Childhood leukaemia around nuclear facilities

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Authors: Andrzej Wojcik
Maria Feychting
This report concerns a study which has been conducted for the Swedish Radiation Safety Authority, SSM. The conclusions and viewpoints presented in the report are those of the authors and do not necessarily coincide with those of the SSM.

Foreword
The first indication of a possible relationship between living close to a nuclear installation and the risk of childhood leukaemia came from the United Kingdom in 1983. A cluster of childhood leukaemia in the town of Seascale which is located close to Sellafield was reported in a TV documentary. Since then almost 200 studies have been carried out in order to investigate the occurrence of childhood leukaemia around nuclear installations. Recently, the issue of childhood leukaemia gained new attention due to a large study that was carried out in Germany.

For children aged below 5 years living within 5 km of a nuclear plant there was a significantly increased risk for leukaemia. On the other hand, the reported overall conclusion from all studies performed are that clusters of leukaemia around nuclear installations are rare, only three well documented clusters, and three possible cases, have been found. The reason for the observed clusters remains unknown. In particular, it has been difficult to find a relation to radiation doses attributable to the normal discharges of radioactive substances.

Understandably, the issue of a possible increased frequency of childhood leukaemia near nuclear installations has attracted considerable public attention. In order for the Swedish Radiation Safety Authority (SSM) to judge the needs for any further studies or other actions on this issue, Professors Wojcik and Feychting were asked to submit this brief overview of the present state-of-the-art findings regarding childhood leukaemia in the vicinity of nuclear installations. Their report, together with other available information on childhood leukaemia, will be input for any decision about further actions to be taken by SSM.

Leif Moberg
Director
Swedish Radiation Safety Authority
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Abstract

In December 2007 the German Federal Office for Radiation Protection (BfS) published a report on the incidence of childhood cancers among children living in the vicinity of 16 German nuclear power plants. The results show a significantly enhanced risk of leukaemia in children aged below 5 years, who live within 5 km from a nuclear power plant. The study is known as KiKK (Epidemiologische Studie zu Kinderkrebs in der Umgebung von Kernkraftwerken) and stirred considerable concern about the safety of nuclear installations. In this review we summarise the present state-of-the art regarding childhood leukaemia in the vicinity of nuclear installations and present the main results of the KiKK study with a critical evaluation.
1. Introduction

The emission of radioactive isotopes by nuclear facilities (NF - including power plants and fuel reprocessing plants) is strictly regulated and controlled. Next to dosimetric measurements performed in the NF, the surrounding environment is regularly monitored and the results are publicly accessible. The doses received by people due to normal operation of NF are a fraction of the annual doses received from natural sources of radiation. Based on our current understanding of the carcinogenic effects of radiation, exposure of people due to radioactivity released from NF is not associated with any measurable risk of cancer. However, a number of reports about increased incidences of cancer around NF, notably of childhood leukaemia, have been published. A recent, large study is that of childhood leukaemia around German nuclear power plants (NPP) (Kaatsch et al. 2008a, 2008b; Spix et al. 2008). Understandably, these reports attract considerable public attention and the aim of this article is to review the current status of the research.
2. What do we know about the causes and mechanisms of childhood leukaemia?

Childhood leukaemia is a rare disease, although it is one of the most common malignancies in children in Sweden, with an incidence of approximately 5/100 000, corresponding to around 80 newly diagnosed cases per year. The most common leukaemia subtype is acute lymphoblastic leukaemia, accounting for almost 80% of the incidence. In developed countries, the incidence of leukaemia rises after birth and has a peak in the age group 2-5 years after which it declines and then rises again throughout adult life (Lightfoot and Roman 2004). The incidence of childhood acute lymphoblastic leukaemia increased during the end of the 1970s, but has been stable in the Nordic countries since 1983 (Svendsen, et al. 2007).

The causes of childhood leukaemia are still largely unknown. Established risk factors are genetic syndromes like Down’s syndrome and high doses of ionizing radiation. Antenatal diagnostic radiography is likely to increase the risk of childhood leukaemia, whereas evidence for an effect of postnatal diagnostic radiography is inconclusive (Wakeford 2008). Various other environmental exposures have been investigated, e.g. parental smoking, alcohol consumption, occupational exposures, children’s exposure to pesticides, extremely low frequency (ELF) magnetic fields, but conclusive causative evidence is still lacking. Greaves and Kinlen have suggested that infections might play a role in the etiology of childhood leukaemia (Greaves 1997; Kinlen 1995). Related to this is the hypothesis that population mixing might increase leukaemia risk. Population mixing may play a role in rural areas, when a large number of people move into the neighbourhood, introducing infectious agents to which the original population lacks immunity (Lightfoot and Roman 2004). Although there is some evidence supporting this hypothesis, there are also contradictory results, and no virus-dependent immunological mechanisms have been identified so far.
3. The childhood leukaemia in Seascale

The first indications about the possible relationship between living close to a NF and the risk of childhood leukaemia came from the United Kingdom. In 1983 a cluster of childhood leukaemia was discovered by TV journalists in the town of Seascale which is located close to Sellafield, the former Windscale NPP, and now the principal nuclear reprocessing plant in the UK (Urquhart et al. 1984). During the period 1955-1983 7 cases were observed in young people under 25 years of age, this being about 10 times more than expected. The initial idea was that the cluster resulted from the environmental pollution with radioactive waste and this was the first explanation considered by the Committee on Medical Aspects of Radiation and the Environment (COMARE) that was set up by the UK Department of Health to review the finding (COMARE 1986). The idea was, however, quickly shown to be untenable, as the doses received by Seascale residents were less than 10% of their total doses and about 200 times too small to account for the observed excess of leukaemia (Doll 1999).

An alternative explanation was proposed by Gardner who suggested that the leukaemia cases were associated with the fathers’ employment at Sellafield before the children were conceived (Gardner et al. 1990). This hypothesis does not accord with the data from Hiroshima and Nagasaki survivors and with what is known of radiation genetics. The evidence was reviewed by members of COMARE as well as by others and it was found that exposure of fathers could not be responsible for the leukaemia cases (Doll 1999). The excess observed was so high that it could also not be explained by chance.
4. Leukaemia clusters around other NF

The Seascale cluster caused considerable public concern and a large number of studies in countries with NF, especially the UK, USA, Germany and France. Several exhaustive review articles have been published where the results of the studies are summarised (Baker and Hoel 2007; Laurier et al. 2002; Laurier et al. 2008). The studies can be divided in two categories: local studies and multi-site studies. The former concentrate on single sites, the advantage being that they can consider some specific characteristics of an installation. The latter pool data from several sites which results in a larger statistical power.

Local studies have been performed on nearly 200 NF. The existence of three childhood leukaemia clusters is unquestionable: the already mentioned Seascale cluster in England, the Dounreay cluster in Scotland and the Elbmarsch cluster in Germany. The Dounreay cluster was discovered in 1986. It involved 5 cases within 12.5 km from the reprocessing plant where less than 1 case was expected. The Elbmarsch cluster was discovered in 1992, also involving 5 cases where less than 1 case was expected. Other clusters have been reported, particularly in the UK close to the Aldermaston and Burghfield sites, as well as close to the La Hague reprocessing plant in France, but the evidence for their existence is not as clear. No consistent excess risk was reported for any of the other ~200 sites analysed (Laurier et al. 2008). In a study published in 1995, no excess childhood leukaemia was also observed around Swedish nuclear power plants (Hjalmars et al. 1996).

About 25 multi-site studies have been carried out in different countries. The results are summarised in the form of relative risk in figure 1. The analysed endpoints include mortality or incidence. Overall the results are variable, with the majority of studies showing no enhanced risk. In some studies, however, a high number of leukaemia cases was observed. A general trend is that, when detectable, a particularly high level of risk is observed among children aged below 10 years.

Interestingly, an elevated risk was also observed around NF before they began operation. Similarly as for the operating NF, the risk is particularly high for children aged below 10 years (Laurier et al. 2002). This strongly indicates that the enhanced risk observed around some sites is not related to radiation but to other factors. The possible causes of an enhanced risk of childhood leukaemia around NF are discussed at the end of this article.
Figure 1. Studies of leukaemia risk among children and young adults in the vicinity of operating nuclear power plants and other nuclear facilities. Dashed line marks the expected level of risk. Error bars represent 95% confidence intervals. a: nuclear power plant; b: other facility, c: NPP plus other facility; d: planned NPP; *: significantly different from 1. Based on Laurier et al. 2008.
5. The KiKK study

Most recently, the issue of childhood leukaemia around NF gained new attention due to a large study that was carried out in Germany. Already exploratory analyses in earlier cohort studies showed an enhanced incidence of leukaemia among children below 5 years of age who lived within 5 km of some German NPP located in the western part of the country. The effect was especially prominent in the town of Elbmarsch, close to the Krümmel NPP (Laurier et al. 2002). In order to study this effect with a greater precision, the German Federal Office for Radiation Protection (Bundesamt für Strahlenschutz - BfS) initiated in 2001 a large case control study, which was carried out by epidemiologists from the German Registry of Childhood Cancer in Mainz (Deutsches Kinderkrebsregister). The study, named “KiKK: the epidemiological study of childhood cancer around nuclear power plants” (Epidemiologische Studie zu Kinderkrebs in der Umgebung von Kernkraftwerken: KiKK-Studie), was started in 2003 and the results were published in 2007 (BfS 2007). In addition to the report, the results were published in several journals (Kaatsch et al. 2008a, 2008b; Spix et al. 2008).

![Figure 2. Nuclear power plants which were analyzed in the KiKK study. Light grey shaded boxes: period of NPP operation; dark grey bars: period of observation.](image)

The aim of the KiKK study was to test the hypothesis of a causal relationship between living in the vicinity of a NPP and the risk of developing leukaemia before the age of 5. Without performing any measurements, the authors of the study assumed that the radiation dose absorbed by the inhabitants decreased steadily with the distance from a NPP. The study covered communities (Landkreis - equivalent to the Swedish “kommun”) in which
the 16 German NPPs of the former West Germany are located (figure 2). For each of the 16 areas, a neighbouring community was chosen where cases and controls where also analysed. The information about the cases was derived from the Childhood Cancer Register in Mainz. The controls were chosen randomly from the same area, based on sex and year of birth. The selection of controls was performed by the communities. The observation period started one year after a NPP began to operate (but not earlier than 1980) and finished 5 years after a NPP was closed down (but not later than December 2003). The total number of cases was 1592 and the number of matched controls was 4735. The most frequent type of cancer was the acute leukaemia (512 cases of the lymphoblastic form and 75 cases of the myeloblastic form), embryonic tumours (486 cases) and tumours of the central nervous system (242 cases). For each case and control the distance between the place of residence and the nearest ventilation window of a NPP was determined with a precision of 25 m. No account was taken of migration: only the place of residence at the time of cancer diagnosis/enrolment as control was noted.

The level of risk for the different tumour types was given for 5 km increments from the NPPs as odds ratios (OR - see Explanation of technical terms). Moreover, the population attributable risk (PAR) was calculated.

<table>
<thead>
<tr>
<th>Distance from NPP (km)</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
<th>Number of cases</th>
<th>Number of controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5</td>
<td>2.27</td>
<td>1.45-3.56</td>
<td>0.0003</td>
<td>37</td>
<td>54</td>
</tr>
<tr>
<td>5 - 9</td>
<td>1.09</td>
<td>0.78-1.52</td>
<td>0.62</td>
<td>57</td>
<td>170</td>
</tr>
<tr>
<td>10 – 29</td>
<td>1.00</td>
<td>-</td>
<td>-</td>
<td>327</td>
<td>1039</td>
</tr>
<tr>
<td>30 – 49</td>
<td>1.12</td>
<td>0.87-1.43</td>
<td>0.38</td>
<td>135</td>
<td>385</td>
</tr>
<tr>
<td>50 – 69</td>
<td>0.95</td>
<td>0.56-1.61</td>
<td>0.85</td>
<td>27</td>
<td>89</td>
</tr>
<tr>
<td>70 +</td>
<td>1.11</td>
<td>0.34-3.63</td>
<td>0.86</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>Sum</td>
<td>2.27</td>
<td>1.45-3.56</td>
<td>0.0003</td>
<td>587</td>
<td>1748</td>
</tr>
</tbody>
</table>

Table 1. Odds ratios for leukaemia among children aged below 5 living within a defined distance from a NPP. CI: confidence limits; p: level of significance as compared to the distance 10-29 km.

No relationship was detected between the distance from a NPP and the incidence of solid tumours. The situation was different for acute leukaemia. For children living within 5 km of a NPP the OR was 2.27, with confidence limits of 1.45 – 3.56. This indicates a significantly increased risk. The PAR was approximately 0.3% meaning that 20 out of 5893 cases of leukaemia cases observed in whole of Germany during the study period was attributed to living in the vicinity of a NPP. No increased OR was seen for any other distance zone. When the study period was stratified into 5 year periods, a decreasing trend was observed with time and the OR was not significantly increased for the period 1996 – 2003 (Kaatsch et al. 2008a). Moreover, the results from the area of the Krümmel NPP had a strong impact on the increased OR in the years 1991-1995 and 1996-2003 (figure 3).
Figure 3. Odds ratios for leukaemia among children aged below 5 living within a radius of 5 km of a NPP during different time periods. Left bars: data from all 16 NPP; right bars data from all NPP except Krümmel. Vertical bars: 95% one sided confidence limits. Asterisks indicate a significant excess risk.
6. A critical evaluation of the KiKK study by the SSK

The German Committee for Radiation Protection (Strahlenschutzkommission - SSK) asked a group of international experts to evaluate the KiKK study. The results were published in autumn 2008 (SSK 2008). The expert group confirmed that the data point towards a raised OR for leukaemia among children living within 5 km of a NPP. However, the experts criticised the methodology of the study. The main points of criticism are described below.

1. The problem of absorbed dose. The authors of the KiKK study assumed that the level of radiation emitted by the NPP, and consequently, the doses absorbed by the inhabitants, decreased with distance between a NPP and the place of inhabitancy. It was not attempted to estimate the doses, although records of doses around each NPP were available. Indeed, the maximal annual effective dose within 5 km of a NPP could not be higher than 0.02 mSv. This is several times lower than what the inhabitants were exposed to from other sources (table 2). Thus, the raised incidence of leukaemia around the NPPs cannot be causally related with the level of ionising radiation emitted by the NPPs.

<table>
<thead>
<tr>
<th>Source of exposure</th>
<th>Effective dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural radiation</td>
<td>1.2 – 4.6 mSv/year</td>
</tr>
<tr>
<td>Surface atomic bomb testing</td>
<td>1963: 0.15 mSv/year</td>
</tr>
<tr>
<td></td>
<td>2000: 0.005 mSv/year</td>
</tr>
<tr>
<td>Chernobyl</td>
<td>1986: 0.11 mSv/year</td>
</tr>
<tr>
<td></td>
<td>1990: 0.025 mSv/year</td>
</tr>
<tr>
<td></td>
<td>Od 2000: &lt; 0.02 mSv/year</td>
</tr>
<tr>
<td>Medical exposure</td>
<td>1972: 0.5 mSv/year</td>
</tr>
<tr>
<td></td>
<td>2006: 1.9 mSv/year</td>
</tr>
<tr>
<td>Aeroplane flight (transatlantic)</td>
<td>0.006 mSv/hour</td>
</tr>
<tr>
<td>Range of possible doses from NPPs</td>
<td>&lt; 0.0001 mSv – 0.02 mSv/year</td>
</tr>
<tr>
<td>Realistic level of dose from a NPP</td>
<td>&lt;&lt;&lt; 0.01 mSv/year</td>
</tr>
</tbody>
</table>

Table 2. Potential sources of exposure to ionising radiation and the average effective doses for inhabitants of areas around the 16 German NPP.

2. The problem of selecting controls. The communities located close to the NPPs were more reluctant than more distant communities to provide addresses of controls. This could introduce selection bias, and lead to an underestimation of the proportion of children living close to nuclear power plants in the population and, consequently, to an overestimation of the OR.

3. The problem of migration. The results of the study are based on estimating the distance between a NPP and the place of residence at the time of cancer diagnosis (for the cases) or of enrolment into the study (for controls). No account was taken of migration during the time preceding the measurement. However, it is known that 30% of cases and controls changed their address...
before the study. From the results of the Hiroshima and Nagasaki survivors study it is known that the latency period for leukaemia, which is the time between initiation and occurrence of the disease, is several years. However, the potential inclusion of subjects with too short latency periods would tend to dilute risk estimates, and cannot explain the observed risk increase. Another aspect of migration is the potential for confounding from population mixing, as suggested in other studies (Kinlen 1988, Dickinson and Parker 1999). If the population mobility is higher within the inner 5 km circle, this may potentially affect the results. The lack of information about the migration habits of the studied population casts doubts about the validity of the observed relationship between distance to NPP and childhood leukaemia.
7. What are the possible causes of the enhanced risk of childhood leukaemia around NF?

The causes of leukaemia clusters in the vicinity of NF are not known. Exposure to radiation can be ruled out: doses received by the public due to emission of radioactivity from a NF are a fraction of the annual doses from natural sources. Moreover, clusters of childhood leukaemia have been detected around NF before they became operational.

One plausible explanation is the assumption that the risk of childhood leukaemia is related to the degree of population mixing. This mechanism was first proposed by Kinlen (1988) and assumes that population mixing would tend to promote epidemics of an underlying infection by increasing the level of contacts between susceptible and infected individuals.

A relationship between population mixing and childhood leukaemia was indeed shown in a large study of people living around the nuclear fuel reprocessing plant in La Hague (Boutu et al. 2002). A similar trend was observed in Sweden, among children of fathers with many work contacts (Kinlen et al. 2002). Finally, a very high degree of population mixing was found in Seascale, which could account for the observed cluster of leukaemia (Dickinson and Parker 1999).
8. Would a Swedish/Nordic epidemiological study provide new information about the risk of childhood leukemia around NF?

Sweden and the other Nordic countries have an excellent infrastructure for the conduct of epidemiological studies, with continuously updated population registers, reliable storage of historical information, and health data registers of high quality, including nationwide cancer registers. This infrastructure makes it possible to perform a retrospective cohort study or nested case-control study without risk of selection bias. In addition, some registry-based information on possible confounding factors is available, e.g. population density, socioeconomic status based on parents’ education, income, and occupation, and child’s mobility. Information about residential history would allow analyses of different induction periods.

The problem is, however, that the Swedish population is small; there are few nuclear facilities in the country, and the population density near these facilities is low. It would not be possible to obtain sufficient statistical power for reliable results even if the entire country is included. Even a Nordic study would have limited statistical power. One has to be aware that a negative result (i.e. the finding of no statistically significant association) will not be informative because confidence intervals would be very wide which would make the result compatible also with a modest risk increase. A positive result (i.e. a statistically significant risk increase), on the other hand, would not be credible because the relative risk would have to be very high to become statistically significant. A relative risk slightly above 1, e.g. 1.8, which inevitably will have wide confidence intervals, might be perceived as supporting the German findings, but might as well be a result of random variation. The value of conducting a study in Sweden lies primarily in the possibility to contribute high quality data to a meta-analysis of a larger number of studies. For example, a study is currently underway in Finland, despite limited statistical power.

Should a study be performed in Sweden, it is important that the full potential of our registries is utilized, to ensure that selection bias is not introduced and to allow control for potential confounding factors. Distance of the child’s home to the nuclear facility needs to be measured with as much precision as possible, and the observation period should include the time from conception to 5 years of age when considering different induction periods. Results must be reported for the distance category <5 km from the nuclear power plant that was used in the German KiK study (Kaatsch et al. 2008), even if numbers are small, as the German study found no association for distances further out than 5 km. Exploratory analyses, using other distance or age categories, should be avoided.
9. References


Explanation of technical terms

**Case control study:** An epidemiological study design where subjects who have the condition (the 'cases') are compared with selected, matched subjects who do not have the condition but are otherwise similar (the 'controls').

**Cohort study:** An epidemiological study design where a group of individuals exposed to a study factor is compared with a non-exposed, matched group of individuals.

**Odds ratio (OR):** The ratio of the odds of an event occurring in one group to the odds of it occurring in another group. The OR is a measure of the relative risk. It is significantly enhanced when its lower confidence limit is larger than 1.

**Attributable risk:** The reduction in incidence that would be observed if the population were entirely unexposed, compared with its current (actual) exposure pattern.