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Abstract

The debate surrounding possible adverse health effects from the civil use of nuclear power under normal operating conditions has been on-going since its introduction. It was particularly intensified by the detection of three leukaemia clusters near nuclear installations, i.e. near the reprocessing plants in Sellafield and Dounreay, UK, and near the Krümmel nuclear power plant, Germany, the last of which commenced between 1990 and 1991 and was first described in 1992; it continued until 2003, and an elevated risk up to 2005 has been reported in the literature. A number of expert commissions and working groups were set up by the governments of the German federal states of Lower Saxony and Schleswig-Holstein to investigate possible causes of the cluster. An overview is given here of the many risk factors that were investigated as a possible explanation of the Krümmel cluster, focussing on radiation, but also including other risk factors. Further, results from related epidemiological and cytogenetic studies are described. In summary, the cause of the occurrence of the Krümmel cluster has to be considered as unknown. Further research on the causes of childhood leukaemia is needed, focussing on epigenetics and on gene-environment interaction. An update of the leukaemia incidence around the Krümmel site shows that the incidence rates are now comparable to the average rate in Germany.

Keywords: childhood leukaemia, cluster, nuclear power plant, Germany

Introduction

The debate surrounding the potential adverse health effects from the civil use of nuclear power under normal operating conditions has been on-going since nuclear power was first used in this way. It started in the United States and in the beginning focussed on infant mortality (Sagan, 1969; Tokuhata and Smith, 1981). However, after the detection of increased leukaemia mortality in young people near the Sellafield reprocessing site in the United Kingdom in 1983 (Black, 1984), the focus moved towards leukaemia, in particular childhood leukaemia. A comprehensive review published almost a decade ago found 198 studies investigating leukaemia incidence or mortality at individual nuclear sites (Laurier *et al.*, 2008). The same review reported on 25 further studies which were investigating whether there is a general increase of this disease around nuclear sites. The last of these 25 studies was a case-control study from Germany (Kaatsch *et al.*, 2008a; Spix *et al.*, 2008) prompting a number of more or less similar studies in other countries (Spycher *et al.*, 2011; Sermage-Faure *et al.*, 2012; Bithell *et al.*, 2013; Bollaerts *et al.*, 2016). When looking at single sites alone, the review of Laurier *et al.* (2008) concluded that there were three confirmed leukaemia clusters, i.e. those close to the reprocessing plants in Sellafield and Dounreay, UK, and close to the Krümmel nuclear power plant in Germany. Since then, no further report about a cluster near a single nuclear site has been published (Laurier *et al.*, 2014). The number of publications examining the British nuclear sites is very large – approximately 80 on Sellafield and 20 on Dounreay can be found in PubMed – and the conclusion Wakeford drew in 2003 (Wakeford, 2003a, b) and that was again repeated by the most recent COMARE report (Elliott *et al.*, 2016) still stands: it is highly unlikely that radiation exposure is the cause of the observed increase, but population mixing could be considered as a plausible explanation.

In contrast to the observations near Sellafield and Dounreay the number of publications on the Krümmel cluster is small, particularly in the English language literature, and considering that radiation was not the only potentially common underlying cause of the different cases around the Krümmel site, it is worthwhile summarising what has been investigated.

This summary is mainly based on a final report written by the chairs of two scientific expert committees looking into the cluster (Wichmann and Greiser, 2004), but analyses done outside the work of these groups are considered as well. These analyses were either not included in the committees' working programme or were additional evaluations, a few of which were initiated by the responsible ministry of the federal state of Schleswig-Holstein after the end of the committees' work; however, the results were never published. The authors have obtained these unpublished results, because they were either chairing one of the committees (EW), or a member of one of them (BG), or as initiating and supervising analyses (BH). Nonetheless, the authors are aware that they might have missed one or two of the analyses, but this is unlikely to have had a major impact.

Setting

The Krümmel nuclear power plant (KKK[1]) is located in the federal state of Schleswig-Holstein on the north bank of the Elbe River in the eastern part of the city of Geesthacht, approximately 17 kilometres from the city limits of Hamburg, which is downstream to the west. Close to the plant is the GKSS[2] nuclear research centre (see Figure 1). To the north is a hilly region, and on the opposite side of the river is

[1] KKK is the official abbreviation for the power plant and stands for Kernkraftwerk Krümmel
[2] GKSS is the official abbreviation of the research centre and stands for its old name: Gesellschaft für Kernenergieverwertung in Schiffbau und Schiffahrt. Today, it is part of the Helmholtz Centre Geesthacht for Materials and Coastal Research.

an agricultural marsh area with a number of small communities, three of which form the joint community of Elbmarsch, i.e. Drage (including the villages of Drage, Drennhausen, Elbstorf, Hunden, Schwinde, and Stove), Marschacht (including Eichholz, Niedermarschacht, Obermarschacht, Olderhausen, and Rönne), and Tespe (including Tespe, Avendorf, and Bütlingen). While the area north of the Elbe is part of the federal state of Schleswig-Holstein, the area south of the river belongs to the federal state of Lower Saxony.

Figure 1 shows the city of Geesthacht with the urban districts Krümmel and Tesperhude north of the Elbe River; while south of the Elbe River lies the joint community of Elbmarsch. The villages of Drage, Rönne, Stove, Schwinde, and Avendorf are outside the 5 km ring around the KKK. All cases of childhood leukaemia in Elbmarsch occurred in the immediate vicinity of the river. As of 31 December 1991, Elbmarsch had a population of 1364 children (aged 0-14 years), while Geesthacht had a population of 4168 children.

The Krümmel power plant was a boiling water reactor, which started operation in 1984, and was closed down in 2011; however, the production of electricity was stopped in June 2007. Under normal operation, the radiation dose to the public was not more than 1 μSv/a for adults and not more than 2 μSv/a for infants. For the GKSS, the values were 0.1 and 0.2 μSv/a, respectively (BMU, 2002). Since 2010, the exposure to both population groups was less than 0.1 μSv/a from the KKK as well as from the GKSS (BMUB, 2012). For comparison, the annual ambient gamma radiation dose is approximately 0.6 mSv/a in this area.

The cluster

The first childhood leukaemia cases in the Krümmel cluster occurred in Elbmarsch (Dieckmann, 1992; Schmitz-Feuerhake *et al.*, 1993). Between February 1990 and

May 1991, five cases of leukaemia in children younger than 15 years of age were diagnosed. As can be seen from Table 1, a case of aplastic anaemia diagnosed in December 1989 was also considered to be part of the cluster. More leukaemia cases occurred in the following years, not only south of the Elbe River, but also north of it in the city of Geesthacht. A list of cases diagnosed between 1989 and 2003 is given in Table 1 (Wichmann and Greiser, 2004). It should be noted that in Table 1 Case No. 1 is not a leukaemia case, and Case No. 6 was older than 15 years of age at the time of diagnosis.

Even when considering the time period 1999 - 2005, the elevated risk in the 5 km area around the power plant persisted, with a standardised incidence ratio (SIR) of 2.66 [95% confidence interval (CI): 0.86;6.20] based upon five leukaemia cases compared to 1.88 expected cases (Hoffmann *et al.*, 2007). In all cases, SIRs were calculated based on mean national rates taken from data of the German Childhood Cancer Registry (GCCR) (Kaatsch *et al.*, 1995).

Committees investigating possible risk factors

Several committees and expert groups triggered investigations into possible underlying common causes of this continuous elevated risk. These were the following: Leukaemia Expert Committee of Lower Saxony, 1990 – 2004; Leukaemia Expert Committee of Schleswig-Holstein, 1992 – 2004; Working Group Exposure Indicators, Lower Saxony, 1993 – 2004; Working Group Tritium, Schleswig-Holstein; Committee of Scientific Civil Servants.

In addition, there was a round table in Elbmarsch and a very active citizens' initiative. The Chairs of the Lower Saxonian Expert Committee and the Working Group Exposure Indicators published a joint final report, which is the major basis for this review (Wichmann and Greiser, 2004).

Investigative approach

To structure the investigations into a possible underlying common risk factor, all known and suspected risk factors for childhood leukaemia were listed. In a second step, whether these factors could play a role in Elbmarsch was analysed. This was done using five major lines of questioning with 16 overall topics as listed in Table 2.

Possible risk factors investigated

This section does not follow the order of the topics given in Table 2 but is subdivided into three parts: investigations related to radiation (in more detail) and to other risk factors (more briefly) as defined by the investigative approach, and finally epidemiological studies. Whenever possible, references for respective publications are given, but in many cases results are only mentioned in the detailed final report (Wichmann and Greiser, 2004[3]) or results were reported only to the government of Schleswig-Holstein.

Investigations related to radiation

One of the earliest reports on the cluster was a letter in The Lancet giving results indicative of increased radiation exposure from analysis of biological samples from adults living in Elbmarsch (Schmitz-Feuerhake *et al.*, 1993). In this study, the number of dicentric chromosomes in peripheral lymphocytes in five mothers or fathers of children with leukaemia and in five other adult residents in the region was investigated. Potential risk factors such as exposure to X-rays and chemicals and previous diseases were evaluated. This was done by questionnaires and by investigating the environment. In addition, 15 controls (aged 17-44 years) who lived

[3] An abridgement of the report – in German – can be downloaded from http://www.ms.niedersachsen.de/download/9232/Abschlussbericht_2004_Kurzfassung_.pdf

in Bremen, about 100 km west from Elbmarsch, were studied. In this non-blinded analysis, the inhabitants of Elbmarsch showed a statistically significant increase in dicentric chromosomes when compared with the controls.

These results prompted a larger blinded study that included 30 children from Elbmarsch and 30 children from a control area (district of Plön, almost 100 km north of the Krümmel site). Because of the observation that the leukaemia cases occurred almost entirely in families using home-grown or local food, 12 more children from Elbmarsch families having the same habit were included. Results were not indicative of an increased number of dicentrics in children from Elbmarsch, neither in general nor from those families using home-grown or local food (Bruske-Hohlfeld *et al.*, 2001). Since the exposure might have happened too long ago to be detectable by unstable dicentric aberrations because of the rapid turn-over in peripheric lymphocytes in children and since there was a further study of adults, which included 21 individuals from Elbmarsch and 25 from Bremen, indicative of an increased number of dicentric aberrations (Schmitz-Feuerhake *et al.*, 1997), the same approach that was used for the children was repeated with women as the study population. This analysis included 30 women from Elbmarsch and 30 women from the district of Plön. Again, the number of dicentric aberrations for women in Elbmarsch was not higher than for those in Plön (Wichmann and Greiser, 2004).

Radioactive releases and subsequent exposure of the public from the two plants (KKK, GKSS) were considered in detail. The releases from both were well below the German standards (see above). The highest exposure to an individual was estimated to be 1 mSv/a when living at the fence of the KKK for an entire year. On the other side of the river, i.e. in Elbmarsch, the dose rate from direct exposure was too low to be detected. There were no radiologically relevant incidents at the KKK and only one at the GKSS, in 1983: the release of 1700 MBq I-131 (half-live, 8 days), which exceeded the annual limits by a factor of 4.6. Radioactive releases from this incident could not be responsible for the occurrence of the cluster, because it happened when 11 of the 14 leukaemia cases observed since 1989 were not yet born. Undetected incidents from the KKK leading to large exposures could be ruled out, as could possible diffuse radioactive discharges (including noble gases) via unplanned pathways (Angelieff *et al.*, 1994).

Analyses of the soil in Elbmarsch were not indicative for an unusual alpha activity, overall activity, or gamma ambient dose rate. There was a report (ARGE Pham, 2002) of a probable increased content of enriched uranium, transuranic elements, atypical proportions of plutonium isotopes, increased tritium content, and radioactive PAC[4] particles in the soil, which could not be verified (SSK, 2003).

There was another report on transuranic elements in dust found in the attics of five of six old houses investigated (Schmitz-Feuerhake *et al.*, 2003). A further 24 samples were taken in Elbmarsch and, for comparison reasons, also in other parts of Schleswig-Holstein. The concentration of transuranic elements in Elbmarsch was not higher than in the comparison settlements (Wichmann and Greiser, 2004).

The tritium concentration in drinking water could have been affected by the liquid discharges from KKK and GKSS, but the respective doses were radiologically irrelevant (< 0.1 µSv/a). Autoradiographic images from discs taken from trees in Elbmarsch showed a blackening that might have resulted from artificial radionuclides. Radiochemical analyses of trees that were cut in Elbmarsch close to the river banks showed slightly elevated tritium and carbon-14 concentrations. For comparison reasons, discs were taken from an area in Lower Saxony (district of Celle) which was far away from any nuclear facility. Analyses were done using tree rings. The fallout

[4] PAC stands for sphere-pac, nuclear fuel beads, used in nuclear fusion research that was postulated for GKSS

from the atmospheric bomb testing and from Chernobyl – though relatively low in Northern Germany and lower than that from the bomb testing – were clearly seen. But there was no indication of an additional radiation burden after the start of the KKK, and there was no difference between Elbmarsch and the Lower Saxony comparison area.

To see whether there was an increased strontium (Sr-90) or caesium (Cs-134 and Cs-137) burden in cows, a vertebra, a rib bone, and a long bone taken from a cow grazing in Elbmarsch and another one from a more distant area (district of Lüchow-Dannenberg, some 50 km to the south-east, upstream the Elbe river) were analysed. The Sr-90 burden in the cow from the distant area was about twice as high as from Elbmarsch, but in both cases values were very low and lower than the value found in a long bone from deer from the Harz Mountains, which are around 150-160 km south of Elbmarsch. The caesium burden in cow´s milk was tested in five samples in 1991. The content was close to the detection limit.

Possible exposure from incorporated radionuclides was analysed for 5 people from Elbmarsch and 7 from Hamburg. The burden of incorporated long-lived gamma emitters was analysed in a whole-body counter, that of tritium and C-14 by urine samples. There were no differences. The caesium burden in six samples of breast milk from Elbmarsch was close to the detection limit.

Radon measurements were taken in the utility rooms, the kitchens, the living rooms, and the bedrooms of five houses in Elbmarsch. In all houses except one, the average annual concentration was below 100 Bq/m³. In two rooms of an older house, 610 Bq/m³ were measured. There was no cellar below these rooms, and the floor was wooden.

One of the children with leukaemia had undergone frequent X-rays because of a disease that had nothing to do with the blood forming organs. One mother had a dental X-ray during pregnancy, one father was working at the KKK, but he was not occupationally exposed to radiation.

Investigations related to other risk factors

Indoor measurements of organic solvents, particularly benzene, in the houses of the diseased children didn't show any increased values. The same was found for the benzene concentration in outdoor air.

There were no underlying common medical risk factors. One child was treated with a cytostatic drug before the leukaemia occurred. The other children didn't have any medication or treatment which could be linked to the development of leukaemia.

Although there is no clear indication that animal viruses may induce leukaemia, this hypothetical question nevertheless was investigated. None of the children's pets or other animals in their environment suffered from a leukaemia-like disease. An analysis of all case children from Elbmarsch who were treated in Hamburg was not indicative for a common infectious viral cause of the diseases.

None of the analyses regarding the other factors as listed in Table 2 were indicative of a common underlying cause of the diseases.

Epidemiological studies

Based on data from the German Childhood Cancer Registry (GCCR) and from the cancer registry of the former German Democratic Republic (GDR), it was investigated whether there were other areas upstream along the Elbe River with an increased number of childhood leukaemia cases. This could be indicative of relevant pollutants carried by the river. For former Western Germany, it was shown at a community level that this was not the case. An inquiry at the GDR cancer registry showed that the same was so for the former GDR at the district level; data were not available at the community level.

There was no indication of an increase in the prevalence of congenital malformations that paralleled the increased incidence of childhood leukaemia. The prevalence rate of congenital malformations was stable over the observation period, based upon small numbers.

For the entire population of Elbmarsch, the age-standardised mortality rate was analysed for 1982-1992. For the entire period, there was no increased rate. However, it was significantly elevated in 1986 and 1988, but the rate was lower than expected in 1985, 1990, and 1992. The variation of the mortality rate was considered to be due to the small number of deaths in each year.

A case-control study on potential risk factors for childhood leukaemia was conducted in the whole federal state of Lower Saxony, including 741 individuals: cases diagnosed between 1988 and 1993, and two matched population controls plus one matched tumour control (Kaatsch *et al.*, 1996). The most important results are as follows: the "Greaves hypothesis" saying an untrained immune system increases the leukaemia risk, was supported based on the questionnaire data; the data did not show a significant association between vitamin K prophylaxis and leukaemia or tumours; measurements of electromagnetic fields showed a weak association between high-level exposure and an increased risk of developing leukaemia; frequent exposure to X-rays and intensive care treatment were associated with the occurrence of leukaemia, but the number of these patients was very small; the only potential job-related hazard was paternal exposure to plastic and resin fumes; the incidence of miscarriages and abortions was increased in mothers of children with leukaemia; the study did not confirm the hypotheses that leukaemia is associated with gestational age, with the consumption of alcohol, nicotine, and medications during pregnancy; nor was any association detected concerning exposure to wood preservatives and insecticides or a high socio-economic status. With respect to the leukaemia cluster, the study was too small to find any yet unknown risk factors that could have potentially contributed to the occurrence of the cluster. Nonetheless, it was the basis for a larger nationwide study (Kaatsch *et al.*, 1998).

Later, another large case-control study in the vicinity of all German nuclear power plants was conducted (Kaatsch *et al.*, 2008a; Spix *et al.*, 2008) which included all childhood leukaemia cases below the age of 5 years diagnosed between 1980 and 2003. Using this data set for a dichotomous analysis (5 km vicinity vs. outside 5 km), a statistically significant odds ratio of 2.19 for all nuclear power plants was revealed. Altogether, 30 children under the age of 5 years from the study area around the KKK were included. The result of the dichotomous analysis with the cut-point at 5 km changed only a little if these 30 cases were left out, with an odds ratio of 1.96 that was still statistically significant (Kaatsch *et al.*, 2008b).

Because of the close vicinity of the Elbmarsch cluster to the KKK and GKSS reactors, the question as to whether there is an increased incidence of malignant haematopoietic disorders amongst the general population, and not only in children, was tested. To this end, a retrospective incidence study was conducted (Hoffmann and Greiser, 1994). A study area was defined consisting of 5-km rings around the nuclear sites, covering overall an area with a 15-km radius. The study period comprised the ten years between 1984 and 1993. In 1993, the entire population was about 524,000. The study included 1985 cases of leukaemia, lymphoma, or myeloma. Overall no elevated risk was found. However, when looking at subgroups, some associations were detected: within 5 km, the incidence was significantly elevated by 56% among males. Taking only people below 65 years of age into account, the increase was also significant for females. There was no trend with distance, and while the increase in childhood leukaemia in the early 1990s occurred in Elbmarsch, the increase among adult males occurred in Geesthacht. For females, results for geographical trends were inconspicuous both in Geesthacht and in Elbmarsch.

Because of these results and because of a possible leukaemia cluster further down the Elbe River (Raspe *et al.*, 1996), a large case-control study was conducted known as the Northern German Leukaemia and Lymphoma Study (NLL), which covered the area around the KKK and GKSS as well as areas downstream from the Elbe River: the districts of Lauenburg, Steinburg (its southern parts), Stormarn (its southern parts) and Pinneberg in Schleswig-Holstein, and Harburg and Lüneburg in Lower Saxony (Hoffmann *et al.*, 2008). The study period comprised the years of 1986 through 1996 (retrospective incidence) and 1997-1998 (prospective incidence). For each case two controls were individually matched by year of birth (+/- 2 years), sex, and region. Interviews were conducted for 1430 cases and 3041 controls. Considered risk factors included ionising radiation, electro-magnetic fields, pesticides, and others. There was no indication that the discharges from routine operation of either of the two reactors were correlated with the risk of developing any of the diseases under study (Hoffmann *et al.*, 2003). A sensitivity analysis investigated whether there is an indication of a systematic change in risk (among adults) over time or whether there is a risk peak in a certain time window in areas close to the nuclear sites. This was not the case, and thus these analyses did not lead to a change in the overall results (Weitmann *et al.*, 2005).

Based on data from the Geesthacht birth registry, the hypothesis of a possible change in the sex ratio towards a larger proportion of girls at birth (see Van Larebeke *et al.*, 2013) was tested but could not be verified.

Development of the incidence rates in the last 25 years

The work of the different committees stopped in 2004, and after 2005 (Hoffmann *et al.*, 2007) incidence rates were no longer reported to the scientific community. Based on data from the GCCR for those aged 0-14 years and applying a standard approach for the analysis of incidence rates in small regional areas, i.e. a 10-year average (Kaatsch *et al.*, 1997), the GCCR performed corresponding analyses. GCCR pooled the two communities, Geesthacht and Elbmarsch (i.e. Drage, Marschacht, and Tespe), as all the leukaemia cases around the KKK lived there at time of diagnosis. Table 3 and Figure 2 show the resulting sliding 10-year average SIRs and 95% confidence limits for 1990-1999 through to 2007-2016. The SIRs are generally elevated, but in the most recent years the SIRs became comparable with expected values. The point of whether reduced numbers appear to be related to the end of electricity production in KKK is dealt with in the discussion section.

Data from the GCCR only go back to 1980. Thus, there is no possibility to look at the SIR for a 10-year time period previous to the occurrence of the cluster.

Discussion

A range of studies, including environmental monitoring and biomonitoring as well as large epidemiological studies were conducted in an attempt to find underlying common risk factors for the cluster of childhood leukaemia near the Krümmel nuclear power station. None of these studies could find a plausible explanation for the increased incidence, neither when looking at radiation-related factors (ionising and non-ionising radiation) nor when looking at other risk factors. Some of the investigations might seem to be somewhat limited because of small size; but in every case the plan was to get a first impression, and if results were suggestive for relevant contamination or exposure larger studies followed. Overall, the final report of two Lower Saxonian committees concluded, that – considering the results from radiological measurements, of biological dosimetry in children and women, and of the large and well conducted Northern German Leukaemia and Lymphoma Study (NLL) – there is no convincing evidence that the cluster was induced by routine or accidental radioactive discharges from the plants (Wichmann and Greiser, 2004).

A further epidemiological comparison which was based on the hypothesis that tritium exposures might be an explanation for the cluster was conducted outside the research programme. It compared the incidence rate around the KKK with that around the Savannah River Site (SRS) in the USA, because both sites discharged relatively large amounts of tritium. Although the discharges from the SRS exceeded those from the KKK by several orders of magnitude, there was no increased incidence near the SRS (41 observed cases compared to 49.6 expected). The authors concluded that the apparent excess leukaemia risk near the Krümmel plant is probably not associated with tritium exposure (Grosche *et al.*, 1999).

There was also no indication that other pollutants not related to radiation might be a common underlying reason for the cluster. The same applied to the medical anamneses of the diseased children, including indications for an infectious aetiology, as was – among other possible risk factors – suggested for a cluster in Fallon (Steinmaus et al., 2004; Pritsos and Walker, 2012; Francis et al., 2012)).

Rural population mixing was suggested by Kinlen as an explanation for the clustering of childhood leukaemia (Kinlen, 2011; Kinlen, 2012). Though Elbmarsch is not as remote as Seacale or the north of Scotland, two areas which were important for further developing this hypothesis (Kinlen, 1993; Kinlen *et al.*, 1993), a constant population influx to both Geesthacht and Elbmarsch could be observed at least from 1975 onwards, and still continues, because commuters to Hamburg moved to the area. Thus, population mixing could be a hypothetical explanation. From 1975 to 2015, the population growth happened almost in parallel in both communities and was almost of the same size in absolute numbers (percentage given in brackets): 5285 (21%) and 5496 (80%), in Geesthacht and Elbmarsch, respectively. A recent cohort study from Switzerland showed that population mixing may have an influence on the risk of childhood leukaemia

(Lupatsch *et al.*, 2016), while a case-control study from Finland didn't find any evidence that childhood leukaemia risk is related to population mobility (Jarvela *et al.*, 2016), although there was a suggestive result of a reduced risk with residential mobility at ages 1–2 years. In his reply to Jarvela *et al.* (2016) Kinlen pointed out that the population mixing conditions in Finland do not allow to test Kinlen's hypothesis, because there is no marked influx into a remote rural area (Kinlen 2016), which also applies to the Krümmel cluster. Thus, with respect to the cluster near the Krümmel site, we consider it unlikely that the constant population growth in the study regions would lead to a temporarily limited risk excess.

The Krümmel nuclear power plant started operation in 1984 and was closed down in 2011, but the production of electricity was stopped already in June 2007. The first leukaemia case in the evolving cluster was born in 1986 and diagnosed in 1990 (see Table 1), i.e. two years and six years after the power plant's start, respectively. Based on sliding 10-year intervals, the highest SIR was observed during the period 1990-1999, and overall significantly elevated SIRs were observed only for two further ten-year periods, i.e. 1994-2003 and 1995-2004 (Table 3).

It has been discussed if there might be conceptual limitations in controlling immission from nuclear power stations in Germany (Schmitz-Feuerhake *et al.,* 2005). Even if that would be the case, the doses to the public were far too small to explain the appearance of the Krümmel cluster (Angelieff et al., 1994; Wichman and Greiser, 2004). The doses that would have been necessary to induce the early cases of the cluster were estimated by the members of the Working Group Exposure Indicators to be 50-100 mSv (Wichman and Greiser, 2004).

From 1990 to 2003, 13 childhood leukaemias occurred within a 5 km distance of KKK (see Table 1). During an extended observation period from 1990 to 2007 and in the slightly larger area of the combined communities of Elbmarsch and Geesthacht, 16 leukaemia cases were recorded in the GCCR (deducible from Table 3), giving an average of 0.9 diagnoses per year compared to 0.3 expected cases. Since the plant stopped electricity production in July 2007 until December 2015, 2 leukaemia cases were observed in 8.5 years, giving an average of 0.2 cases per year. When considering radiation exposure from the KKK and GKSS, there was almost no change over time, and the exposure was too low to explain the occurrence of the cluster, as noted above. A case-control study from France (Sermage-Faure *et al.*, 2012) of childhood leukaemia near nuclear installations found almost the same result as was found in the German study (Kaatsch *et al.*, 2008b), i.e. a twofold increase of the risk for those below the age of 5 years in the 5 km zone around nuclear sites. The French study could also use estimates for red bone marrow doses, using factors such as wind direction. When taking this into account, the odds ratio was 1.0 with no elevated risk (Sermage-Faure *et al.*, 2012), which is an indication that non-radiation factors are involved.

Another explanation for the Krümmel cluster is chance or currently unknown causes. Little is known about the causes of childhood leukaemia, although strong investigative efforts have been made. Portier (2008) estimated that approximately only 10% of all childhood leukaemia cases can be explained by known risk factors. Based on the small extent of current knowledge, the increased incidence of childhood leukaemia near nuclear reactors or the appearance of clusters in their vicinity – as reported in some studies – have to be considered as unexplained events. To overcome the problem of unexplained events and to learn more about the causes and pathogenesis of childhood leukaemia, large international and interdisciplinary research programmes would be needed, a focus of which should be gene-environment interaction (e.g., Vijayakrishnan *et al.*, 2017). Possible topics of such interdisciplinary studies and their interrelationship were defined in two international workshops (Laurier *et al.*, 2014; Ziegelberger *et al.*, 2011). Like most of the known leukaemia clusters, such as the notable cluster of Fallon, NV, away from any nuclear installation, the Krümmel cluster has to be considered as unexplained.

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Table 1: Children (<15 years) (and one young adult aged 21 years) with leukaemia in the Krümmel cluster, 5 km radius circle* around the KKK, diagnosed 1989 – 2003 (Wichmann and Greiser, 2004)

Case number	Year of birth	Sex	Residence	Diagnosis	Date of diagnosis
1	1982	F	Elbmarsch	Aplastic anaemia	12/89
2	1986	F	Elbmarsch	c-ALL	02/90
3	1981	M	Elbmarsch	c-ALL	03/90
4	1981	M	Elbmarsch	AML	04/90
5	1989	F	Elbmarsch	c-ALL	01/91
6	1970	M	Elbmarsch	AML	04/91
7	1988	M	Geesthacht	c-ALL	05/91
8	1993	M	Geesthacht	AML	09/94
9	1984	M	Elbmarsch	ALL	07/95
10	1991	M	Geesthacht	ALL	08/95
11	1993	M	Geesthacht	ALL	06/96
12	1998	F	Elbmarsch	ALL	08/01
13	1991	M	Geesthacht	ALL	10/02
14	1999	M	Geesthacht	ALL	03/03
15	2001	M	Elbmarsch	ALL	06/03

*) Two villages of Elbmarsch (Drage and Schwinde) are about 6 km away from the KKK

ALL – acute lymphoblastic leukaemia; c-ALL – common ALL; AML – acute myeloblastic leukaemia

Table 2: Questions and topics of the Elbmarsch investigation programme (Wichmann and Greiser, 2004)

Question	Topic
Is the cluster caused by the Elbe river?	1. Search for other leukaemia clusters along the river
	2. Measurement of pollutants in aerosols near a barrage
	3. Toxicological assessment of the pollutants load of the Elbe water
	4. Measurement of pollutants in the milk of cows grazing in floodplains
	5. Environmental burden because of using river sediments for dyke construction
Are there peculiarities with respect to local environmental sources?	6. Ionising radiation (reactors, Chernobyl)
	7. Electro-magnetic fields (antennas, power lines)
	8. Chemical pollutants from industrial activities
	9. Polluted sites or polluted playgrounds
Are there particular risk factors in the homes?	10. High indoor concentrations of radon or solvents

	11. Concentration of heavy metals, organic chlorine compounds in mother's milk
	12. Peculiarities of home-grown vegetables (use of fertilizers, fungicides, pesticides, polluted water)
	13. Pesticides against insects and rodents
Are there specific indicators for medical risks?	14. Antibodies of leukaemogenic viruses
	15. Effect monitoring of radiation therapy (biological dosimetry)
Is the cluster caused by drinking water?	16. Tap water contaminated by fungicides or from polluted sites

Table 3: Observed and expected number of leukaemia cases in the two communities of Elbmarsch and Geesthacht in ten-year intervals, 1990-2016, age < 15 years (data from the German Childhood Cancer Registry)

Time interval	Observed	Expected	SIR	95% CI
1990-1999	9	2.7	3.4	(1.5-6.4)
1991-2000	6	2.7	2.2	(0.8-4.8)
1992-2001	5	2.8	1.8	(0.6-4.2)
1993-2002	6	2.8	2.2	(0.8-4.7)
1994-2003	8	2.8	2.8	(1.2-5.6)
1995-2004	8	2.9	2.8	(1.2-5.5)
1996-2005	7	2.9	2.4	(0.97-5.0)
1997-2006	7	2.9	2.4	(0.96-4.9)
1998-2007	7	2.9	2.4	(0.97-5.0)
1999-2008	7	2.9	2.4	(0.96-4.9)
2000-2009	7	2.9	2.4	(0.97-5.0)
2001-2010	7	2.9	2.4	(0.98-5.0)
2002-2011	7	2.8	2.5	(0.99-5.1)
2003-2012	6	2.8	2.1	(0.8-4.7)
2004-2013	4	2.8	1.5	(0.4-3.7)
2005-2014	3	2.7	1.1	(0.2-3.2)
2006-2015	3	2.7	1.1	(0.2-3.3)
2007-2016*	3	2.6	1.1	(0.2-3.3)

[*] the expected number of cases and the SIR, 95% CI are preliminary because the population numbers for 2016 are not available yet and were projected for this analysis

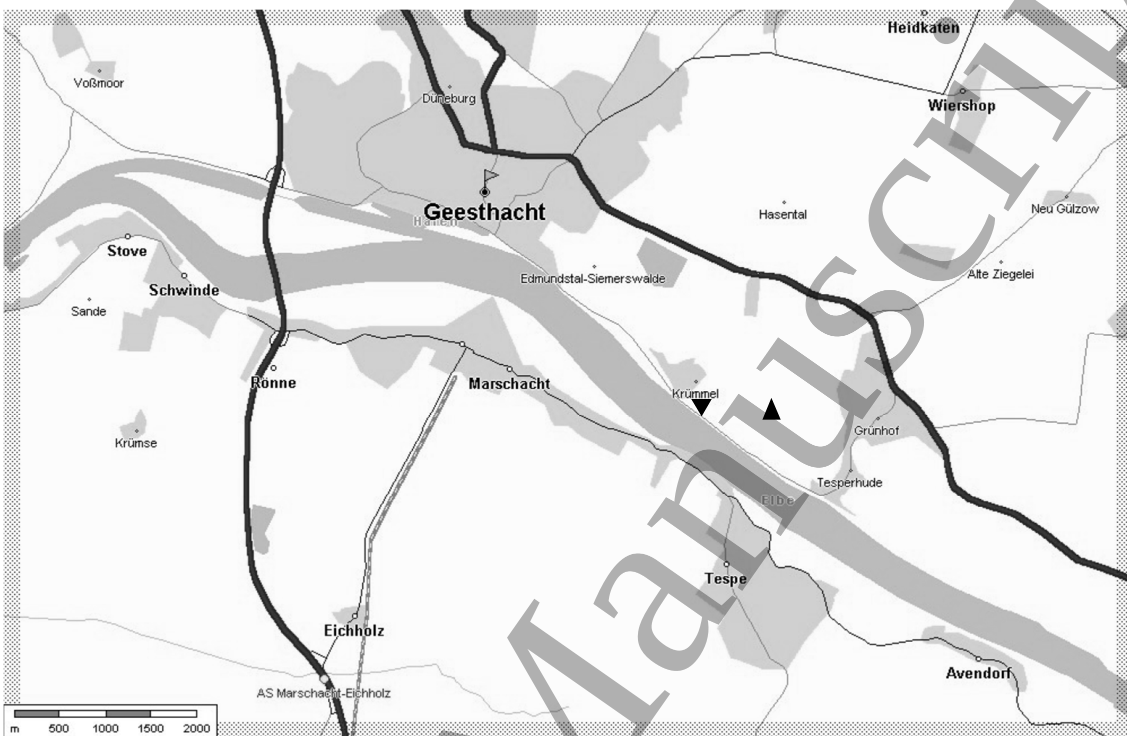

Figure 1: Map of the area in which 14 childhood leukaemia cases were diagnosed in the period 1989 – 2001. The KKK nuclear power plant is located in Krümmel (▼). The Nuclear Research Centre GKSS (▲) is located 1 km east of Krümmel (adopted from (Wichmann and Greiser, 2004))

The City of Geesthacht, with the districts Krümmel and Tesperhude, is situated north of the Elbe River. The joint community of Elbmarsch is situated south of the Elbe River. The following districts of Elbmarsch form a “street village”: Tespe and Marschacht within a 5 km distance from the KKK, and outside the 5 km ring Avendorf, Ronne, Schwinde, Stove, and Drage (3.5 km west of Stove, not on the map)

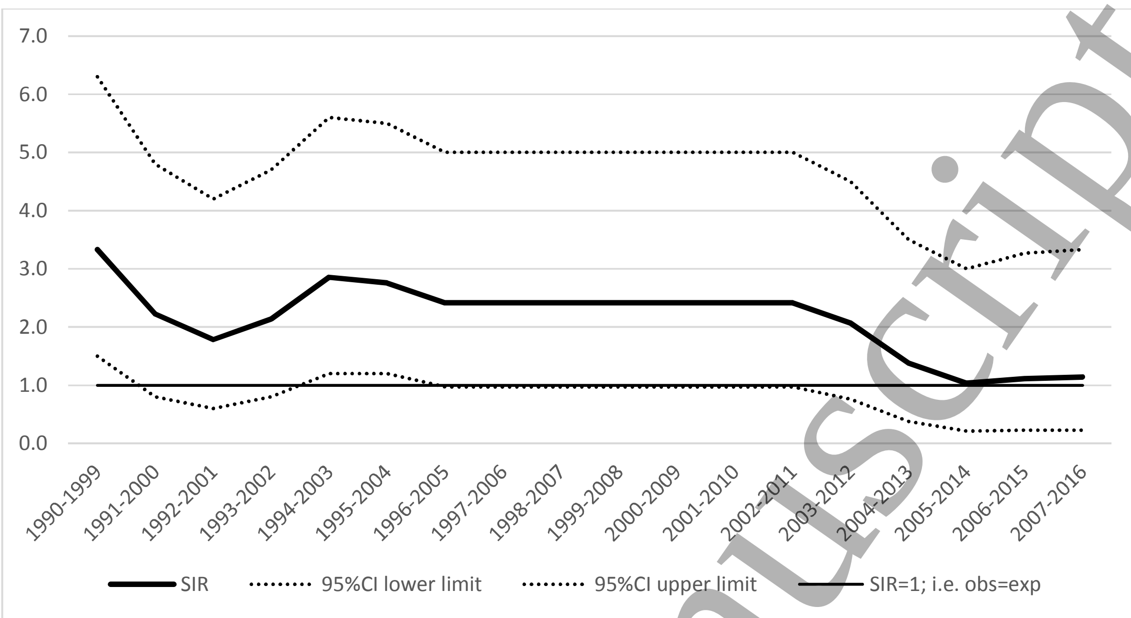

Figure 2: Sliding ten-year SIRs for childhood leukaemia (2 communities: Geesthacht and Elbmarsch) with 95% confidence limits, 1990 - 2016, age < 15 years