

# Childhood Cancer

## 5. Possible causative factors – chemicals and infections

Exposure to chemicals and infections have both been linked to the occurrence of childhood cancer. Here we look at some of the data that points to this link.

### Chemical exposure

#### Residential exposure

#### Air pollution, including traffic-related pollution

The majority of exposure to air pollution arises from vehicle exhausts, especially from the polycyclic aromatic hydrocarbons (PAHs), such as benzo[ $\alpha$ ]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. 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' team in California has reported a number of studies with different effects. In [2001](#) and [2004](#) no increased risk in leukaemia was found, but in [2002](#) they found that in areas of high traffic density the incidence of childhood cancers, including leukaemias and gliomas was elevated, but they concluded that this finding was not conclusive and that further studies should be more precise about timing and measures of exposure. The team also pointed out (Gunier [2003](#)) that high traffic areas were lived in more by non-whites and those with low incomes. They suggested that differences by income and race or ethnicity should be clearly included in any study designs as this may skew results.

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 synergistic effect would have been considered in many studies and may therefore explain some of the different findings.

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. 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.

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 µm. A 2.8-fold increased rate of heritable mutations in “exposed” mice was observed.

## **Water pollution**

### *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).

## **Parental lifestyle exposure to chemicals in the home**

It is assumed that any link to child cancer from smoking, alcohol consumption and ingestion of drugs, both prescribed and recreational, is likely to be due to toxic chemical ingestion, causing the relevant changes. There may also be other lifestyle issues that are not considered, which may explain some of the different conclusions come to in the studies.

### *Smoking*

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

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 fetuses of smoking mothers. Clavel (2005) suggested that

maternal smoking may be a risk factor for leukaemia in children who carry CYP1A1 or GSTM1 genotypes. No association has been found between maternal smoking and ALL. Maternal smoking during pregnancy has also been associated with CNS tumours (Michaelis [2000](#)), though Filippini ([2002](#)) found no such a link.

Ortega-García ([2010](#)) found that tobacco smoke exposure not only during the mother's pregnancy, but also during the grandmother's pregnancies increased the risk of cancer in the descendants, implying some germline genetic effect.

There does seem to be some evidence for paternal preconception smoking and subsequent childhood leukaemia (Sorahan [1995](#), [1997](#), Ji [1997](#)), though in a review by Chang ([2009](#)), less than half the studies looking at paternal smoking found a positive association. Paternal smoking has also been associated with brain tumours (Plichart [2008](#)).

Wilhelm-Benartzi ([2011](#)) suggested that bladder cancer could be linked to secondhand smoke exposure in childhood.

#### *Parental alcohol consumption*

Metabolites of alcohol are likely carcinogens, which is why parental alcohol consumption has been the subject of several papers looking at potential links to childhood leukaemia and brain tumours. Heck's review of 3 papers ([2009](#)) found an increased risk of neuroblastoma with alcohol consumption during pregnancy though Yang ([2000](#)) found no consistent link. 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](#)).

#### *Prescription and recreational drugs*

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

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.

Maternal use of marijuana has been reported to increase the risk of childhood ALL (Wen [2002](#)). 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.

*Cosmetic products*

Efird (2005) found links between beauty products and hair dyes and sprays and childhood brain tumours. It is assumed here, that it is to do with chemicals getting through the skin into the bloodstream, and thence passed on to the child rather than to other lifestyle factors.

*Cleaning products*

Cleaning supplies used in 13 California school districts were found to pollute the air with agents linked to asthma and cancer. The incidence of childhood cancer rose by 28% from 1974 to 1998, with especially significant increases in leukaemia, non-Hodgkin's lymphoma and several brain and nervous system cancers. For more information, see <http://www.ewg.org/schoolcleaningsupplies/pressrelease>

**Other parental exposure to chemicals, including occupational exposure**

In studies on occupational exposure, maternal/paternal or parental exposure (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 (2011), and AML with solvent exposure.

Some studies (Eguchi-Ishimae 2005, Money Penny 2006) have found when pregnant women are exposed to particular chemicals, especially solvents, these can cross the placental barrier and produce the MLL fusion genes that are responsible for infant ALL. Eguchi (2006) also suggested that such fusion genes may be more vulnerable to further DNA damage and mutation in the presence of chronic exposure to the agent(s) that induced the MLL fusion itself. Other MLL translocations have been associated with the development of infant leukaemia (MT Smith 2002).

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) suggest 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.

Paternal occupational exposure to aniline, benzene and petroleum/coke pitch/tar was associated with an increased risk of ALL (Feingold 1992). A UKCCS study by McKinney (2003) 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.

*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.

## **Pesticide exposure**

Zahm and Ward's extensive review of 26 studies on pesticide exposures and risk of brain tumour (1998) concluded that there were risks and they depended upon the time of exposure, whether this was preconceptual, pre- or postnatal. They suggested that children were more susceptible than adults and the risk factors were greater. Infante-Rivard and Weichenthal (2007) brought the subject up to date with the 21 studies published since the Zahm & Ward review. 15 of these studies showed significantly increased risk between pesticide exposure to parents or child and childhood cancer.

Searles Nielsen (2005) suggested that there is an inverse association between brain tumour occurrence and PON1 levels, probably because of PON1's ability to detoxify organophosphorous insecticides common in children's environments. This suggestion arose from a study where childhood brain tumours were associated with chemical treatment of the home for pests during pregnancy or the child's childhood, and PON1 polymorphisms were measured.

Children are exposed to pesticides from a number of sources, including residential and agricultural applications. Childhood leukaemia (Meinert 2000, Reynolds 2002, 2005) especially AML (Carozza 2008) has been associated with the use of agricultural pesticides. Parental exposure is also of concern, due to possible germline effects for fathers and exposure of pregnant women due to cross placental transfer from mother to baby. 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. Vinson (2011) reported increased risk of childhood lymphoma and leukaemia as a result of maternal exposure to pesticides during pregnancy, and brain tumours with paternal exposure before or after birth.

Despite these caveats, associations have been reported between childhood leukaemia (ALL or AML) and exposure to pesticides for either parent (Daniels 1997, Infante-Rivard 1999, Meinert 2000), especially maternal occupational exposure (Van Maele-Fabry (2010). Rull (2009) found that moderate lifetime (child's) exposure, but not high exposure, to certain categories of pesticides, were linked to increased leukaemia risk.

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, van Maele-Fabry 2010, 2011) has been associated with an increased risk of childhood cancer. Soldin (2009) also found higher levels of urinary pesticide metabolites, especially organophosphates, in children with ALL.

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.

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.

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).

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."*

## Exposure to infections

Speculations concerning a link between infections and childhood leukaemia were 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 cancer:

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

There is some evidence to suggest that some maternal infections may increase the risk of childhood leukaemia (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.

Fear (2001) found that children whose mothers had documented evidence of a clinically diagnosed viral infection during pregnancy had an approximately 11-fold increase in risk of

developing a malignant neoplasm of the brain or other part of the nervous system. McNally and Eden (2004) linked maternal infections during pregnancy with an increased risk of childhood leukaemia, especially ALL. It may not just be the infection, but also the treatment which has a role, as Shaw (2006) concluded that childhood brain tumours may be associated with exposure to infective agents, particularly the use of antibiotics during pregnancy.

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) and Ozdilli (2010) 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. 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.

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.

Infections as a cause of childhood cancer have been well-researched. Sometimes day-care, or social contact has been used as a surrogate for infections, as it is assumed that children in day care, with older siblings, or having a lot of social contact are likely to be exposed to more bacterial and viral infections than children without these lifestyle experiences.

Harding (2009) looked at the relationship between infectious exposure in the first year of life and the likelihood of developing a CNS tumour. The studies they looked at had findings that were inconsistent with respect to tumour subtype, and Harding's team concluded that an early exposure to infections is not strongly implicated in the aetiology of CNS tumours, but the effect for social contact outside the home warrants further investigation.

Shaw (2006) concluded that childhood brain tumours may be associated with exposure to infective agents, particularly the use of antibiotics, removal of tonsils, adenoids or appendix, being at least second in the family and having siblings.

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)
- Bunin (2004) in a review of non-genetic causes of childhood brain tumours concluded that polyomaviruses may have an aetiologic role

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](#)), or which show a reduction in risk as a result of neonatal infection, particularly in 0-4 year olds (McKinney [1999](#)).

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 theory behind delayed exposure after the first year of life, or a rare response to common infections is, in part, based on the hygiene hypothesis 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 also been suggested that clinically diagnosed leukaemia occurs as a result of a rare response to common infections (Greaves & Alexander [1993](#), Petridou [2001](#), 11<sup>th</sup> 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 ([1999](#)), 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. Flores-Lujano ([2009](#)) found that children with Down syndrome who required hospitalisation in the first year of life had infections related to a risk of developing acute leukaemia.

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 (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](#), Mallol-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) 11<sup>th</sup> 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 ([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, including near nuclear reprocessing sites ([2010](#)). 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 (Francis [2011](#)), 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 6.