

Cancer in Children and Young People

The Cancer in Children and Young People set of articles is separated into 12 sections, each of which can be individually downloaded. It is a 'work in progress' incorporating new information whenever time permits.

Section 5

Chemicals and infections

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Childhood Cancer

5. Possible causative factors – chemicals, metals and infections

Exposure to chemicals and infections has 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[α]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.

ALL, germ cell tumours (particularly teratomas), and retinoblastoma (particularly bilateral retinoblastoma in children younger than 6) have been associated with traffic density during pregnancy or the child's residence at birth (Heck [2013](#)).

Other epidemiological evidence supports the suggestion that air pollution may feature in the causes of childhood leukaemia and other cancers (Knox [2005a](#), [2005b](#)), including astrocytoma and ALL if the exposure was in the first trimester (Lavigne [2017](#)). 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. In a study by Weng ([2009](#)) there was a significant exposure-response relationship between petrol station density and the risk of leukaemia development in children 14 years of age or younger. 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 (Crosignani [2004](#)) using nitrogen dioxide as an indicator of exposure (Weng [2008](#), [2008](#)), from a busy road within 500 metres (Amigou [2011](#)), were more likely to develop acute leukaemia or CNS tumours (Danysh [2015](#)).

The risk of childhood ALL was increased in houses where vacuumed dust contained polycyclic aromatic hydrocarbons (PAHs), which can be found in the homes of smokers and from frying or grilling meat (Deziel [2014](#)) or amounts of agricultural or residential herbicides (Metayer [2013](#)).

The odds of acute lymphoblastic leukaemia increased by 9%, 23%, and 8% for each 25-ppb increase in average nitric oxide, nitrogen dioxide, and nitrogen oxide levels, respectively, over the entire pregnancy. Second- and third-trimester exposures increased the odds of bilateral retinoblastoma. These results lend support to a link between prenatal exposure to traffic exhaust and the risk of acute lymphoblastic leukaemia and bilateral retinoblastoma (Ghosh [2013](#)).

Higher concentrations of indoor pollutants, including nitrogen dioxide and many volatile organic compounds (VOCs) were associated with the increased risk of childhood acute leukaemia. The use of synthetic materials for wall decoration and furniture in bedrooms was related to the risk of childhood AL. Renovating the house in the last 5 years, changing furniture in the last 5 years, closing the doors and windows overnight in the winter and/or summer, paternal smoking history and outdoor pollutants affected VOC concentrations (Gao [2014](#)).

The main artificial sources of outdoor air pollution are transportation, stationary power generation, industrial and agricultural emissions, and residential heating and cooking, notes the International Agency for Research on Cancer (IARC) (Irish Examiner September 2016). In 2014, the Childhood Leukaemia International Consortium (CLIC) found that when either parent is exposed to pesticides during pregnancy or conception, there was an increased risk of leukaemia for their child. IARC classes electromagnetic fields (EMF), of the type associated with our electricity supply, as 'possibly carcinogenic' to humans, based on studies that reported an approximate doubling of leukaemia risk for children exposed at average levels above 0.3 - 0.4 microtesla.

In a study by Ortega-García ([2017](#)) the incidence of paediatric cancer showed significant high incidence around some industrial pollution facilities. We observe a major incidence of non Hodgkin lymphomas (NHL) considering all facilities, and high incidence of Sympathetic Nervous System Tumour (SNST) around Energy and Electric and organic and inorganic chemical industries. Three significant clusters were identified: the first of SNST was around energy-generating chemical industries, another of NHL was around residue-valorisation plants and finally one cluster of Hodgkin lymphoma around building materials.

Professor Denis Henshaw, from Children with Cancer UK, believes around 30% of childhood cancer in urban areas is linked with air pollution. Radiation is known to increase cancer risk in children and it is suggested that 5% of childhood leukaemia is linked to radon, a radioactive gas found naturally in the ground.

Reynolds' team in California has reported a number of studies with different effects. In [2001](#), [2004](#) and [2008](#) (Von Behren), 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. Raaschou-Nielsen & Reynolds ([2006](#)) found no increased risk for childhood cancer associated with exposure to traffic-related air pollution. They suggested that non-differential misclassification of exposure might have masked true, weak associations.

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. However, Whitworth ([2008](#)) Houot ([2015](#)) and Filippini ([2015](#)) found an increased incidence of leukaemia, especially AML with residential heavy-traffic road density, due to benzene exposure. Symanski ([2016](#)) observed positive associations between 1,3-butadiene (emitted from motor vehicles), benzene and

polycyclic organic matter (POM) in the home and the early childhood risk of acute lymphocytic leukaemia.

In a study by Heck (2014) the risk of ALL was elevated with 3rd trimester exposure to polycyclic aromatic hydrocarbons, arsenic, benzene, and three other toxins related to fuel combustion. Risk of AML was increased with 3rd trimester exposure to chloroform, benzene, and two other traffic-related toxins. During the child's first year, exposure to butadiene, ortho-xylene, and toluene increased risk for AML and exposure to selenium increased risk for ALL.

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.

Intriguing experiments on the heritable effects of exposure to ambient air pollution levels have been carried out in Ontario. 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). Half of all fluoride ingested is stored in the body, accumulating in calcifying tissue such as teeth and bones (more than 90%). Ramesh (2001) found a correlation between high fluoride content in the bone and osteosarcoma.

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

Two studies (Hernández-Morales 2009, Kumar 2015) 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 (Mucci [2004](#)) but not ALL (Mucci [2004](#)), and De la Chica ([2005](#)) found chromosomal abnormalities in foetuses of smoking mothers. Clavel ([2005](#)) suggested that maternal smoking may be a risk factor for leukaemia in children who carry CYP1A1 or GSTM1 genotypes. Maternal exposure to secondhand smoke during pregnancy and children's exposure to secondhand smoke has been associated with ALL (Farioli [2014](#)).

Maternal smoking during pregnancy has also been associated with CNS tumours (Michaelis [2000](#)), though Filippini ([2002](#)) found no such 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. Metayer ([2013](#)) found that exposure to tobacco smoking was associated with increased risks of childhood ALL and AML; and risks varied by timing of exposure (before and/or after birth) and cytogenetic subtype. The authors recommended that parents should limit exposures to tobacco smoke before and after the child's birth.

There have been suggestions that there is a link between paternal preconception smoking and subsequent childhood leukaemia, 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. 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 (Latino-Martel [2010](#)) 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 (Macarthur [2008](#)).

A moderate intake of spirits by fathers was associated with an increased risk of childhood brain tumours (Milne [2013](#)). It seemed that the intake of wine was inversely associated with cancer risk, except at a high level of intake. High levels of beer also seemed to increase risk.

Prescription and recreational drugs

One study has reported an association between childhood ALL and maternal use of antihistamines and allergy remedies (Wen [2002](#)).

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. <http://www.ewg.org/schoolcleaningsupplies/pressrelease> for more information.

Other parental exposure to chemicals, including occupational exposure

In studies on occupational exposure, maternal/paternal or parental exposure (Colt & Blair [1998](#), Shu [1999](#), [2004](#), Schüz [2000](#), Sung [2008](#), McKinney [2008](#), Bailey [2014](#)) to solvents, thinners, and paint (also petroleum Zhou [2014](#)), during the pre-conception period and during pregnancy, were related to an increased risk of ALL, AML or brain tumours (particularly gliomas) (Greenop [2014](#)). 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.

In a study by McKenzie ([2017](#)) there were more cases of ALL in children and young people of 0-24 years old who lived in an area with the highest number of gas and oil wells within 16 kilometres. Oil and gas development has potential to expose a large population to known haematologic carcinogens.

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.

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. Hernández & Menéndez (2016) reviewed the available experimental and epidemiological evidence linking pesticide exposure to infant and childhood leukaemia and provide a mechanistic basis to support the association, focusing on early initiating molecular events. Bailey (2014), in a meta-analysis of 13 case-control studies found a significantly increased risk of AML in the offspring with maternal exposure during pregnancy, consistent with previous reports. They also found a slight increase in risk of ALL with paternal exposure around conception which appeared to be more evident in children diagnosed at the age of 5 years or more and those with T cell ALL which raises interesting questions on possible mechanisms. Ferreira (2013) found increased risks of ALL and AML for children exposed in utero to pesticides.

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, as have germ-cell tumours, non-Hodgkin lymphoma and Burkitt lymphoma (Carozza 2009). The results of a study by Gómez-Barroso (2016) suggest that living in the proximity of cultivated land could be a risk factor for several types of cancer in children. Booth (2015) found statistically significant exposure-response relationships for dry beans and total leukaemias (RR per 1% increase in crop density = 1.09) and acute lymphoid leukaemias (ALL) (RR = 1.10); oats and acute myeloid leukaemias (AML) (RR = 2.03); and sugar beets and total leukaemias (RR = 1.11) and ALL (RR = 1.11). State-level analyses revealed some additional positive associations for total leukaemia and CNS tumours and differences among states for several crop density-cancer associations.

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 (Infante-Rivard [1999](#), Meinert [2000](#), Gunier [2017](#)), 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](#), Gunier [2017](#)) 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. Cooney ([2007](#)) found exposure to household insecticides (but not other pesticides) in the month before pregnancy through to the diagnosis date was associated with an increased risk of Wilms tumour. 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 (Menegaux [2006](#), van Maele-Fabry [2010](#), [2011](#)) has been associated with an increased risk of childhood cancer. Chen ([2015](#)) found that childhood exposure to indoor but not outdoor residential insecticides was associated with a significant increase in risk of childhood leukaemia and childhood lymphomas. A significant increase in risk of leukaemia was also associated with herbicide exposure. Also observed was a positive but not statistically significant association between childhood home pesticide or herbicide exposure and childhood brain tumours.

Soldin ([2009](#)) and Y Zhang ([2015](#)) 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 and 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. Ding ([2012](#)) also found an elevated risk of childhood ALL with the use of pyrethroid pesticides, including household insecticides. Pyrethroid pesticides are toxic to beneficial insects such as bees, dragonflies and fish and other aquatic organisms.

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.”*

Diet

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.

Construction in the home between birth and diagnosis was associated with a significant increase in ALL risk and a nonsignificant increase in AML risk. A positive relationship between ALL risk and painting was evident in Hispanic children (Whitehead 2017).

Heavy metal exposure

The results of health risk assessment in a review by Tan (2016) show that carcinogenic risk exists among children. Hence, this proves that future studies need to focus on children's carcinogenic risk in indoor dust studies in order to find out the sources of heavy metals in indoor dust.

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.

McNally (2014) found possible common aetiological factors between different diagnostic groups. The authors suggested a common aetiology for the following pairs of diagnostic groups: Hodgkin lymphoma (HL) and intraspinal embryonal tumours (IIET); older cases of lymphoid leukaemia (LL) and HL; younger cases of LL and soft tissue sarcoma (STS). They felt that the possibility of common infectious mechanisms should be explored.

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, Wiemels 2015). 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. In 2000 McNally had suggested a causal involvement of infections in precursor B-cell ALL.

Seror (2008) reported a child who developed ALL two months after having been infected by the human herpesvirus 6 (HHV-6). Antibodies for Herpes Simplex viruses and the Epstein-Barr virus were significantly higher in children with ALL (Mahjour 2010), especially B-ALL (Ateyah 2017), and 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. A further study by Vasconcelos (2011) looking at Parvovirus B19 infection found that data indicated that a common viral illness may drive specific DNA methylation patterns in susceptible B-precursor cells, contributing to the leukemogenic potential of such cells. Infections may impact childhood leukaemia by altering DNA methylation patterns and specific key genes in susceptible cells; these changes may be retained even after the clearance of infection.

Infections as a cause of childhood cancer have been well-researched. Sometimes day-care, position in family or social contact have been used as surrogates 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 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](#)). Liu ([2016](#)) found that a small proportion of individuals infected with EBV develop nasopharyngeal carcinoma (NPC), especially in children who are the oldest in a family.

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](#)). Richardson ([2011](#)) suggests that a non-hygienic environment primes the adaptive immune response and is protective against ALL, while multiple infections occurring later increase the risk of childhood ALL. In affluent societies, the characteristic ALL incidence peak in early childhood, and the shortened time to diagnosis, arise from surviving recurrent infections and the accumulated loss and recovery of lymphoid tissue.

One factor in susceptibility that has been suggested is that in early childhood children are less exposed to common infections, including influenza, (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 (Petridou [2001](#), Greaves [2006](#), 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 ([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. In a letter in response to the Cardwell paper, Professor Greaves & Buffler say ([2009](#)) that "*nowhere in the 'delayed infection' hypothesis does it state or predict that the relevant 'protective' infectious exposures in infancy or early childhood will necessarily elicit overt symptoms or pathology. It is perfectly plausible that only particular, albeit common, infections are competent to appropriately modulate the neonatal immune system network.*"

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.

Morgenstern & Anderson (2011) suggests that it is unlikely that chronic inflammation plays a causative role in childhood cancer, though it may have a significant part to play in the promotion of mutated cells to a full blown tumour.

Vaccinations

The situation with respect to vaccinations seems mixed, some vaccines seeming to have a protective effect (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, 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) 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 (2001, 2011) 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. '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. 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.