ([2000](#)) showed a small but significant increase in the risk for AML (not ALL) among the children of personnel who had served in Vietnam or Cambodia, especially with a diagnosis under the age of 2. It may be that it has to do with chemical exposure. A study on Gulf War veterans might be useful to see if the same effect was found.

2. Infectious exposure

Our ability to fight infections is determined, in part, by our genes. There is a group of genes that code for molecules on our lymphocytes (known as HLA molecules) and determine how they respond to foreign invaders. Different people have different HLA molecules and will therefore respond in varying ways to infections. Dorak ([1999](#)) found that one particular type of HLA molecule was increased in his childhood leukaemic patients, especially males, and another was decreased, suggesting that particular HLA molecular changes are genetic risk factors for childhood ALL. GM Taylor ([2008](#)) and Yari ([2008](#)) found the same results. Only one of 21 possible HLA-DPB1 supergenotypes was significantly more frequent in B cell precursor ALL (BCP ALL) (GM Taylor [2008](#)). The authors believed that this may help identify particular infection(s) that may be involved in leukaemia initiation.

Speculations concerning a link between infections and childhood leukaemia were first published as long ago as the 1920s (Poynton 1922), based on the observations that the age distribution of the disease was similar to that of common childhood infectious diseases and that many patients had a record of infections around the time of diagnosis.

There are now three main hypotheses concerning the possible role played by infection in childhood leukaemia:

1. infectious exposure *in utero* or around the time of birth increases the risk of childhood leukaemia
2. delayed exposure beyond the first year of life to common infections increases the risk of childhood leukaemia
3. unusual population mixing introduces new infections to previously unexposed populations and childhood leukaemia may be an unusual result of such an infection

Infectious exposure *in utero* or around the time of birth

There is some evidence to suggest that some maternal infections may increase the risk of childhood leukaemia (Fine [1985](#), Canfield [2004](#)). A model proposed by M Smith ([1997](#)) suggests that an infectious agent causes a primary infection in the mother which is subsequently passed on to the foetus, and as a result of this infection the child is more likely to develop leukaemia in the next few years, perhaps because of stress and genetic instability caused by the infection. Chang ([2009](#)) found a positive association between childhood leukaemia and elevated levels of maternal

serum total IgE, especially among Hispanics. In addition, a positive association was observed between childhood leukaemia and maternal respiratory or food IgE status, suggesting that maternal immune function may play a crucial role in the aetiology of childhood leukaemia.

McNally and Eden (2004) linked maternal infections during pregnancy with an increased risk of childhood leukaemia, especially ALL. Adenovirus DNA was detected in 13 of 49 children who developed ALL and only in 3 of 47 who did not (Gustafsson 2007), though this was not found to be the case by Vasconcelos (2008). It is interesting to note that 3 control children showed the change without developing leukaemia and 36 children developed leukaemia without the change, again demonstrating the complexity of causation in childhood cancer.

There are several good studies showing an increased risk with infections (Roman 1997) and some which looked at specific infections:

- a history of sexually transmitted disease (Kwan 2007)
- maternal lower genital tract infection, especially for infant leukaemia and those diagnosed after the age of four (Naumburg 2002)
- Epstein-Barr virus (EBV) reactivation (Lehtinen 2003, 2005, Tedeschi 2007, Sehgal 2010)
- Helicobacter Pylori (Lehtinen 2005.)
- possibly neonatal adenovirus-C infection (Gustafsson 2007)

but there are also good studies which show no such association, with respect to influenza (Nyari 2003), EBV (Bogdanovic 2004), and parvovirus B19 (Isa 2004).

Many of the studies are generally reliant on small numbers of cases, and it may not be one particular infection but infections in general which impact on risk, so it is difficult to draw firm conclusions.

The adrenal hypothesis discussed by Azevedo-Silva (2010) proposes that the risk of childhood B-cell precursor ALL is reduced when early childhood infections induce qualitative and quantitative changes in the hypothalamus-pituitary-adrenal axis.

Delayed exposure beyond the first year of life, or a rare response to common infections

This theory is, in part, based on the hygiene hypothesis first proposed by Strachan (1989) which suggests that infections and unhygienic contact with older siblings or through other exposures may confer protection against the development of allergic illnesses (Chang 2009). This protection may come from either overt or unapparent infections with viruses and bacteria, non-invasive microbial exposures in the environment, or some combination of the two (von Mutius 2007).

Greaves (1997) has suggested that one factor in susceptibility is that in early childhood children are less exposed to common infections, including influenza, (Kaatsch 1996, Dockerty 1999, Ma 2002, Perrillat 2002) than they used to be in the past. In fact many chronic infections have been eliminated entirely. This may result in a less developed, or dysregulated (Roman 2006) immune system and an increased risk of leukaemia later in childhood, i.e. delayed infection (Chan 2002).

It has been suggested that clinically diagnosed leukaemia occurs as a result of a rare response to common infections (Greaves & Alexander 1993, Petridou 2001, 11th COMARE report 2006). This is both plausible and logical in view of the biology of how leukaemia appears, but it of course does not address the underlying environmental factors linked to the disease.

That the final stage of leukaemia is triggered while the immune system is otherwise occupied (fighting a common infection) is plausible. There is also the possibility of 'inverse causality' that

pre-leukaemic children are themselves prone to contract common infections. McKinney (1987, 1999), Hartley (1988) Simpson (2007) and Roman (2007) found a link with leukaemia and increasing numbers of illnesses before the age of 1 year, although Cardwell (2008) found no such link.

As ALL is more common in developed, more affluent societies, Greaves suggests that not only hygiene (MA Smith 1998), but also other lifestyle influences such as childrearing, social and breastfeeding practices may be involved in immune system inadequacy.

Vaccinations

The situation with respect to vaccinations seems more mixed, with some work finding a positive association with childhood leukaemia (Buckley 1994) whilst others found the opposite, that some vaccines seemed to have a protective effect (Hartley 1988, McKinney 1987, Nishi & Miyake 1989, Kaatsch 1996, Schüz 1999b, Auvinen 2000, Groves 1999, 2001, 2002, Ma 2005b, 2005) and yet others found it seemed to make little, if any, difference (Dockerty 1999, Petridou 1997, von Kries 2000, Mallo-Mesnard 2007). Whether there is a link or not may depend on the particular type of vaccine.

Unusual population mixing leading to a rare response to infection

The most recent Committee on Medical Aspects of Radiation in the Environment (COMARE) 11th report concluded “*there is some good evidence for a weak case aggregation of acute lymphoblastic leukaemia. The term weak is used because the average numbers of cases in each ward is low, but the results reinforce the concepts that case occurrence is not entirely random.*” What is not clear is what is causing this clustering.

Kinlen (1988, 1990, 1993, 1993, 1994, 1995, 1997, 2001) proposed that childhood leukaemia was a rare response to infection, possibly occurring *in utero* or postnatally, arising from an influx of population into a small, otherwise relatively isolated community. Whereas this hypothesis may have some validity in some of the examples examined, they certainly cannot explain most of the incidences, which don't conform to this picture (MacMahon 1992). ‘Extreme’ population mixing was looked at with regard to new towns, commuter belts, major construction sites and country areas used for wartime evacuation or for military camps. There seem to be other possible factors which may be common to these places, such as chemicals, building materials, etc. that might be as important as the infection hypothesis.

Clearly, studies designed to assess the infection hypothesis need to take the critical time windows into account – the first year of life and the period 3 to 12 months prior to diagnosis. The situation remains unclear whilst there is an inadequate definition of what is meant by ‘population mixing’ which means that many of the studies are looking at different mixtures in different settings. Feltbower (2005) found that population mixing was significantly associated with ALL in Yorkshire, and commented that the association found for large regions was weaker for small areas. Alexander (1997) found clustering for cALL in the childhood peak (age 2-7) in Hong Kong, but not for other age groups, or for leukaemia subsets that did not have peak times of diagnosis. Schmeidel (2010) found no evidence of clustering in Germany.

On balance, it appears that population mixing in areas that were originally very isolated results in an increasing rate of childhood leukaemia, especially during the childhood 2-5 year old peak (Bellec 2008, Stiller 2008), when children are least likely to possess sophisticated immune systems. By comparison, population mixing in urban areas where there is a consistently high level of mixing results in a decreased rate of leukaemia, though Alexander (1998, 1999) and Ross (1999) found an increased risk of ALL, and some evidence of clustering, in areas of higher population

density. When parental social contact at work was investigated, as a surrogate for a child's risk of infection, Chang (2007) found that there was an increased risk for leukaemia in children where the parents' job was of sufficient duration, though Fear (1999) did not. There was also a link with living in a rural area. Research into population density and the risk of childhood leukaemia seems to be equally inconclusive, and may depend on the type of leukaemia and the age of diagnosis as much as the actual level of population.

Some of the studies that have found associations between infection (or its proxies) and childhood leukaemia, have found them most strongly for the cALL sub-type. If infection is involved in the aetiology of childhood leukaemia then it may be specific to cALL.

Other factors have been associated with the development of childhood leukaemia, or the reduction in risk of developing childhood leukaemia. These are covered in section 5.