Review and Discussion of Epidemiologic Evidence for Childhood Leukemia Clusters in Germany

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Abstract

Increased incidence of childhood leukemia in small geographical areas have in several instances raised concern with respect to possible environmental exposures. In many, but not all of these, clusters were somehow associated with nuclear installations. In Germany the first reports on so-called „clusters" of leukemia in the vicinity of nuclear installations date back to 1987. A spatial/temporal analysis of the distribution of leukemia cases among children and young adults in the Federal State of Bavaria revealed elevated incidences in the vicinity of two nuclear research reactors.

In 1988, increased mortality among children due to malignant tumors (ICD-9 140-200) and leukemias and malignant lymphomas (ICD 200-209) was observed in a county adjacent to the nuclear boiling water reactor Lingen. In the same year, a significantly increased incidence of childhood leukemia was again reported in a circular region of 20 km around the nuclear reactor Würgassen (study period 1980-1987).

Descriptive epidemiology confirmed an excess of childhood and juvenile leukemia around a uranium processing plant near Ellweiler, Rhineland-Palatinate. Between 1970 and 1989 7 cases were observed (2.27 expected) in a circular region of 5 km around the plant. Drinking water contamination with Radium-226 and other radionuclides was hypothesized as an exposure pathway which could explain at least part of the observed excess of leukemia.

Increased incidences were also observed in the vicinity of two East German facilities. Results, however, were based on small numbers. A nationwide incidence study published in 1992 revealed a statistically significant 3fold excess of acute leukemia in children below age 5 in the 5-km regions around all 22 West-German nuclear power plants (compared with individually matched control regions).

In 1991, an expert committee was established by State authorities to investigate into possible causes after a geographical cluster of childhood and juvenile leukemias in the small rural commune of Sittensen had generated considerable attention and media coverage (6 observed, 0.49 expected between 1985-1990). An exhaustive array of potential environmental exposures was screened intensively but no environmental clue toward causation of the cluster could be established. Semi-structured interviews later revealed unusually high exposures to diagnostic radiation in 4 of the leukemia cases.

Recently, a striking cluster of childhood leukemias was observed in the immediate vicinity of the nuclear boiling water reactor Krümmel in northern Germany. The excess of 7 cases since 1990 (the latest case was diagnosed in July 1996) is hitherto unprecedented in both its spatial and temporal dimension. The discussion as to any possible impact of radioactive releases from the plant is ongoing.

So far, results in Germany have been more often positive than negative though observed excesses are quantitatively not compatible with permissible levels of radioactive releases. This, however, does not necessarily exclude a causal role of ionizing radiation because (1) Radioactive releases could have escaped environmental surveillance or (2) standard procedures of radiation risk as-

sessment might not be applicable to the situation in the vicinity of nuclear installations. Finally vicinity to nuclear plants could be associated with other, hitherto undetected risk factors which alone, or in combination with radioactive releases, could increase leukemia risk.

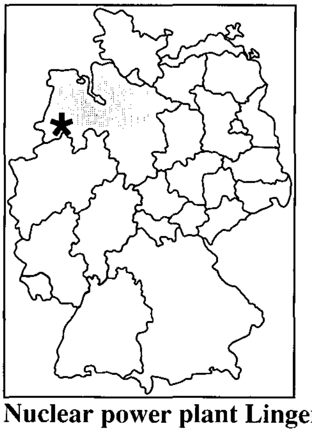
Introduction

„Cluster analysis" in a purely ecological sense is the crudest of all methodological approaches to study environmental determinants of disease. However, in the absence of better options, ecological studies may still be used as a comparatively fast and economic way which can serve as a first step in the evaluation of an epidemiologic problem - particularly with respect to the generation of hypotheses which can be tested in subsequent analytical studies [1-3]. In the literature cluster analyses have in several cases given rise to, and often significantly facilitated, the identification of environmental, occupational, and medical hazards [4-8].

The epidemiologic discussion about possible adverse health effects of nuclear power plants in normal operation today is almost exclusively based on results of cluster analyses in the sense of geographical incidence or mortality studies around a putative „point source". This methodological approach has been recommended by health authorities in the US as a first step in the epdemiologic evaluation of any perceived disease cluster, particularly of chronic diseases (mostly cancers) due to its high efficiency to eliminate „false positives" at an early stage of the evaluation [8-12]. Moreover, both positive and negative results are easy to communicate to the public since using distance as a proxy for exposure (all too) readily meets lay conceptions of environmental disease causation [12-15].

This review will focus on examples of ecological approaches to childhood leukemia clusters in Germany, considering both the areas of former East and West Germany. Investigations and results will be presented mainly in historical order. Most but not all of the examples concern geographical incidence studies in the vicinity of nuclear installations. Some of the material presented herein has never been published before or is hard to access in the international scientific literature. Original data will therefore be provided wherever possible together with a brief account of the background and significance of each of the investigations.

Some of the studies and results presented in this review are clearly anecdotal and should be so regarded. Completeness with respect to studies related to nuclear facilities in Germany is intended, however, cannot be guaranteed. Examples presented are listed in Tab. 1.



Nuclear power plant Lingen, Lower Saxony

The 268 MW (electric) boiling water reactor Lingen/Ems (Federal State of Lower Saxony) was commissioned in 1968 as one of Germany's first atomic power plants. Operation was terminated in 1977. Early on the reactor had been a focus of anti nuclear protest in Germany [16], mainly due to its radioactive emissions which were among the highest of all German nuclear power plants. Concerns about potential adverse health effects, however, were investigated by laymen and several reseachers with varying degrees of scientific accuracy. In 1980, the Ministry for Social Affairs of the Federal State of Lower Saxony conducted a mortality analysis for all counties of Lower Saxony for all malignancies (ICD9 140-199) and haematolymphopoietic malignancies (ICD9 200-209) including the leukemias (ICD9 204-208), respectively. In a global comparison of counties with and without nuclear installations, no statistically significant difference was found (period 1970-1977). A major critique concerned differential misclassification of the geographical units. Counties were labelled „exposed" irrespective of the year of the first criticality of their respective facility [17]. For example, the nuclear power plants Würgassen and Brunsbüttel were commissioned in 1972, and the nuclear power plant Unterweser even only after the study period (1978) but their counties of location were nevertheless classified „exposed".

Methods: Stein (1988) focused on the nuclear power plant Lingen, but attempted a more comprehensive approach using routine data for childhood cancer mortality, perinatal mortality and stillbirths in a geographical analysis with respect to time and distance from the plant [17] (Fig. 1).

Results: In one of the two counties closest to the reactor (Bentheim) only one leukemia death in a child below 15 years had occured in each of the years 1968 and 1969. In 1970 8 deaths were counted (2.3 expected, SMR 3.5, p<0.01). 3 of the deceased children were less than one year old (0.43 exp., SMR=7, p<0.01). The SMR for childhood malignancies in the other county (Emsland) was above 1.26 (95%CI 0.69; 2.14) in the period 1968-1969 and 1.10 (95%CI 0.69; 1.64) in the period 1970-1973. A similar pattern was observed with respect to perinatal mortality. In the county Bentheim rates were lower than German average before 1970, but markedly higher in the years 1970-1979. In Emsland county rates used to be higher than German average already before 1968, and plateaued only after 1976. Stillbirth rates peaked in 1969 in both counties, declined markedly in subsequent years and reached German average between 1976-1978 (Fig. 1). Unfortunately, since this analysis was based on routine mortality data, geographical resolution was restricted to the county level. As a consequence, the exact distance of the cases' residences to the plant is unknown, but could be up to about 100 km. The fact that no information exists about the situation in the direct vicinity of the plant not only precludes any meaningful etiological interpretation, but also any direct comparison with the findings around other plants in Germany.

The authors discuss their ecological findings with respect to the temporal distribution of radioactive emissions of the plant. In 1969/1970, released activities were highest throughout the operation of the reactor ($6 \cdot 10^{15}$ Bq, predominantly noble gases). A second distinct peak occurred in 1975, when $5 \cdot 10^{10}$ Bq Iodine-131 were released (usually <1.0*1010 Bq/year; Fig. 1) [17].

Nuclear installations in Bavaria

Partly as a reaction to the discussion concerning potential health effects around the nuclear power plant Lingen/Ems, the Ministry for Development and Environmental Affairs of Bavaria (Bayerisches Staatsministerium für Landesentwicklung und Umweltfragen) in 1981 commissioned a geographical incidence study for all leukemias in the area of the Federal State of Bavaria.

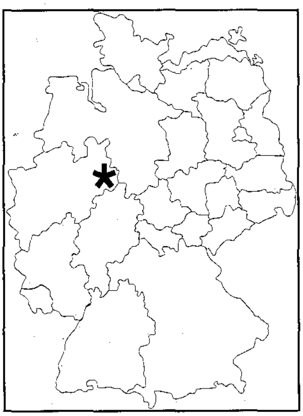
Methods: In the absence of a cancer registry in Bavaria, all incident cases in both children and adults had to be ascertained from primary sources (predominantly hospitals, some few selected practicing physicians). In order to comply with confidentiality requirements, only month and year

of birth, sex, and municipality of residence could be used in the analyses, together with the date of first diagnosis of a leukemia, the cyto-/histological diagnosis, number of recurrences, and present status of the disease. All relevant hospitals (N= 301) were contacted, but response was low (29.6 %) and, due to limited resources, could not be supplemented to any relevant extent by inclusion of physicians in private practice. As a result, ascertainment was considerably less than complete. According to the results of a previous mortality study [18] 4608 leukema cases would have been expected in the period 1976-1981. In the incidence study, however, only 2893 cases (57.8 %) could be ascertained. By comparison mortality and morbidity data from the Saarland cancer registry, where registration is close to complete, it was deduced, that under-ascertainment predominantly concerned older ages (Figg. 2, 3). Completeness seemed to be more acceptable for acute leukemias in people below 40 years (Fig. 4).
The results of this study were published in 1987 [19, 20].
Acknowledging these limitations, the authors restricted all geographical analyses to acute leukemias in persons below 40 years. Incidence in the vicinity of 6 Bavarian nuclear installations (3 commercial nuclear power plants, 1 experimental nuclear power plant, 2 research reactors; Fig. 5, Tab. 2) was compared to control regions.
Control regions were selected to match the study regions with respect to number of industries and intensity of farming (quantified as a weighed composite index including per capita area of plough-land and pasture-land, and per capita number of cattle and chicken). „Exposure" to the nuclear installations was operationalized by three geographic regions around the plants as a proxy for geographical diastance:

1. municipality of the nuclear reactor
2. all municipalities with a third or more of their respective area within a circle of 5 km around the facility (excluding the municipality where the site is located)
3. all municipalities with a third or more of their respective area within a circle of 10 km around the facility (excluding all municipalities that were included in 2.)

Standardized incidence ratios (SIR) were calculated for both sexes and the agegroups 0-14 years and 15-39 years, respectively.
Results: While the SIR was not significantly different from unity around all commercial nuclear power plants and the experimental plant, significant excesses were observed in the vicinity of both research reactors.
In the 5 km-region around the research reactor Garching SIR of acute leukemias in males below 15 years was 7.83 ($p<0.05$). The SIR was not significantly different from unity for males below age 15 in both the site municipality and the 10 km-region, and in all regions for males aged 15-39, and females of both age groups. Due to confidentiality constraints, the respective case numbers are not given in the report.
Around the research reactor Neuherberg a borderline significant increase was observed in the 10 km-region, again only for males below age 15 (SIR 1.56, $p=0.06$; based on 23 cases/91933 personyears in the site region and 143/888817 in the control regions).
Discussion: These two findings are hardly independent. The 5-10 km-region around Garching widely overlaps with the 5km-region around Neuherberg. The authors point out that both excesses are attribtable to basically the same incident cases. Hence the significant result really concerns the immediate vicinity of the research reactor Garching, which is operating since 1957 at a capacity of 4 MW (thermic). Despite its comparatively minute radioactive inventory, the reactor's releases contribute measurably to environmental contamination (Tab. 3).

The 5 km-region around Garching consists of only one municipality (Ismaning). From the published material, it can not be determined on how many cases the significantly increased SIR in Ismaning is based. Apparently incident cases were also reported from the municipality, where the reactor is located (Garching bei München). The statement of the authors, that SIR for the site municipality was not significantly different from unity is unsatisfactory in this respect - rather than the result of a statistical test it would be interesting to know whether or not the SIR was elevated in Garching as well and, if so, on how many cases this increase was based. Moreover, to be better able to interpret the ecological association the two communities should have been pooled.



Nuclear power plant Würgassen, Northrhine-Westphalia

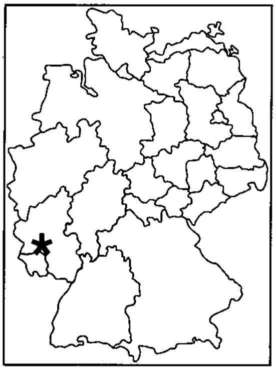
Early in 1987, a group of citizens had speculated about a potential increase of childhood and juvenile leukemia incidence in the region around the nuclear power plant Würgassen, a nuclear boiling water reactor situated some 30 km north of the town Kassel in Northrhine-Westphalia, close to the borders of the Federal States Lower Saxony and Hessen. It was put into operation in 1971 and operated until 1996 at a capacity of 640 MW(electric).

Methods: Dr. Demuth, a local pediatrician, became interested and started a systematic documentation of incident cases that were reported to him by parents, patients, citizen activists and various other sources. After one year his data were validated against the registry of childhood malignancies in the Federal Republic of Germany. Most cases were confirmed with respect to date of birth, gender, diagnosis, date of first diagnosis, postal code of residence and treating hospital or center. One child who had died in a peracute first manifestation of leukemia had not been reported to the National Registry before. Another child had previously not been reported to the pediatrician but although the registry only provided a very limited set of data, the case could later be ascertained from a local source.

Expected cases were calculated using national incidence figures provided by the registry of childhood malignancies in the Federal Republic of Germany [221, 22]. Population data wereobtained from local authorities [23]. The analyses were based on some 550,000 personyears under 15 years, and 835,000 personyears under 20 years, respectively. In Feb. 1988,. Demuth compiled all data in a first report which was circulated mainly in the region [23]. After some criticism concerning the statistical evaluation of the rates, in a revised report was issued in January 1989 [24]. Besides appropriate calculation of the p-values, the 1989 report contained two new cases who had been ascertained in the meantime (1 below age 15, 1 between ages 15 and 20). In the same year these findings were presented at a scientific symposium and subsequently appeared in the proceedings of this symposium [25].

Results: In all publications, data were shown for cumulative regions (0-10 km, 0-15 km, 0-20 km, 0-25 km; Tab. 1, 2) and distinct age-groups (0-14 years, 15-19 years). To allow for comparison with other

studies in this review, data were recalculated for mutually exclusive concentric regions and cumulative age-groups (Tab. 4).
Discussing his observations, the author hypothesizes gaseous emmissions of the plant which are released through a high chimney (overall height 70 m) and which are consequently distributed over a relatively wide area. This could explain why areas distant from the plant (say, 15-20 km) might be more exposed than the immediate vicinity (<10 km). The fact that the geographical distribution of leukemia cases within the 25 km-area around the plant seems to somewhat follow the main wind directions (as measured on the immediate compound of the plant) supports this hypothesis to some extent.
In 1993, Prindull, head of the Dept. of Pediatrics, University of Göttingen, together with Demuth and another colleague published a comprehensive incidence study including all childhood malignancies in the 25 km-region around the nuclear power plant Würgassen for the period 1980-1988 [26]. Expected values were calculated according to the national registry of childhood malignancies of the Federal Republic of Germany and to a control region which was selected a priori because of its similarity to the study region in terms of population and settlement structure, and population density. This area, the region of Groß-almerode, was also served basically by the same hospitals and treatment centers. The distance of the control region to any nuclear power plant is at least 30 km.
In the report again all analyses are presented for cumulative regions (Tab. 5,6). Population and case data given in the paper allowed for a recalculation for mutually exclusive regions only with respect to the reference region Grossalmerode (Tab. 7).
Discussion: Pooling of malignant lymphoma, Hodgkin's lymphoma and the leukemias eliminated the elevation in the 15-10 km region which had originally been observed by Demuth. Irrespective of whether Federal figures or the matched region were used as the reference incidences for all malignancies are highest in the immediate vicinity of the plant. However rate ratios in both analyses are not statistically significant different from unity. In the 0-5 km region around Würgassen, 2 cases of CNS-malignanncies were diagnosed over thestudy period (no cases in the 5-10 km region). These cases, together with the haematolymphopoietic cases explain the increased rate ratio in the innermost zone. Since in the reference region Grossalmerode, no cases of CNS tumors and of „others" occurred during the study period, rate ratios could not be calculated.



Uranium processing plant Ellweiler, Rhineland-Palatinate

Since the late 1980s, the local population around Ellweiler had been concerned that the incidence of leukemia could be increased in their region. This was attributed by some to suspected radioactive emissions from the Uranium processing plant „Gewerkschaft Brunhilde", which had been operating since the 1950s in the Steinautal near the village Ellweiler close to the border between the Federal States Rhineland-Palatinate and Saarland.
In the absence of a national epidemiological cancer registry, however, this supicion could neither be readily verified nor falsified.

Methods: To evaluate the epidemiologic situation a retrospective incidence study was conducted in 1990/1991 [27]. For the 20 years between 1970 and 1989, all incident cases of childhood malignant disease were ascertained in a circular region of 20 km around the plant. Primary data sources including all hospitals, county Departments of Health, and practicing physicians in the study area, were used exclusively. Inclusion criteria were (1) place of residence in the study area at time of first diagnosis; (2) first diagnosis of a malignant disease before age 20.

Of all cases, a limited data set containing complete birthdate, sex, place of residence, date of first diagnosis, diagnosis (in clinical terminology as well as ICD-9), and treating hospital or center (if applicable) was abstracted manually from the original records by a trained physician. All cases, for whom relevant information could not be confirmed in official documents were excluded from the analyses.

Incidence density was calculated for 4 concentric circular regions of 0-5 km, 5-10 km, 10-15 km and 15-20 km around the plant, respectively. Denominators were derived from annual sex- and 5-year-agegroup-specific population data in high geographical resolution.

Incidence densities were compared to control values derived from a reanalysis of data of the epidemiologic cancer registry of the Saarland [28] and from the German registry of childhood malignancies [22, 29], respectively. One-sided p-values were calculated under the assumption of a Poisson distribution.

Results: 28 solid tumors (11 central nervous system tumors, 4 neuroblastomas, 2 Wilm's tumors, 3 osteosarcomas, 1 Ewing's sarcoma, 2 Teratomas, 4 others), 12 malignant lymphomas (4 Hodgkin's lymphoma, 8 non-Hodgkin's lymphoma), and 38 leukemias (19 acute lymphatic, 9 acute myeloid, 1 chronic myloid, 9 others) were observed. While for solid tumors and malignant lymphoma, respectively, observed incidences were very close to the expected leukemia incidence was higher in the innermost circle around the plant (Tab. 8). For children under 15 years of age incidence density was significantly increased in the 0-5 km-region around the plant (obs. 5 cases, exp. 1.77; p= 0.034). When two additional cases between age 15 and 19 are included, incidence density further increases (7 obs., 2.27 exp.; p=0.009). Incidences were comparable to the reference in all other regions for children below 15, and in the 5-10 km-region for young adults below 20, respectively.

Discussion: Data ascertainment outside the 5-10 km-region was incomplete for young adults (15-20 years of age). In Germany children under age 15 are treated in pediatric departments exclusively, which considerably facilitates complete ascertaiment from primary data sources. Young adults, on the contrary, are often referred to Depts. of Medicine or Hematology/Oncology. Given the limited resources of this project in terms of funds and personnel it was decided to restrict complete ascertainment of 15-20 year-old cases to the two inner zones of the study area. Another incidence study was conducted in the same region by scientific staff of the national registry of childhood malignancies in the Federal Republic of Germany [30]. However, since the registry was initialized in 1980 case ascertainment was restricted to the period 1980-1988. By means of a comparison of all individual cases it was shown, that for the two innermost circles, all cases reported to the registry were identical to those ascertained independently from primary sources in the study of Hoffmann et al. for the respective period. Data for the 10-15 and 15-20 km circles were likewise confirmed. Minor differences concerned single cases or data but did not change the overall figures to any meaningful extent. The excess of cases in the 5-km-region was confirmed by the registry (4 observed, 95%CI 1.1;10.2; 1.1 expected) [30], however, due to the limited study period, the study did not provide any evidence over and above an independent validation of the completeness of Hoffmann et al.'s case ascertainment.

The ecological nature of this investigation prohibits any interpretation toward causality in the first place. However, other findings support a potential impact of the plant toward the increased leukemia incidence. Levels of background gamma-radiation in the region of the plant are among the highest in Germany which is a consequence of the high content of natural radionuclides in the subsoil [31]. The same is true for Radon-222, which, as a gaseous decay product of Radium-226, emanates from the soil. Its radioecological significance results from its potential to accumulate in buildings. It is incorporated predominantly through inhalation, causing mainly an exposure of the bronchial epithelium. However, a considerable proportion of Radon's decay products is also absorbed in the blood and accumulates in the lipophilic environment of the bone marrow to some extent [32, 33]. This biophysical mechanism could account for the ecological associations between radon exposure and leukemia incidence, which were reported from several countries [33-35].

However, levels of background radiation are similar in all regions studied around the pant [31]. Indoor radon activities measured in the homes of leukemia patients in the innermost region were low [36]. Moreover, no childhood and juvenile leukemias were observed in the village of Ellweiler, where exceptionally high specific indoor radon activities were measured [36-38].

Analysing the geographical distribution of the cases in the innermost region revealed that 4 of the 7 cases had lived in two villages (together accounting for only 20% of the total population of this circle). As a peculiarity, these villages had in common that for most of the study period surface water from the local river Nahe contributed to their drinking water supply to a variable extent. This was changed eventually in 1987, when through a newly constructed conduit, these two villages were also connected to the regional drinking water supply system. All other villages and the small town of Birkenfeld in the 5 km circle had been supplied exclusively with spring water throughout the study period.

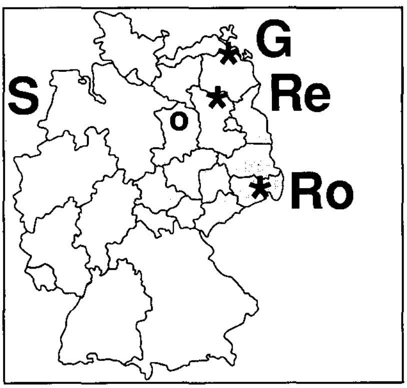
Some 2.5 km upstream from the waterworks, where the raw water is taken from the Nahe, the brook Steinausbach empties in the Nahe. On yearly average, the Steinaubach contributes some 10% to the raw water in the waterworks.

Before emtying in the Nahe, the Steinaubach runs through the Uranium processing plant, right between the dumps where the contaminated residues were stored under plain air after the Uranium had been extracted. While routine surveillance of the Steinaubach was not performed for most of the time of operation of the plant, sporadic measurements revealed a contamination with alpha-emitting radionuclides. In a series of measurements, total alpha-activity in the Steinaubach was always higher downstream the uranium processing plant than upstream of the plant [39] (Fig. 6).

In the absence of nuclide-specific measurements, it must be assumed that besides radon the alpha-emitting nuclides could contain Radium-226 to an unknown, but possibly significant extent. In a simple radioecological model [40] it was shown, that, if this were in fact the case, ingestion of drinking water could cause considerable red bone marrow doses. Through accumulation in the skeleton, doses would be highest for unborn children [41], whose susceptibility for the induction of leukemia is also highest [42].

According to the recommendations of an international symposium in Birkenfeld in

November 1989 the Uranium processing plant was closed down in early 1990. Since 1989, fortunately, no more childhood and juvenile leukemia cases have been reported from the 5 km-circle. A radioecologically appropriate storage of the contaminated residues, however, is still pending.



Nuclear installations in former East Germany (German Democratic Republic)

Prior to the reunification, the GDR had operated five nuclear power plants in Greifswald (1973-1990; Symbol „G“), one in Rheinsberg (1966-1990; „Re“), and a nuclear reseach reactor in Rossendorf (1956-1989; „Ro“). Two other nuclear power plants were planned in Stendal (S), but construction was terminated before first criticality [43].

Methods: Using incidence data from the National Cancer Registry of the former German Democratic Republic for 1961 to 1988, Möhner and Stabenow (1993) have investigated cancer rates in the vicinity of these plants [44]. Since in the GDR reporting of cancer cases was mandatory since 1953, ascertainment is supposed to be rather complete (estimated degree of completeness: 95%). Both all cancers and leukemias among children under age 15 were analysed in circular regions of 0-5 km, 5-10 km, and 10-15 km around the plants [44]. Stendal served as a control region. However, census data in municipality resolution were only available after 1979-1988 so that the analyses were restricted to this period. 90% confidence intervals are given under the assumption of a Poisson distribution (Tab. 9, 10). Due to small numbers, observed and expected cases in the two innermost areas were pooled in all analyses referring to specific nuclear installations.

Results: Relative risks are listed in Tab. 9 for all malignancies and Tab. 10 for leukemias, respectively.

The authors mention the slightly increased risk in the 0-10 km-region, which was mostly attributable to the findings around Rossendorf. For all malignancies combined, the RR reaches borderline statistical significance (one-sided p = 0.05). In the discussion the authors point out that the four counties with highest childhood cancer rates in the GDR, however, were distant from the nuclear establishments.

Cluster of childhood malignancies in Sittensen, Lower Saxony

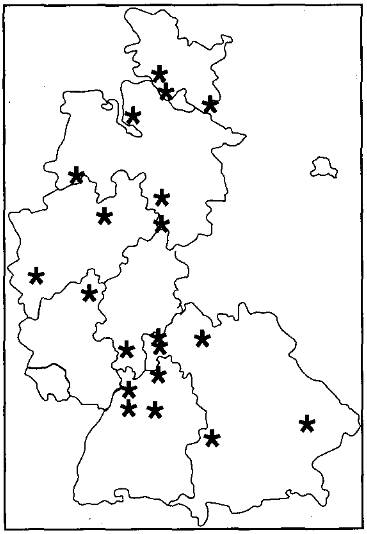
Sittensen is an administrative unit which consists of nine rural municipalities. It is situated approximately halfway between the Federal States Bremen and Hamburg in Lower Saxony. Between 1985 and 1989 nine cases of malignant diseases in children and young adults (below age 20) were diagnosed in a population of some 2300 people below 20 years of age. Six of the cases were acute leukemias (5 ALL, 1 AML), and the remaining diagnoses concerned one case each of Hodgkin's disease, rhabdomyosarcoma and Wilms' tumor.

Methods: Resulting incidence densities in Sittensen for acute leukemia for both children (below age 15) and young adults (below age 20) are shown in Tab. 11. According to a general convention, incidences were calculated for a period of ten years. Restricting the reference period to the five years of the highest incidence instead would not have been appropriate because it would introduce a potential bias due to the case-driven (a-posteriori) definition of the study period [45]. Population data for 1990 were provided by local authorities. For the purpose of the incidence study it was assumed, that no major migration of the respective age-groups has occurred over the study period. Expected values for children below 15 years were derived from figures for the Federal Republic of Germany [29]. For young adults, expected cases were based on data from the Federal State of Saarland cancer regisry [36].

Results: Incidence density rate ratios of acute leukemias for both children and young adults (0-19 years) are shown in Tab. 11.

Discussion: This geographical „cluster" of childhood and juvenile leukemias was extensively covered by both local and national media. The excess was shocking, but it could not readily be attributed to any plausible cause. Particularly, in this case, an association to a nuclear power plant was highly unlikely. The closest nuclear facility, Stade, is situated some 50 km distant to Sittensen. However, neither could the existence of a local risk factor be excluded, a situation which generated considerable concerns in the local population. In January 1990, the Ministry of Social Affairs of the Federal State of Lower Saxony established an expert committee to investigate possible causes for the cluster. The experts suggested a comprehensive scheme of environmental measurements covering an array of physical, chemical and biological parameters. Nevertheless, after one year no significant environmental risk factor had been discovered. However, questionnaire based personal interviews revealed a previous exposure to diagnostic radiation in four out of the six leukemia patients. At least three of the four had been X-rayed repetitively in the same local practice [46]. Unfortunately, the respective X-ray machine could not be evaluated after the practice had been sold to another physician. For two of the children sufficient information could be retrieved from the patient documentation of the practice to allow for an individual reconstruction of the diagnostic procedures. One child had had at least 16 X-rays for scoliosis before age 15, starting at age 5. The other child was X-rayed at least 5 times for hip dysplasia between 3 months and age 2. Using an X-ray machine of identical make and type and standardized phantoms, exposure conditions were modelled and accumulated doses for the children were derived [47]. Phantom doses in the case of the girl with scoliosis corresponded to an accumulated red marrow organ dose of 9.0 mSv. In the case of the boy with hip dysplasia, a dose of 0.5 mSv was measured. To evaluate whether or not the radiological standard in the practice was appropriate, 5 healthy children who had previously been X-rayed in the practice, volunteered to be investigated by means of biological dosimetry. This technique allows for an estimation of accumulated equivalent whole body radiation dose by comparing the frequency of a specific structural chromosome aberration (dicentric chromosomes) in peripheral blood lymphocytes with an in vitro calibration curve [48-51]. Biologically estimated doses where then compared with physical measurements obtained from simulations of the children's respective X-ray investigations using phantoms as described above (resulting physical doses were between 1.7 and 18.3 mSv whole body dose). Comparing physically and biologically recorded doses revealed a close correlation. Biologically recorded doses, however, exceeded physical doses consistently by a factor of about six [47]. Hence physical simulation in fact yielded an underestimation of the „real" accumulated doses of the children. The observed range is not unusual in diagnostic radiology. Phantom measurement are usually performed under optimized experimental conditions thus minimizing the required doses. In radiological practice, exposure doses are usually up to one, in cases of bad practice even two orders of magnitude higher than the physical optimum [52]. Applying a correction factor of 6.0, accumulated doses (red bone marrow) of 54 and 3.0 mSv for the two children would result.

Hence diagnostic radiation so far appears as a relevant causal factor in the evaluation of the leukemia cluster in Sittensen.



Nuclear power plants and major research reactors in the Federal Republic of Germany

In 1989, the Federal Ministry for the Environment, Nature Protection, and Reactor Safety initiated a systematic incidence study which should cover the vicinities of all of the then 20 nuclear power plants in the Federal Republic of Germany (area of former „West" Germany). Investigators from the registry of childhood malignancies in the Federal Republic of Germany were appointed to compare the incidence of childhood malignancies in the 0-5 km, 5-10 km, and 10-15 km around the nuclear sites with control regions. 18 regions were defined as „exposed", together containing 18 commercial power plants and two major research reactors.

The study was designed to detect a 10% increase of risk in the 0-15 km region around all West German nuclear power plants for all childhood malignancies combined at the 0.01 level of statistical significance with a power of 95% [53]. To achieve the necessary case numbers, all years between 1980 and 1990 were included.

Methods: For each individual site region a control region was selected according to predefined criteria [53, 54]:

- distance between 30 and 100 km of the „exposed" region
- a similar regional structure
- a similar population density (± 50 inhabitants/km^2)
- a large proportion (some 60 %) of pediatric cancer patients treated in the same regional centers as patients from the „exposed" regions

The control regions were likewise divided into mutually exclusive concentric regions of 5, 10, and 15 km around an arbitrary center. In a first step standardized incidence ratios (SIR) were calculated for both „exposed" and control regions separately (reference: average incidences in West Germany). Relative risks (RR) were then defined as the ratio between the SIR of the regions containing the nuclear power plant and the SIR of the control region. Shortly after methods and results were published in a comprehensive Technical Report (in German, Feb.1992 [54]), a summary paper appeared in Cancer Causes and Control [53].

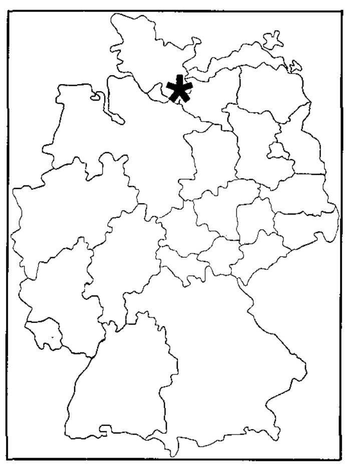
Results: As the main result of their study the authors concluded that the RR of all childhood malignancies in the 0-15 km-region around West German nuclear power plants was 0.97 compared to individually matched control regions. For acute leukemias, RR was 1.06. However, for some diagnostic groups SIR were increased in the

„exposed“ regions. Non-Hodgkin's lymphomas were significantly more frequent in the „exposed“ regions (RR 1.67, p=0.017) and so was a group of diagnoses, a priori defined by the authors which included leukemias and non-Hodgkin's lymphomas together with the tumors of early infancy (neuroblastoma, nephroblastoma). This group comprised some 60% of all malignancies (RR 1.14, p=0.042; Tab. 12).

Discussion: Often taken out of context, the study was quoted by the nuclear industry as well as by representatives of the Federal government as an „all-clear“ signal after several years of controversial discussion on health effects around nuclear facilities in normal operation. However, while the methodology of the study as well as the completeness of case ascertainment [55, 56] is generally acknowledged, the appropriateness of the endpoint „all malignancies in children of all ages in the 0-15 km region“ with respect to the hypothesis was questioned by some experts.

With respect to the original hypothesis, findings for radiation-inducible malignancies would be of particular interest. The lowest doubling doses have been reported for acute leukemias, particularly in young children [57, 58], and after prenatal exposure [42, 59]. In the study of Keller et al. (1992) RR for acute leukemias was significantly increased (1.28, p=0.037) for young children (below 5 years of age), in the „exposed“ 0-15 km-regions. The increase was more pronounced in the immediate vicinity of the plants (0-5 km-region: RR=3.01; p=0.015), but there was no consistent trend with increasing distance (5-10 km: RR=0.98; 10-15 km: RR=1.38; Fig. 7). RR was highest for a subgroup which included only those nuclear power plants that were operating prior to 1970 (RR=7.09, p=0.021; Fig. 8). In fact, this RR was the highest of all subgroup analyses in the study.

A panel of German epidemiologists critized the authors account of their results on basically the same grounds as dicussed above [60]. Based on the hypothesis of a potential carcinogenic impact of radioactive releases from the nuclear power plants the panel suggested to focus on findings in the most relevant subgroups and stressed the potential biological importance of the leukemia findings. The panel did not follow Keller et al.'s argument that the increased RR in the vicinity of nuclear installations was attributable to unexpectedly low incidences in the control regions. According to the panel, it should be considered, that the reference regions were carefully selected, and were matched to the „exposed“ regions a priori and in the most appropriate way. If higher incidences are later observed in the site regions, these should be discussed in terms of the hypothesis rather than comparing them to national figures [60].



Nuclear power plant Krümmel, Lower Saxony

Between February 1990 to the end of 1995 six cases of childhood leukemia were diagnosed among residents of the small rural community Elbmarsch in Northern Germany. Five of these occured in only 16 months between Feb. 1990 and May 1991 (Tab. 13). All cases all lived in close proximity (< 5 km) to Germany's highest capacity nuclear boiling water reactor Krümmel (1300 MW electric, commissioned in 1984) and a nearby nuclear research facility GKSS (Gesellschaft zur Kernenergieverwertung in Schiffbau und Schiffahrt; Fig. 9). GKSS was established in 1958, and operates radionuclide laboratories as well as two nuclear research reactors of 5 and 15 MW capacity, respectively [61]. Since only the 1990 cases were included in the study of Keller et al., 1992 (study period 1980-1990, please refer to previous paragraph) [54], incidence in the vicinity around the nuclear reactor Krümmel is not yet significantly increased in their final report. The cluster therefore requires separate consideration.

Methods: Standardized incidence ratios (SIR) and exact 95% confidence intervals were calculated for a circular area with 5 km radius around the plant. Using population figures in community-wide resolution, some 28990 person years below age 15 have accumulated from 1990 to 1995 in the 0-5 km-region. SIR-calculations are based on agegroup-specific leukemia incidences provided by the German Childhood Cancer Registry (agegroups <1, 1-4, 5-9, and 10-14 years at diagnosis; [62]).

Results: For the time period 1990 to 1995 the SIR was 460 (210-1030). If the analysis is restricted to the years 1990 and 1991, the SIR increases to 1180 (490-2830). About 80% of the population within the 5-km region lives north of the river Elbe. However, five of the six leukemia cases, were diagnosed in villages south of the river, the population of which represents only 20 % of the total population of the 5 km-region around the nuclear power plant. The sixth case also had lived in the southern part for all of his life. The family had moved to the northern part just a few months prior to his diagnosis. Including only the villages south of the river Elbe, the SIR becomes 2400 (6 cases, 5712 person years, 95%CI 1080-5340) for the period 1990-1995. Considering only the years of peak incidence, the SIR becomes 6030 (5 cases, 1892 person years, 95%CI 2510-14510).

Discussion: Immediately after the cluster had been identified (Feb. 1992), the governments of the two adjacent federal states (Lower Saxony and Schleswig-Holstein) established a board of experts to investigate into possible causes for the cluster. In fact, most members of the Lower Saxony board had previously served in the expert committee which had evaluated the Sittensen cluster. However, neither a multitude of samples from all kinds of environmental media in the region nor various kinds of biological samples (blood, urine, breast milk) taken from members of the afflicted families and other inhabitants of the Elbmarsch yielded any unusual contamination from chemical, biological, or radioactive sources [63].

A thorough review of medical and hospital records of all cases was undertaken and supplemented by extensive semi-structured personal interviews with all membersof the afflicted families. Again no clue toward any unsusual exposures was revealed. None of the children had a preexisting medical condition known to be associated with higher risk of leukemia. The children were all born in the area and most of the parents had lived there for many years, but none of the families is related to any of the others and the children had no more than casual contact, if any, prior to their diagnoses.

The hypothesis of a potential impact of radioactive releases of the nuclear power plant Krümmel or the nearby GKSS, however, is supported by increased rates of chromosome aberrations in 5 adults from the 0-5 km region, each a parent to one of the leukemia children, and 5 other persons. Particularly the rates of dicentric chromosomes were significantly more frequent than would have been expected according to our laboratory control [64]. This class of unstable rearrangement aberrations is typically induced by ionizing radiation. The finding is of particular significance since according to the questionnaires none of the persons in the sample had been exposed to any of the few potential confounders of the assay i.e. unusual doses of medical or occupational radiation or leukemogenic drugs. This unprecedented cluster of childhood leukemia cases cannot presently be explained in terms of established and putative risk factors for childhood leukemia, including radiation from medical sources.

Recently, an elevated leukemia incidence has been observed also for adults in the 0-5 km-region around the facilities in the period 1984-1993 (all leukemias: 41 cases observed, 30 expected, standardized incidence ratio 128; $p<0.05$) [56, 65].

General Discussion

Obviously the evidence obtained from cluster analyses in Germany is insufficient in several respects to answer the question of a possible health risk of nuclear power plants in normal operation. All studies so far have been ecological in nature. However, some of the investigations have been conducted in a systematical and comprehensive fashion and with epidemiologically sound methodology. In most studies no reference has been made to exposure doses of the population due to ionizing radiation. Many authors have stressed that radioactive releases of nuclear facilities in normal operation are orders of magnitude to low to cause any measurable increase in cancer incidence [66-70].

Methodological issues

- All studies in Germany so far ecological (some including limited information on environmental contamination and case exposure status)
- Geographical resolution varies from county to municipality level
- Operationalization of exposure includes geographical distance, temporal correlation with releases from putative poinr sources, modelling of exposure pathways
- No comprehensive measurements of exposure
- Evidence-based hypothesis generation in some instances („Texan sharpshooter")
- No epidemiologically sound analytical study

However, the consistency of findings which are generally, but not always, towards the positive side, i.e. an increased incidence in the immediate vicinity of nuclear installations precludes any quick and easy „all-clear"-signal. The comprehensive incidence study of Keller et al., 1992 has revealed a pattern of results which would well be compatible with the hypothesis of a causal impact of nuclear power plants (highest risks for (1) acute leukemias, (2) for young children, (3) in immediate vicinity of the plants, (4) around „first generation" facilities, commissioned before 1970). In-depth evaluation of exposure pathways such as has been attempted in Ellweiler can lead to causal hypotheses as well as to clues toward preventive measures.

Childhood leukemia clusters in general

- No „general clustering" in Germany (* Poisson-statistics applicable
- Public health/Political context require appropriate response by authorities
- Cluster investigation scientifically not pointless

Increased rates of radiation-typical chromosome aberrations in Krümmel would be compatible with the hypothesis of unscheduled releases of the nuclear power plant Krümmel. Sittensen has proven once again that careful cluster evaluation can be worthwhile. Findings in this cluster may influence the ongoing discussion on potential hazards of medical dignostic radiation.

Finally, despite a common misconception, childhood leukemia does not „come in clusters", at least not in Germany. Westermeier and Michaelis (1995) have recently shown, that the geographical distribution of childhood malignancies can reasonably be described by a Poisson distribution [71]. The mere fact, that several leukemia clusters have been observed in close vicinity of nuclear installations thus becomes a significant result of its own right which still awaits etiologic explanation.

Childhood leukemia clusters with respect to nuclear facilities

- „Circle-studies" around facilities more often positive than negative
- Tendency toward higher risks ...
  - for immediate vicinity of sites (say, <5 km)
  - for young children /say, <5 years)
  - when matched control regions are used instead of national figures (Würgassen, GDR, IMSD)
- No geographical incidence data on adults (exception: Elbmarsch)
- Exposure assessment of cases usually poor or completely absent
- Exposure assessment of „controls" completely absent
- Chromosome findings indicative for sign. exposure (Ellweiler, Elbmarsch)
- Health effects incompatible with radioactive emissions of plants and/or ICRP/BEIR/UNSCEAR risk factors

Future research clearly must put a major focus on individual exposure assessment. In case-control studies, lifelong residential and occupational history of cancer cases as well as controls need to be considered as well as exposure to chemical, physical, and possibly biological risk factors be quantified which could (and, actually, are likely to) confound any geographical association.
In Germany today there are 21 nuclear power plants either in operation or ready for operation [43]. Altogether, nuclear power plants provide some 23 Million kW (=23 GigaWatt GW) of electric energy, and, hence, contribute to some 28 % to the total generation of electricity in Germany. A total of 431 nuclear reactors presently generate 360 GW worldwide. Hence Germany's nuclear power plants comprise only 4.6 % of the facilities worldwide, and some 6 % to the generation of electricity.
It is save to assume that if there is any health risk related to the operation of nuclear power plants it will not be confined to Germany. Rather, safety standards will supposedly be lower in some countries, as a consequence of economical, political and technical constraints. This did not only cause a number of nuclear accidents and radioactive releases at all stages of the so-called „nuclear fuel circle" worldwide. Different standards also directly translate into very different levels of environmental contamination throughout any operation, even in the absence of accidents.
A small additional cancer risk, if there should be any, due to use of nuclear energy may well be acceptable after careful consideration of the alternatives. However, to jugde this balance responsibly, valid, accurate, and precise information is indispensable. Epidemiologists are presently still far from being able to provide the respective data.

Conclusions

At the present stage, there are four potential explanations for the findings in both Germany and possibly other countries:

- Epidemiological findings are not valid (e.g. statistical artifacts)
- Releases of facilities are higher than reported (and, consequently, must have been missed by routine environmental surveillance)
- Other exposures are associated to vicinity of plants
- Radiation risk factors are not applicable to the general population in the vicinity of nuclear facilities

Tab. 1 Cluster studies in Germany

Location	putative point source	study disease	age-group(s)
Lingen/Ems (Lower Saxony)	nuclear power plant	leukemia perinatal mortality	children (0-14 years)
Bavaria	3 nuclear power plants 1 experimental plant 2 research reactors	leukemia	children (0-14 years) young adults (15-39 years)
Würgassen (Northrhine-Westphalia)	nuclear power plant	leukemia all malignancies	children (0-14 years) young adults (15-19 years)
Ellweiler (Rhineland-Palatinate)	uranium processing plant	leukemia all malignancies	children (0-14 years) young adults (15-19 years)
Former East Germany	2 locations with a total of 6 nuclear power plants 1 research reactor	leukemia all malignancies	children (0-14 years)
Sittensen (Lower Saxony)	(geographical cluster)	leukemia all malignancies	children (0-14 years) young adults (15-19 years)
Federal Republic of Germany	18 locations with a total of 20 nuclear power plants 2 research reactors	leukemia selected diagnoses all malignancies	children (0-14 years)
Elbmarsch (Lower Saxony)	nuclear power plant	leukemia	children (0-14 years)

Tab. 2 Bavarian nuclear power plants (1976-1981)

Name/Location	Type	Capacity [MW]	Com.	De-com.	Symbol
Kahl/Main	BWR	16 (exp.)	1960	1985	**K**
Gundremmingen	BWR	250 (el.)	1966	1977	**G**
Isar I (Essenbach)	BWR	907 (el.)	1972	-	**I**
Niederaichbach	PTR	100 (el.)	1972	1974	**N**
Neuherberg	(res.)	1 (th.)	1957	-	**rN**
Garching	(res.)	4 (th.)	1972	1982	**rG**

el.=electric; th.=thermic; BWR=Boiling Water Reactor; PTR=Pressurized Tube Reactor

Tab. 3 Bavarian nuclear power plants: Environmental exposure (1974-1980) (according to [20], modified)

Plant	capacity [MW]	maximum exposure [mSv/year]	...at distance
Ohu (Isar 1)	907 (el.)	0.001	750 m
Grundremmingen	1308 (el.)	0.001	600 m
Neuherberg	1 (th.)	0.0005	50 m
Garching	4 (th.)	0.002	10 m

Tab. 4 Observed vs. expected cases of childhood and juvenile leukemia in concentric regions around the Würgassen nuclear power plant
(Mutually exclusive regions, cumulative agegroups, recalculated after [24])
Reference: German childhood cancer registry 1980-1986

	<15 years			<20 years		
Radius [km]	**obs.**	**exp.**	**p**	**obs.**	**exp.**	**p**
0 -10	1	1.58	0.79	2	1.99	0.59
10 -15	3	1.47	0.18	4	1.86	0.12
15 - 20	7	3.05	0.036	9	3.90	0.019
20 - 25	3	4.52	0.83	3	5.76	0.93

obs. = observed number of cases; exp. = expected number of cases; p = one-sided p-value under the assumption of a Poisson distribution (=Poisson-probability to observe as many or more cases than expected)

Tab. 5 Incidence rate ratios of malignant disease in children with respect to cumulative concentric regions around the Würgassen nuclear power plant, 1980-1988 [26]
(Reference: Federal Republic of Germany; in parentheses: exact 95% confidence intervals)

Radius [km]	all neoplasms	haemato-lympopoetic	CNS	other
0 - 5	1.7 (0.6;4.0)	1.7 (0.2;6.0)	3.1 (0.3;10.3)	1.0 (0.0;5.6)
0 - 10	1.3 (0.5;2.6)	0.9 (0.1;3.1)	1.6 (0.2; 6.0)	1.5 (0.3;4.4)
0 - 15	1.1 (0.5;1.9)	0.6 (0.1;1.9)	1.6 (0.4; 4.1)	1.2 (0.4;2.9)
0 - 20	1.3 (0.8;1.8)	1.4 (0.8;2.4)	1.6 (0.7; 3.2)	0.9 (0.4;1.8)
0 - 25	1.1 (0.8;1.5)	1.0 (0.5;1.6)	1.7 (0.9- 2.8)	1.0 (0.5;1.6)

haematolymphopoetic=all leukemias, non-Hodgkin's lymphomas, Hodgkin's disease; CNS= malignant tumors of the central nervous system; other= complement to (haematolymphopoietic + CNS)

Tab. 6 Incidence rate ratios of malignant disease in children with respect to cumulative concentric regions around the Würgassen nuclear power plant, 1980-1988 [26]
(Reference: Grossalmerode; in parentheses: exact 95% confidence intervals)

Radius [km]	all neoplasms	haemato-lympopoetic	CNS	other
0 - 5	3.5 (0.6; 36.6)	1.4 (0.1; 19.1)	-	-
0 - 10	2.6 (0.6; 15.7)	1.1 (0.1; 15.5)	-	1.1 (0.0; 88.0)
0 - 15	1.9 (0.8; 4.8)	1.1 (0.2; 5.5)	3.6 (0.5; 39.3)	2.22 (0.5;11.2)

(please refer to Tab. 5 for legend)

Tab. 7 Recalculation of incidence rate ratios of malignant disease in children with respect to mutually exclusive regions around the Würgassen nuclear power plant, 1980-1988 [26]
(Reference: Grossalmerode; in parentheses: exact 95% confidence intervals)

Radius [km]	all neoplasms	haemato-lympopoetic	CNS	other
0 - 5	3.46 (0.57; 36.16)	1.38 (0.10; 19.14)	- [1]	- [1]
5 - 10	1.66 (0.09; 97.49)	-	- [1] [2]	- [2]
10 - 15	1.50 (0.39; 5.20)	0.80 (0.02; 9.97)	2.40 (0.17; 33.24)	3.20 (0.54; 21.91)

(please refer to tab. 5 for legend)
[1] no cases observed in the control region; [2] no cases observed in the "exposed" region

Tab. 8 Observed vs. expected cases of childhood and juvenile leukemia in concentric regions around the Uranium processing plant
Reference: Saarland Cancer Registry 1970-1986

	< 15 years			< 20 years		
Radius [km]	**obs.**	**exp.**	**p**	**obs.**	**exp.**	**p**
0 - 5	5	1.77	**0.034**	7	2.27	**0.009**
5 -10	4	3.63	0.49	6	4.61	0.32
10 -15	8	6.92	0.39	(data incomplete)		-
15-20	14	15.15	0.65	(data incomplete)		-

obs. = observed number of cases; exp. = expected number of cases; p = Poisson-probability to observe as many or more cases than expected

Tab. 9 Observed vs. expected cases of childhood malignancies in the vicinity of nuclear installations in the former GDR, 1979-1988
A. All malignancies
Reference region: Stendal

Radius [km]	obs.	exp.	RR	90% CI
Rossendorf				
0 - 10	15	9.89	1.52	0.94; 2.34
10 - 15	24	27.40	0.88	0.60; 1;23
Rheinsberg				
0 -10	6	3.40	1.76	0.77; 3.48
10 -15	0	2.23	0.00	0.00; 1.02
Greifswald				
0 -10	2	2.38	0.84	0.10; 3.03
10 -15	7	6.85	1.02	0.48; 1.92
Total				
0 - 5	3	2.65	1.13	0.23; 3.31
5 -10	20	13.02	1.54	1.02; 2.23
10 -15	31	36.48	0.85	0.62; 1.15
0 - 10	23	15.67	1.48	1.00; 2.08

obs.= observed cases; exp.= expected cases, RR=Relative risk (=obs./exp.);
90%CI= 90% confidence interval under the assumption of a Poisson distribution

Tab. 10 Observed vs. expected cases of childhood malignancies in the vicinity of nuclear installations in the former GDR, 1979-1988
B. Leukemias
Reference region: Stendal

Radius [km]	obs.	exp.	RR	90% KI
Rossendorf				
0 - 10	6	2.84	2.11	0.92; 4.17
10 - 15	8	7.89	1.01	0.50; 1.83
Rheinsberg				
0 -10	2	0.97	2.06	0.25; 7.44
10 -15	0	0.65	0.00	0.00; 3.51
Greifswald				
0 -10	0	0.70	0.00	0.00; 3.26
10 -15	3	1.99	1.51	0.31; 4.40
Total				
0 - 5	1	0.77	1.30	0.03; 7.24
5 -10	7	3.84	1.82	0.86; 3.42
10 -15	11	10.54	1.04	0.58; 1.73
0 - 10	8	4.51	1.77	0.88; 3.20

(please refer to Tab. 9 for legend)

Tab. 11 Incidence of acute leukemias in Sittensen, 1980-1989
Reference: Federal Republic of Germany (0-14 years), Saarland cancer registry (0-19 years)

		No. of cases		rate ratio	
Age [years]	ageyears	observed	expected	(95% CI)	p
<15	15342	5	0,7	7.58 (2.45;17.72)	0.0003
<20	22827	6	0,8	8.0 (2.88; 17.94)	0.0001

ageyears = cumulative ageyears in the respective agegroup; 95%CI= 95% confidence interval for the incidence density rate ratio; p= one-sided p-value

Tab. 12 Observed vs. expected cases in 20 regions around West-German nuclear power plants and matched control regions
Reference: individually matched control regions
(data according to appendix in [54], modified)

	O_{NucPP}	E_{NucPP}	O_{Contr}	E_{Contr}	SIR_{NucPP}	SIR_{Contr}	RR	p
All malignancies, 0-14 years								
0 - 5	81	82	59	67	0.99	0.88	1.13	0.272
5 - 10	346	354	247	234	0.98	1.05	0.93	0.823
10 - 15	378	444	305	345	0.85	0.88	0.96	0.706
0 - 15	805	879	611	646	0.92	0.95	0.97	0.736
0-4 years								
0 - 5	45	43	25	34	1.05	0.74	1.43	0.093
5 - 10	175	180	125	120	0.97	1.04	0.93	0.738
10 - 15	200	228	139	176	0.88	0.79	1.11	0.186
0 - 15	420	451	289	330	0.93	0.88	1.06	0.219
Acute leukemias, 0-14 years								
0 - 5	30	27	17	22	1.10	0.76	1.44	0.143
5 - 10	113	118	82	78	0.96	1.05	0.92	0.752
10 - 15	131	149	91	115	0.88	0.79	1.12	0.230
0 - 15	274	294	190	216	0.93	0.88	1.06	0.285
0-4 years								
0 - 5	19	15	5	12	1.26	0.42	3.01	0.015
5 - 10	63	63	43	42	1.00	1.02	0.98	0.578
10 - 15	70	80	39	62	0.87	0.63	1.38	0.061
0 - 15	152	158	87	116	0.96	0.75	1.28	0.037
Non-Hodgkin's lymphoma, 0-14 years								
0 - 5	4	5	2	4	0.78	0.47	1.67	0.431
5 - 10	29	22	8	15	1.29	0.54	2.40	0.016
10 - 15	26	28	16	22	0.92	0.73	1.27	0.280
0 - 15	59	56	26	41	1.06	0.63	1.67	0.017
0-4 years								
0 - 5	1	1	0	1	0.90	0.00	-	-
5 - 10	1	5	0	3	0.21	0.00	-	-
10 - 15	5	6	2	5	0.84	0.44	1.93	0.345
0 - 15	7	12	2	9	0.60	0.23	2.57	0.191
Selected diagnoses, 0-14 years								
0 - 5	41	46	31	37	0.89	0.83	1.08	0.421
5 - 10	206	198	123	131	1.04	0.94	1.11	0.190
10 - 15	224	249	150	193	0.90	0.78	1.16	0.090
0 - 15	471	492	304	362	0.96	0.84	1.14	0.042
0-4 years								
0 - 5	26	27	13	21	0.97	0.61	1.59	0.112
5 - 10	117	113	70	76	1.03	0.93	1.12	0.255
10 - 15	128	143	69	111	0.89	0.62	1.43	0.009
0 - 15	271	283	152	208	0.96	0.73	1.31	0.005

O_{NucPP} = observed cases in "exposed" region; E_{NucPP} = expected cases in "exposed" region; O_{Contr} = observed cases in control region; E_{Contr} = expected cases in control region; SIR_{NucPP} = standardized incidence ratio "exposed region"; SIR_{Contr} = standardized incidence ratio in control region; RR = relative risk= SIR_{NucPP}/SIR_{Contr}; p = one-sided p-value, assumption: Poisson-distribution of the cases

Tab. 13 Childhood and juvenile leukemia cases in the rural community Elbmarsch, Northern Germany, 1990-1995

Sex	month/year of diagnosis	age at diagnosis [years]	diagnosis	village of residence
F	2/'90	3	c-ALL	Avendorf
M	3/'90	9	c-ALL	Tespe
M	5/'90	9	AML	Tespe
F	1/'91	1	c-ALL	Tespe
M	4/'91	21 [1)]	AML	Marschacht
M	5/'91	2	c-ALL	Avendorf [2)]
M	5/'95	10	T-ALL	Tespe

c-ALL=Common acute lymphoblastic leukemia; AML: Acute myeloid leukemia; T-ALL: Acute lymphoblastic leukemia, T-cell type
1) young adult, not included in the analyses
2) this family moved to Geesthacht a few months prior to the boy's final diagnosis

Fig. 1 Temporal and spatial correlations of biological endpoints with release patterns of the Lingen nuclear power plant 1968-1977 (Stein, 1988)

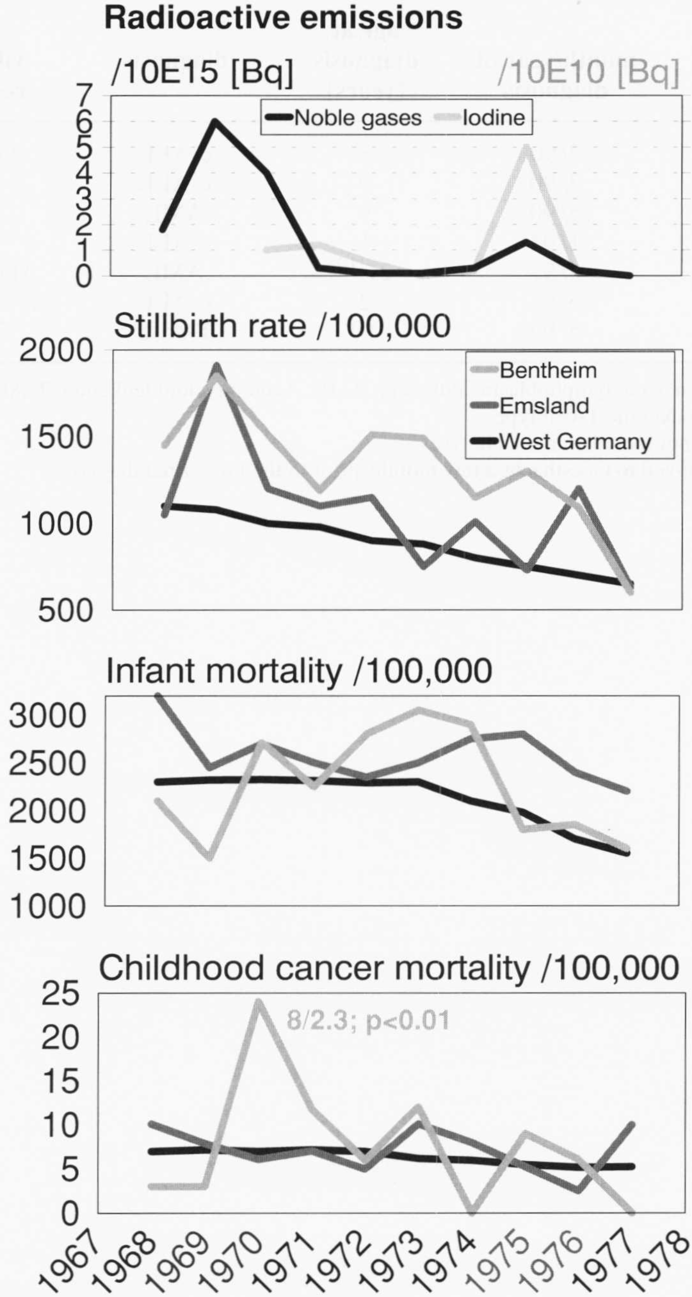


Fig. 2 Bavaria 1976-1981: Comparison of age-specific incidence and mortality data
I. All leukemias

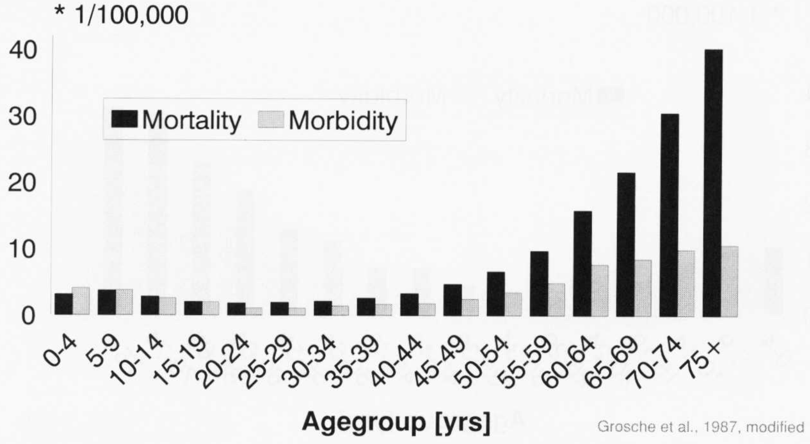


Fig. 3 Saarland: Expected age-specific Morbidity/Mortality ratio for all leukemias
(Data: Saarland Cancer Registry 1980, '81, '85, '86, '88)

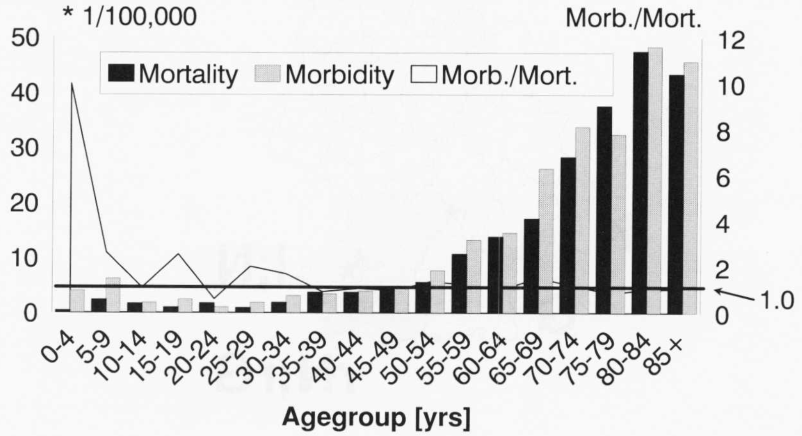


Fig. 4 Bavaria 1976-1981: Comparison of age-specific incidence and mortality data
II. Acute leukemias

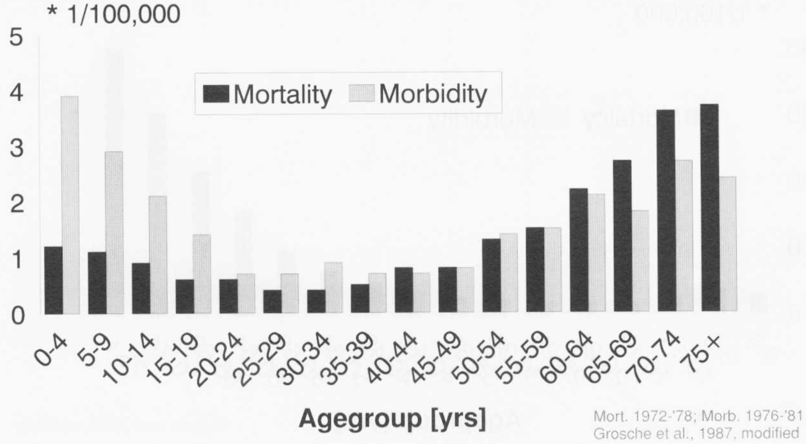


Fig. 5 Location of nuclear power in Bavaria (1976-1981)

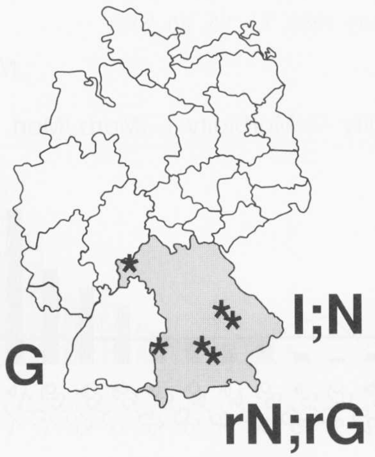


Fig.6

Radioactive contamination of the Steinaubach

Series of measurements upstream and downstream of the plant

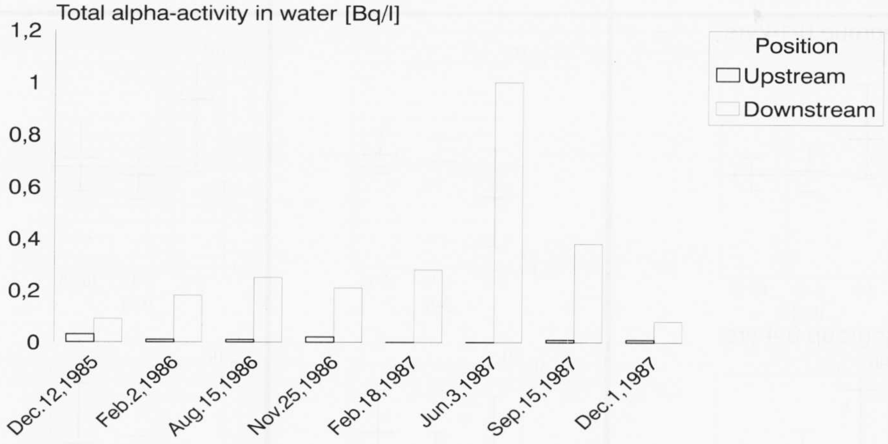


Fig. 7 Relative Risks (RR) for childhood malignancies in the vicinity of West German nuclear power plants. Trends with distance ?

(95% CI; Data: Keller et al. 1992)

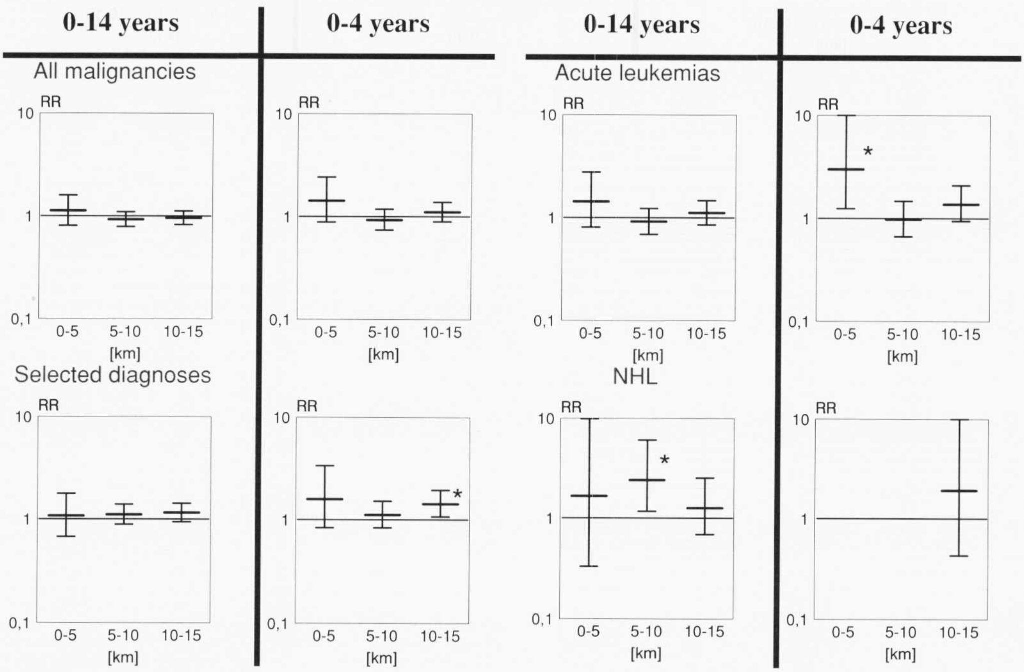


Fig. 8 Relative Risks (RR) for childhood malignancies in the vicinity of West German nuclear power plants. Trends with distance and year of commissioning ? (95% CI; Data: Keller et al. 1992)

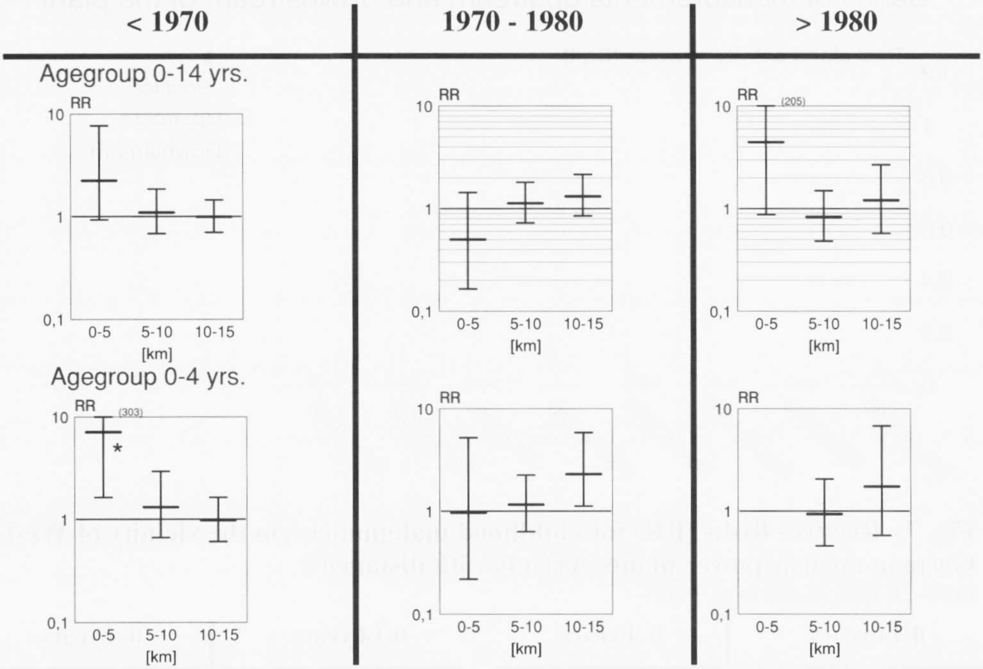
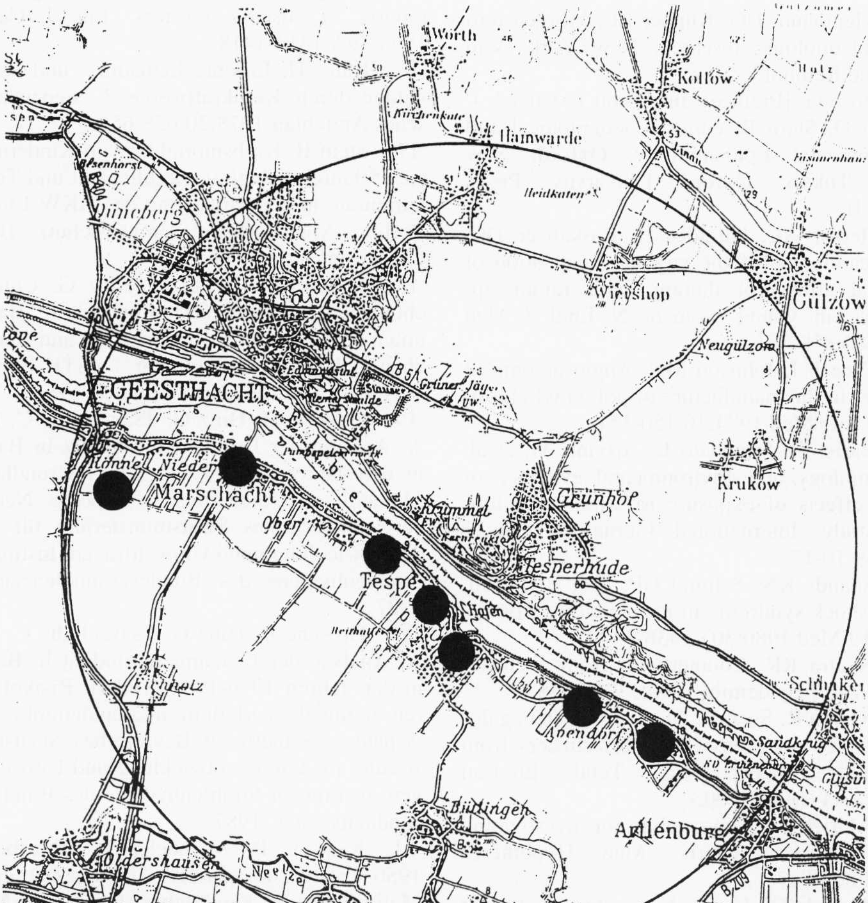


Fig. 9 Map of the region around the nuclear power plant Krümmel and residences of six childhood and one juvenile leukemia cases[1]
(Radius of the circle: 5 km)



[1] Note added in proof: In July 1996, another leukemia (c-ALL) has been diagnosed in a 3-year old boy who lived some 2 km from the plant on the northern bank of the river Elbe

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