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 3

Ionising Radiation

Childhood Cancer
3. Possible causative factors – ionising radiation

There is a well-established link between exposure to ionising radiation and cancer. Ionising radiation can be either natural background radiation such as radon, or man-made such as bomb testing, or nuclear power and weaponry. It also includes ionising radiation used for medical diagnosis (X-rays and CT scans) and treatment (radiotherapy).

A paediatrician in Germany explained in very clear terms why children may be more at risk than adults when exposed to ionising radiation, even low grade (Eisenberg 2009).

She said:-

- Growth means a high rate of cell division in all organ systems. Cell division is the risky phase for radiation damage; an embryo grows at an almost explosive rate. Its cells are constantly dividing, which is why even tiny amounts of radiation are extremely hazardous.

- The repair mechanisms that our organism uses to identify and eliminate mutated cells are not yet effective in children, especially in unborn children.

- Children have a positive substance balance – in order to thrive they have to consume more than they excrete, in contrast to adults who merely have to maintain their fully grown bodies. The positive balance in children leads to a prolonged biological half life in incorporated radioactive isotopes.

- Malignancies have a long latency period; in pathologies caused by radioactivity, decades may lie between exposure and detectable onset of illness. Children have their lives ahead of them; in contrast to older people, they may have the misfortune of experiencing the end of the latency period.

There is no fixed agreement on the method of cancer causation or affected part of the body as a result of ionising radiation. A study by Hudson (2011) suggested the the most susceptible organs were the thymus and spleen (lymphoid) and the least susceptible were the lungs and brain. The exception to this is the link between exposure to radon and the incidence of lung cancer. Professor Denis Henshaw suggests that 5% of childhood leukaemia is linked to radon, a radioactive gas found naturally in the ground. It diffuses into open air and a house can trap radon gas.

Atom bombs, older strength medical X-rays and radiotherapy are established causes of cancer. Only thyroid cancers have significantly increased after the Chernobyl accident, according to official sources, and links between cancer and residential or parental occupational exposure to nuclear facilities has produced mixed results. Lane (2010) asks for the development of credible radiological/nuclear event scenarios that will assist in identifying probable sources of radioactivity and pathways of exposure for children, to develop appropriate protection strategies. For instance, many cases of thyroid cancers were prevented after the Three Mile Island accident by giving high levels of iodine supplement which meant cells were saturated enough not to take in further contaminated iodine from the environment. This was not done at Chernobyl.

Because of the high dose of radiation exposure in childhood cancer therapies, the risk of developing thyroid cancer within ten years of radiation exposure, was nearly 3 times normal, based on 42 exposed cases, and remained elevated 50 years and more after exposure to the

therapeutic radiation. Chemotherapy was significantly associated with thyroid cancer, in addition to the association with radiation (Veiga 2016).

Information about the effect of ionising radiation on leukaemia and other cancer rates comes primarily from atomic bomb survivors; *in utero* irradiation of the foetus by obstetric X-rays; occupational exposure to radiation in, and residential proximity to, nuclear facilities; nuclear fallout from power station accidents, such as Chernobyl and Fukushima; bomb testing; and natural sources of ionising radiation, such as radon.

Natural radiation

Natural radiation sources comprise cosmic rays, terrestrial gamma rays, radionuclides in food and inhaled isotopes of radon with their decay products. These deliver doses to all organs and tissues including red bone marrow (RBM), the tissue in which leukaemia is thought to originate. Kendall & Fell (2011) calculate the age-dependent annual RBM doses from natural radiation sources to young people and to adults at average levels of exposure in the UK. The contributions to dose are generally less complex than in the case of doses to foetuses and young children where it is necessary to take into account transfer of radionuclides across the placenta, intakes in mother's milk and changes in gut uptake in young infants (Kendall 2009). However, there is high uptake of alkaline earths and of similar elements in the developing skeleton and this significantly affects the doses from radioisotopes of these elements. The total equivalent dose to the RBM from all natural sources of radiation at age 15 years is calculated to be about 1200 μSv a year at average UK levels. About 60% of the equivalent dose is contributed by the low energy transfer (LET) component. Radionuclides in food make the largest contribution to equivalent doses to RBM and much the largest contribution to the absorbed dose from high LET radiation (mainly alpha particles). It is estimated that background ionising radiation is implicated in around 34% of cases of childhood leukaemia, particularly AML, with exposure during preconception, *in utero* and in the postnatal period being important.

There have been a number of studies that show an association between radon, a naturally occurring gas, and childhood leukaemia (Henshaw & Allen 2002, Evrard 2006, Pedersen 2014), even if the association is a weak one (Raaschou-Nielsen 2008). It is similar to the radiation risk estimates in another study by Evrard (2005) at 10 mSv, which is comparable with the natural background radiation in e.g. areas of Cornwall, where there is a high level of exposure to radon. Due to the relatively ubiquitous exposure to background natural radiation, any childhood leukaemia excess would be undetectable in a case-control study. A report by Kaletsch (1999) found a link between residential radon exposure and CNS tumours, though the number of children affected was small, and radon levels vary from area to area and country to country. See also the separate article on Radon. Should you be concerned about the level of radon you and your family are exposed to you can buy a radon meter from EMFields, which will give you an accurate reading in about 24 hours.

In a complex multi-factorial illness such as childhood cancer, more than one factor may have to occur at the same or similar time, or sequentially. This may have some bearing on the inconsistency found in studies. Brauner (2010) found that air pollution from traffic may enhance the effect of radon on the risk of childhood leukaemia.

All journeys by air expose plane travellers to cosmic ionising radiation which is less shielded by the atmosphere at high altitude.

In the UK, the percentage of cases of childhood leukaemia attributable to natural background radiation is suggested to be between 15 and 20% (Wakeford 2009, Little 2009). The magnitude of the risk depends on the dose of radiation, the duration of exposure, and the age and susceptibility

of the individual at the time of exposure. The results of a study by Nikkilä (2016) provide further support to the notion that low doses of background ionising radiation increase the risk for childhood leukaemia, particularly between the ages of 2 and 7 years.

Ionising radiation is relatively ineffective at inducing mutations in DNA, but is effective at inducing DNA strand breaks. Most single stranded breaks are rapidly repaired, but double-stranded breaks can result in chromosome re-arrangements. Such aberrations, if they are not lethal, or if they are mis-repaired, can lead to cancer.

The explosion of research into radiation-induced genomic instability (both direct and transgenerational, Vorobtsova 2008) and the bystander effect has brought into sharp debate the risks of exposure to radiation at low doses.

Medical diagnosis and treatment

X-rays, CT scans, radiotherapy & ultrasound

Sir Richard Doll showed a 40% increase in risk to a child as a result of a radiographic examination. Excess cancer deaths decreased suddenly for births in and after 1958, largely as a result of campaigning for change by Dr Alice Stewart. Due to her pioneering work, X-rays as a matter of course during pregnancy were discontinued and they are rarely done now. The risk associated with X-ray exposure has decreased over time as once the damage from ionising radiation was acknowledged, the diagnostic and therapeutic levels were reduced to the minimum necessary for its purpose. In the 1970s the rate of X-raying increased again and so did cancer risk but not significantly.

Other studies found that obstetric X-rays of the foetus produce an increased risk of leukaemia later in childhood (Boice & Miller 1999, Shu 2002). Wakeford (2008) found an increase in risk of leukaemia for prenatal X-ray exposure, but not postnatal, however, he expressed uncertainty about the safety of paediatric CT scans. Verreet (2016) reviewed evidence for brain defects following prenatal ionising radiation exposure such as that from CT scans. The review provides an overview of the current knowledge on brain developmental and persistent defects resulting from *in utero* radiation exposure and addresses the many questions that still remain to be answered.

Hammer (2009, 2010, Meinert 1999, Naumberg 2001) found no increase in cancer, or in some studies specifically leukaemia, risk for children from very low doses of diagnostic ionising radiation (X-rays). Different types of leukaemias may be more likely to result from X-ray exposure. Hammer (2011) found a positive dose-response relation in 5 patients with endocrine or metabolic disease who underwent diagnostic X-rays. Shu (2002) noted a significantly increased risk for children with pre-B cell ALL, especially if they had 3 or more X-rays, and they were more than 5 years old. Bartley (2010) found an association between post-natal diagnostic X-rays and B-cell ALL, but not AML or T-cell ALL. It may be that, in some cases, the medical reasons that women receive prenatal X-rays might be responsible for the increased leukaemia risk and not the X-ray exposures themselves. One study (Schmitz-Feuerhake & Pflugbeil 2011) recommended a reduction in diagnostic exposures as a measure for preventing several cancers.

Chaparian & Aghabagheri (2013) suggested that there may be some risk of childhood cancer and small head size due to maternal X-rays of abdomen, lumbar spine and pelvis.

Chokkalingam (2011) found that X-ray exposures in conjunction with certain genetic subtypes were more likely to result in ALL.

An increased risk of high-grade gliomas was associated with childhood radiological procedures, though based on small numbers (Milne 2014).

Neonates in special care baby units who have X-rays had a mean increased risk of cancer between 4.21 x 10(-7) and 2.72 x 10(-6) (Faghihi 2011).

In a review of 25 studies published between 1990 and 2006, there was no association found between pre- and postnatal X-rays and brain tumours (Schulze-Rath 2008). Khan (2010) found no association between head injury and exposure to diagnostic head X-rays and medulloblastoma or PNET. Patton (2004) found no association between neuroblastoma risk and maternal exposure to radiation, and only a slight one with paternal radiation exposure. No consistent pattern of association between Wilms tumour (nephroblastoma) and maternal radiation exposure during pre-pregnancy or pregnancy was found in a study by Goel (2009).

Mellemkjaer reported a cohort study (2006) of children classified as 'immature' at birth. They found an excess of CNS tumours in such children and more cases had been exposed to diagnostic X-rays than controls. Th authors commented that *"An explanation behind the excess of CNS tumours could not be identified, but the effect of diagnostic X-rays in newborns may deserve further attention."*

Bunin (2011) found that both paternal and maternal exposure to medical radiation of the gonads increased the risk of their child's developing retinoblastoma by more than 3 times or 7 times respectively.

X-rays have been superseded in most cases by ultrasound scans, which have not been associated with the same level of risk. Ultrasound exposure has not been found to be a risk for brain tumours (Stålberg 2008), or cancer generally (Rajaraman 2011) but there are other concerns about ultrasound exposure leading to neurological changes, including autism, which suggest that they should only be used where there are concerns about the child's wellbeing, rather than an automatic procedure.

Diagnostic X-rays are the largest man-made source of radiation exposure to the general population, contributing about 14% of the total annual exposure worldwide from all sources. It is accepted that about 0.6 per cent of UK cancers in general are due to medical X-ray procedures (Berrington de González & Darby 2004), rising to a figure as high as 3% in Japan.

Fahey (2011) urges that it is incumbent on practitioners of paediatric nuclear medicine to have an understanding of dosimetry and radiation risk to communicate effectively with their patients and their families, especially given the proliferation of CT scans. The benefits of ionizing imaging in children, especially in those with congenital heart disease, are immense and often life-saving, even more so with the advent of invasive fluoroscopy and CT, yet the use of radiation in children raises special concerns and offers a unique challenge for the current generation of paediatric cardiologists (Andreassi & Picano 2014).

CT scans are increasingly used to diagnose medical problems. A single CT scan exposes the patient, on average, to a 7 times higher dose than a normal X-ray. A chest CT scan is the equivalent dose of 60 normal chest X-rays. Although the risk from a single CT scan to an individual is small, there are concerns about the build-up of risk over time, especially for children, who are more susceptible to radiation. Bernier (2012) studied paediatric CT scans, discovering that 43% were less than 1 year during their first exposure, 9% aged less than 1 month. The examinations included head in 63%, chest in 21%, abdomen and pelvis in 8% and others in 8%. Brain and eye lenses received the highest cumulative doses from head examinations. They concluded that CT scan exposure in childhood is responsible for relatively high doses to radiosensitive organs. The excess risk of developing thyroid cancer from paediatric CTs was 13% for males and 25% for females (Muchow 2012).

A study by Journy (2016) looked at the difference in cancer risk for those children who had predisposing factors (PF) before the CT scan and those without. In children without PF, hazard ratios of 1.07 for CNS tumours (15 cases) and 1.16 for leukaemia (12 cases) were estimated for each 10 mGy increment in CT x-rays organ doses. In children with PFs, no positive dose-risk association was observed, possibly related to earlier non-cancer mortality in this group. Other authors (Muirhead 2015) responded that the findings of Journy do not indicate that the association between cancer risk and radiation exposure from CT scans has been confounded by predisposing factors for cancer.

In strong language, McHugh & Disini (2011) comment *"Enough literature now exists such that doing a non-contrast abdominal or chest computed tomography (CT) scan for suspected mass lesions in childhood borders on malpractice."* They suggested that an entirely unnecessary CT study does more harm than good. Not all CT scans should be banned, though, they conclude *"When a chest or abdominal mass is suspected in a child, only a post-intravenous contrast enhanced CT examination is needed."*

Wakeford (2010) and Rajaraman (2011) recommended caution when considering administering paediatric and pregnancy CT scans, because of the small, extra risk of developing leukaemia attached to each one. Obese people require more radiation to get the same amount of physiological information. Many CT centres are set up for adults, and are therefore not suitable for children, who need adjustments to limit dose and radiation risk, without making appropriate changes in exposure.

According to Berrington de González (2009), 15% of cancers resulting from CT scans were due to scans at ages younger than 18 years, though the study did not make it clear what the latency period might be. Smith-Bindman found (2009) that "*within each type of CT study, effective dose varied significantly within and across institutions, with a mean 13-fold variation between the highest and lowest dose for each study type. The estimated number of CT scans that will lead to the development of a cancer varied widely depending on the specific type of CT examination and the patient's age and sex.*"

Pflugbeil (2011) suggested that there are 3 excess tumours (especially meningiomas) in the head out of every 1000 annual paediatric CT scans of the skull (cataracts were also a potential problem), as well as an increased risk of childhood leukaemia as a result of CT scans of the bone marrow. Knüsli & Walter (2013) confirmed that the risk of cancer incidence after CTs increased and that ultrasound and MRI scans should be preferred whenever appropriate.

MRI could be an alternative to CT for staging of children and young adults with cancer that is free of ionising radiation (Klenk 2014).

Acoustic neuromas are usually benign and often asymptomatic, though many cause significant morbidity. There is an association between acoustic neuromas and childhood radiation exposure, and they can appear after a long latency and continue to occur many decades afterward (Schneider 2008). Children treated between 1939 and 1962 to reduce the size of tonsils and adenoids received substantial radiation exposure. Some went on to develop acoustic neuromas, the earliest 20 years later and the latest 55 years after exposure.

Nuclear facilities

The world has 435 nuclear reactors, 104 of which are in the USA. There have been over 60 epidemiological studies on the incidence of leukaemia and other childhood cancers near nuclear power plants. Bollaerts (2016) found a two- to three-fold increase in leukaemia incidence rates in children aged 0-14 years living in the 0-5, 0-10 and the 0-15 km near Belgian nuclear sites. For one particular site, there was evidence for a gradient in leukaemia incidence with increased proximity, prevailing winds and simulated radioactive discharges, suggesting a potential link with the site that needs further investigation. Ghirga (2010), reviewed scientific articles and

government documents on the incidence of childhood cancer near nuclear power plants and concluded that there may be increases, irrespective of the country concerned. Fairlie (2010) suggests that doses from environmental nuclear power plant emissions to embryos/foetuses in pregnant women near the plants, may be larger than suspected, and Wakeford (2010) suggests that maybe the leukemogenic effect of radionuclides taken into the body has been seriously underestimated, which could explain the increased incidence of childhood leukaemia near some nuclear installations.

Many studies have investigated the possibility of paternal occupational exposure to ionising radiation being a potential risk factor in the development of leukaemia in their children.

The risk of leukaemia has been found to be higher in children born near Sellafield, and for children of fathers employed at the plant at their conception, and that the higher the dosage they were exposed to (particularly the testicles), the higher the risk (Roman 1999). Other studies did not find the increased risk in children whose fathers worked at Sellafield, but who lived further away from the installation. It could be that there was a synergistic effect of paternal exposure and something else nearer the child's home before the leukaemia was initiated. This hypothesis is further substantiated by Davies (2007) who found that fathers (particularly) of children both with and without leukaemia had high levels of germline mutations. It implies that the children who went on to develop leukaemia were subject to something else involved in carcinogenesis.

Dickinson & Parker (2002) including all children born to mothers who lived in Cumbria between 1950 and 1991, found that the children of radiation workers had an increased risk of developing leukaemia and non-Hodgkin's lymphoma. Gathering data about occupational exposure is complicated by the fact that external radiation exposure does not necessarily correlate with potential internal contamination of workers, through ingestion or inhalation of radionuclides, which was not measured.

Meinert (1999) found that there was an association between maternal occupational exposure to radiation and some forms of childhood cancer dependent on the age of the child.

It has been suggested that nuclear power facilities (Sellafield, La Hague, etc.) have cancer clusters in the residential areas around them and that merely living nearby could increase the likelihood of a child developing cancer (Spix 2008). Some study authors have acknowledged that the number of children suffering from leukaemia in Berkshire (Barton 2001) and Germany (Hoffmann 2007, Kaatsch 2008, 2008, Nussbaum 2009) was higher than would be expected, but they were unsure of the cause. Nussbaum found a doubling in risk in children under 5 living within 5 km of plant exhaust stacks. Sermage-Faure (2012) found a possible excess risk of acute leukaemia in the close vicinity of French nuclear power plants in 2002-2007. The authors felt that the absence of any association with a dose-based geographic zoning may indicate that the association is not explained by gaseous discharges. Laurier (2008) found no such link in children below the age of 5 years with French nuclear power plants, neither did Heinävaara find an increase in childhood leukaemia near Finnish nuclear power plants (2010), though the study authors acknowledged that the small sample size limited the strength of the conclusions. Spycher (2011) found little evidence of an association between childhood cancer and nuclear power plants in Switzerland. We wonder whether governmental reliance on nuclear plants for electricity supplies may, in some way, influence the outcome of specific studies.

Dr Körblein commented on the leukaemia cancer clusters (2009) saying *"ecological studies are much less able to detect regional clusters than more elaborate case-control studies. When the authors refer to the results of a recent study from England that, in contrast with the German study, has not shown a leukaemia increase in the vicinity of nuclear power stations, it has to be borne in mind that this study, again, is an ecological study."* Bithell (2008) commented *" this apparent discrepancy* (in study findings) *could be accounted for by a number of differences in approach, especially those relating to the distances from the*

power stations and the ages of the children studied." Laurier (2008) in a review of 198 nuclear sites in 10 countries concluded *"A large variability was noticed in the quality of the data as well as in the definition of the study population and in the methods of analysis"* although the review also confirmed that *"some clusters of childhood leukaemia cases exist locally."*

A study looking at tritium exposure from a nuclear power station in Canada (Wanigaratne 2013) showed female childhood cancer cases to be significantly higher than expected.

A large meta analysis was carried out by Baker & Hoel (2007) on studies that included 136 nuclear facilities, and found that the majority of these found elevated levels of childhood leukaemia in nearby residents.

Whether parental preconceptual or *in utero* exposure to radiation increases the risk of infant leukaemia remains controversial. Busby (2009) looked at the records of over 15 million children born in the UK, Greece, and Germany between 1980 and 1990. He found an excess of infant leukaemia reported from 5 different countries; Scotland, Greece, Germany, Belarus and Wales and Scotland combined. The excess risks showed a biphasic response to exposure. Busby concludes *"Since the cohort is chosen specifically on the basis of exposure to internal radionuclides, the result can be expressed as evidence for a significant error in the conventional modelling for such internal foetal exposures."* Fairlie (2009) looked at studies of leukaemia near nuclear installations and suggested that *"the observed high rates of infant leukaemias may be a teratogenic effect from incorporated radionuclides. Doses from environmental emissions from nuclear reactors to embryos and foetuses in pregnant women near nuclear power stations may be larger than suspected. Hematopoietic tissues appear to be considerably more radiosensitive in embryos / foetuses than in newborn babies."*

Nuclear accidents

Exposure to ionising radiation during childhood increases the risk of thyroid cancer (Schlumberger 2011). In case of accident, children can be given potassium iodide which can help prevent damage.

A review of research into the genetic damage done to children by accidental exposure to ionising radiation (Fucic 2008) concluded that *"the evidence from the studies conducted following the Chernobyl accident, nuclear tests, environmental radiation pollution and indoor accidental contamination reveals consistently increased chromosome aberration and micronuclei frequency in exposed children."* They suggested that further research should be carried out with regard to the combined effects of low doses of radiation and chemical agents from food, water and air. It is important that not just *in utero* exposure is considered, as Mangano, looking at the Three Mile Island as well as the Chernobyl accidents (Mangano 2006) documents that there is a short latency of cancer onset in young children who are especially susceptible to adverse effects of radiation exposure, even at relatively low doses.

There have been various investigations into the after effects of the Chernobyl accident. Noshchenko (2001) found that *in utero* exposure caused the rates of ALL to be dramatically elevated for males and to a lesser extent for females. A study by Peterka (2007) found that a significantly decreased number of male babies were born in the areas most affected by Chernobyl fallout. This may reflect a greater susceptibility to radiation for males rather than females, especially prenatally. For both genders combined, the risk for ALL was more than three times greater in the exposed compared to the unexposed regions, although Steiner (1998) was ambivalent. The incidence of thyroid cancer in children and adolescents in the Russian Federation has been directly linked to the radiation pollution in the area of residence (Romanchishen 2010).

It is difficult to compare many of the studies due to a) difficulties of getting information following the breakup of the Soviet Union into its constituent countries; b) differences in cancer registration

systems; and c) means of case ascertainment. A study looking at the population exposed to fallout from Chernobyl (Maenhaut 2011) concluded that *"Several lines of evidence suggest that the predisposition to developing cancer after radiation exposure is variable in the general population."* 39% of children exposed to radioactive fallout from Chernobyl as children had changes to chromosome 7, that none of the unexposed children had (Hess 2011). The authors concluded *"it is likely that different molecular subgroups and routes of radiation-induced carcinogenesis exist."*

Nations outside the former Soviet Union received high doses of radioactive fallout, most notably Norway, Sweden, Finland, Yugoslavia, Bulgaria, Austria, Romania, Greece and parts of the United Kingdom and Germany. About 550 million Europeans and 150 to 230 million others in the Northern Hemisphere received notable contamination. Fallout reached the United States and Canada nine days after the disaster.

The proportion of children considered healthy born to irradiated parents in Belarus, the Ukraine and European Russia fell from about 80% to less than 20% since 1986. These include increased foetal and infant deaths, birth defects and diseases of the respiratory, digestive, musculoskeletal, nervous, endocrine, reproductive, haematological, urological, cardiovascular, genetic, immune and other systems, as well as cancers and non-cancerous tumours.

In the early 1990s, a few years after the meltdown, thyroid cancer in Connecticut children had nearly doubled.

Foods produced in highly contaminated areas in the Soviet Union were shipped and consumed worldwide, affecting people in many other countries. Americans also ate contaminated food imported from affected countries. Four years later, 25% of imported food was found to be still contaminated.

Americans have been warned to learn from the Fukushima disaster. 23 American nuclear plants are of the same design as the Fukushima reactors, some sitting on earthquake fault lines.

Atomic Bomb and fallout survivors

Yamamoto & Goodman (2007) investigated patterns of leukaemia incidence in the United States and reported that Asian-Pacific Islanders had the highest rates of AML. A possible explanation for this may be that DNA damage due to bomb testing was passed on to successive generations.

The Atomic Bomb survivors' risk factors for leukaemia were based on radiation doses of much higher levels (from 0.1 to 10 Sieverts (Sv) than the average UK natural background level of 2.2 millisieverts (mSv) per year). It is likely that using Atomic Bomb survivors as subjects for research could distort the effect of ionising radiation, as it is certain that those susceptible to varying (even small) amounts will have died as a result of their exposure, leaving a more resistant (i.e. not necessarily random) group of survivors.

The standardised mortality rate for Japanese boys exposed to low doses of radiation in 1945 was significantly higher for solid cancer (Goto 2011).