ORIGINAL ARTICLE

Childhood Leukemia in the Vicinity of Nuclear Power Plants in Germany

Peter Kaatsch, Claudia Spix, Irene Jung, Maria Blettner

SUMMARY

Introduction: The causes of leukemia are largely unclear. The question whether leukemia rates are increased near nuclear power plants is controversial. The German Childhood Cancer Registry has published an epidemiological case-control study on childhood cancer and nuclear power plants.

Method: The study was based on the distance of children's residences from nuclear power plants and addressed the question whether children under age 5 with cancer live closer, on average, to nuclear power plants than randomly selected controls. Odds Ratios (OR) for distance categories and standardized incidence ratios (SIR) were calculated.

Results: An association was found between the nearness of residence to nuclear power plants and the risk of leukemia (593 cases, 1766 controls). Within the 5-km zone, the OR for the development of leukemia in children under 5 years of age was 2.19 compared to the rest of the region, and this elevation of the OR was statistically significant. The incidence of leukemia in the overall study region was the same as that in Germany as a whole (SIR=0.99; 95% confidence interval 0.92–1.07).

Discussion: Based on the available information about radiation emissions from German nuclear power plants, a direct relation to radiation seems implausible. Many factors may conceivably cause leukemia, possibly operating in combination, and these factors may be present to a greater extent in the vicinity of German nuclear power plants.

Dtsch Arztebl Int 2008; 105(42): 725–32
DOI: 10.3238/arztebl.2008.0725

Key words: child health, leukemia, nuclear power plants, epidemiology, cancer registry

Institut für Medizinische Biometrie, Epidemiologie und Informatik, Klinikum der Johannes Gutenberg-Universität Mainz: Dr. rer. physiol. Kaatsch, Priv.-Doz. Dr. rer. nat. Spix, Jung, Prof. Dr. rer. nat. Blettner

Every year some 1800 children under 15 years of age in Germany develop a malignant disease, including around 600 who become ill with leukemia (1). The data of the German Childhood Cancer Registry show that a high proportion (79.1%) of cases in this age group are accounted for by acute lymphoblastic leukemia (ALL), followed by acute myeloid leukemia (AML; 14.0%) (1). Chronic leukemia is considerably less frequent in children than in adults. The median age at onset is 5 years. The incidence of ALL in Germany is 4.1 per 100 000, that of AML 0.7 per 100 000. European data show a statistically significant increase in childhood leukemias in recent years (1978 to 1997: mean 0.6% per year) (2). This is confirmed by the German data (3).

The higher incidence of childhood leukemias in industrialized countries, together with repeated observations of temporally limited local clusters of leukemia in rural areas, has led to the hypothesis that infectious pathogens play a part (4). Children whose immune system was inadequately modulated in infancy seem to be at greater risk of leukemia when they later have increased exposure to agents of infection (5). Environmental influences were long suspected of causing a large proportion of leukemias in children; however, it has since emerged that only a small number of cases result from such factors. The authors published a review of the possible causes of childhood leukemia in 2005 (6).

Despite the great number of large epidemiological studies carried out, the causes of leukemia in childhood remain largely unclear. Nevertheless, one factor generally accepted to represent a risk for leukemia is exposure to ionizing radiation. The effect of low-dose radiation is less clear. Therefore, the question frequently arises of whether the risk of leukemia is greater in the vicinity of nuclear power plants (NPP).

Leukemia, especially in children, is usually a central topic in the discussion of the possible consequences of nuclear technology. This is related to the relatively swift development of leukemia after exposure to ionizing radiation and the fact that leukemia is the most frequent malignant disease of childhood.

In 2007 the German Childhood Cancer Registry published the findings of the Epidemiological Case-Control Study of Childhood Cancer and Nuclear Power Plants (KiKK study) (7–9). Earlier studies were completed and published in 1992 (10, 11) and 1998/1999 (12, 13).

BOX

Materials and methods—background detail

For every case, three sex- and age-matched controls were randomly selected from the same district in the year of diagnosis (total 4735 controls, including 1766 for children with leukemia). For both cases and controls the residential address at the time of diagnosis (the corresponding date for controls) was geo-coded and the distance r to the outlet tower of the nearest nuclear power plant (NPP) established.

According to the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), 1/r approximates the radiation exposure as function of the distance r from a corresponding point source (16). Therefore 1/r was included as a variable in the regression model used in the study. Odds ratios (OR) and the 95% confidence interval (CI) were estimated by means of conditional logistic regression analysis. If the lower limit of the CI lies above 1, the result is termed "statistically significant" (5% level).

Also calculated were standardized incidence ratios (SIR = O/E), i.e., the ratio of observed cases of disease (O) to expected cases (E). In this simple approach, commonly employed in analyses of regional data, disease rates at administrative unit level (at community or district level for example, i.e., not at individual level) are compared with the rate at national level. E is calculated from the number of inhabitants under 5 years of age in the region under investigation and the national disease frequency during the same time within the study period. The SIR is always given together with the corresponding 95% CI. SIR are presented for

- the whole KiKK study region (including, in contrast to the KiKK study, some cases for which name and address were unknown) and
- all 15 groups of administrative districts assigned to the individual NPP sites. It should be noted that some of the administrative districts were assigned to two or more NPP and thus were included in two or more SIR calculations (e.g., the administrative district of Stade belongs to the NPP at Brunsbuettel, Brokdorf, and Stade).

The study period was defined individually for each NPP. (The year of diagnosis had to be between 1980 and 2003, and the diagnosis had to be made no less than 1 year after the commissioning date of the NPP and no more than 5 years after the NPP ceased operation.)

The type of settlement in a community is divided by the German Federal Office for Building and Regional Planning into 17 categories (as of 31 December 2001), grouped into three classes : "urban," "mixed," and "rural." The classification applies to the whole community, so that an outlying settlement defined administratively as part of a nearby town will count as "urban," despite its possibly rural character.

The question the recent study sets out to answer was whether children with cancer lived, on average, closer to an NPP than randomly selected healthy control children. Specifically, it was investigated whether there is a connection between the distance from residence to nearest NPP and the occurrence of a malignant disease (formulated statistically as a one-sided proposition).

In the KiKK study, as in the preceding studies, an increased risk of leukemia was observed for children under the age of 5 years who live within 5 km of an NPP. In light of the available data on the radiation emitted by German power reactors during normal operation, however, a direct link with the radiation seems implausible on the basis of current knowledge.

In this article the authors report the results of a series of analyses extending beyond the original evaluation concept and the concluding report *(tables 1, 2, 3)*, as well as additional analyses solely on the basis of data from the German Childhood Cancer Registry *(tables 4, 5)*.

Materials and methods

The methods of the KiKK study are described in detail elsewhere and are therefore outlined only briefly here *(box)* (7, 9). The KiKK study was a case-control study. A total of 41 administrative districts (Landkreise) in the vicinity of 16 NPP in western Germany were defined as the study region *(figure)*. Cases, as defined in the study, were all the children under 5 years of age diagnosed with a malignant disease (definition: [14]) between 1980 and 2003 who lived in the study region at the time of diagnosis and whose cases were notified to the German Childhood Cancer Registry (15). Altogether there were 1592 children with malignant diseases, including 593 with leukemia. Two NPP, Lingen and Emsland, were built at the same site with different operating periods; thus, the study region comprised 15 sites with 16 NPP.

Results

KiKK study

The KiKK study showed that in Germany a relationship can be observed between proximity of residence to an NPP and the risk that a child will develop cancer before reaching 5 years of age. This connection, statistically confirmed in this study, holds only for the leukemias; for all other previously established diagnoses (brain tumors, embryonal tumors), no statistically significant results were found.

Table 1 shows the odds ratios (OR) for leukemia as a whole and its subgroups for the categories up to 5 km and up to 10 km. Within the 5-km zone the risk of leukemia is twice that elsewhere in the study region (OR = 2.19); for the 10-km zone the OR = 1.33. For *table 2* the zone of the study region more than 70 km from the nearest NPP was selected for comparison (reference category). An increased—albeit not statistically significant—OR of 2.27 can be seen for the 5-km zone, while in all other, more distant zones of the study region the OR lies between 0.90 (50- to 70-km zone) and 1.11 (30- to 50-km zone), with no distance trend discernible.

Time-dependent odds ratios and the influence of the "Krümmel region"

The KiKK study embraced the period from 1980 to 2003. The first NPP study covered the years 1980 to 1990, while the second took place in the period 1991 to 1995. The current third study additionally included the years 1996 to 2003; thus only some of the data are "new."

Table 3 shows the OR for these three consecutive periods for the 5-km zone around the NPP (leukemia: OR = 3.00 for 1980 to 1990, OR = 2.10 for 1991 to 1995 [both statistically significant], OR = 1.78 for 1996 to 2003).

Since 1990 considerably more children than would be expected have developed leukemia around the NPP at Krümmel, Schleswig-Holstein. Intensive investigations have failed to identify a reason. From 1990 to 2006, 16 cases of leukemia were detected in children under 15 years of age in the communities of Geesthacht and Elbmarsch. Up to 2003 (the end of the KiKK study period) there were 14 cases of leukemia. Eight of the children affected were under 5 years old at disease onset and living in the 5-km zone, and were therefore included in the KiKK study *(table 3)*. Altogether, 30 children under the age of 5 from the study area around the NPP Krümmel (administrative districts Duchy of Lauenburg, Harburg, and Lueneburg) were included in the KiKK study ("Krümmel cases"). The result of dichotomous analysis with the border at 5 km changes only little if these 30 cases are left out of consideration: OR = 2.19 for 1980 to 2003 for all 16 NPP; OR = 1.96 without Krümmel *(table 3)*.

Standardized incidence ratios (SIR) for the whole study region and individual NPP areas

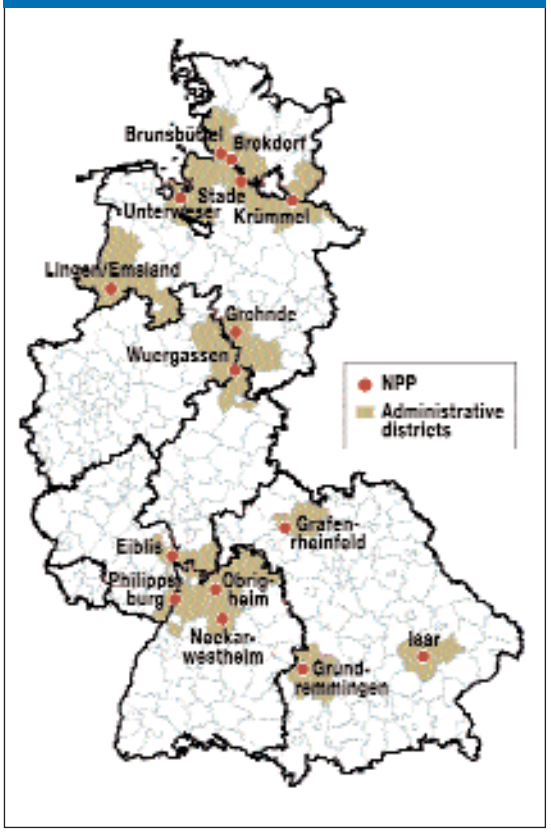
Table 4 shows the SIR for the whole study region and for the areas around the 15 NPP sites. Neither for the whole study region nor for the individual NPP areas was a statistically significant deviation from the national average observed. The overall SIR for all 41 administrative districts was 0.99 (CI 0.92 to 1.07). The SIR values varied from 0.85 to 1.21 for the 15 groups of administrative districts around the individual NPP sites.

Table 5 shows SIR by distance from the center of the community to the nearest NPP. The SIR value for the 5-km zone was 1.41. The 95% CI spans 1, so this SIR is not statistically significantly increased. The SIR values for communities whose centers are more than 5 km from the nearest NPP (5 to 10 km, 10 to 30 km, 30 to 50 km, 50 to 70 km, over 70 km) were statistically insignificant; they lay between 0.85 and 1.00.

Dividing the communities whose central points lay in the 5-km zone by type of settlement, the SIR was 1.81 (CI 0.73 to 3.72, based on 7 cases of disease) for rural localities, 1.18 (CI 0.69 to 1.90, 17 cases) for mixed settlements, and 1.71 (CI 0.82 to 3.14, 10 cases) for urban areas. None of these SIR values are statistically significantly elevated, and no trend is discernible (data not shown).

Evaluation of the case-control study showed a clear-cut increase in risk for cases from rural localities.

FIGURE



The KiKK study region, showing the names of the nuclear power plants and the extent of the administrative districts

Nevertheless, the estimator for the OR of the 5-km zone varied hardly at all after adjustment for these variables (2.21 vs 2.19). Thus the observed effect cannot be explained by the fact that NPP are preferably located in rural areas.

Discussion

The strength of the KiKK study lies in its consideration of all NPP regions of Germany collectively, enabling conclusions based on the greatest available number of relevant cases of disease. Notably, even after the pooling of all data, in the 24-year study period only 37 cases of leukemia in children under 5 within the 5-km zone were included in the evaluation (out of a total of 5893 cases of leukemia). Separate analysis for each individual NPP is therefore not meaningful with the selected study design.

The KiKK study has repeatedly been described as "the most painstakingly designed and most exhaustive survey worldwide" (e.g., press release of the Federal Office for Radiation Protection, 10 December 2007). This statement is not intended to conceal the fact that the present study, in common with almost all empirical, nonexperimental investigations, features potential distortions and limitations that can be clearly enumerated and must be taken into consideration when evaluating the findings. Some have already been described by Schulze-Rath et al. (17). Compared with the earlier incidence studies, the new case-control study has a different

TABLE 1

Estimated odds ratios (OR) with lower limit of one-sided 95% confidence interval (CI) for two distance classes: all leukemias and diagnostic subgroups*1

	Odds ratio	Lower limit of 95% CI	Cases in 5-km zone (n)
All leukemias			
≤ 5 km vs > 5-km zone	2.19*2	1.51	37
≤ 10 km vs > 10-km zone	1.33*2	1.06	95
Acute lymphoblastic leukemia			
≤ 5 km vs > 5-km zone	1.98*2	1.33	30
≤ 10 km vs > 10-km zone	1.34*2	1.05	84
Acute myeloid leukemia			
≤ 5 km vs > 5-km zone	3.88*2	1.47	7
≤ 10 km vs > 10-km zone	1.30	0.66	10

*1 Age under 5 years, according to (8)
*2 Significant at 5% one-sided

TABLE 2

Estimated odds ratios (OR) with lower limit of one-sided 95% confidence interval (CI) and numbers of cases and controls by distance from nearest nuclear power plant*1

Zone	Categorical OR	Lower limit of 95% CI	Cases n	Controls n
< 5 km	2.27	0.80	37	54
5 to < 10 km	1.09	0.40	58	173
10 to < 30 km	1.01	0.38	332	1048
30 to < 50 km	1.11	0.41	135	387
50 to < 70 km	0.90	0.32	27	92
≥ 70 km*2	1.00	–	4	12

*1 Leukemias in children under 5 years, according to (8)
*2 Reference category

method with different disadvantages. Some important limitations of the KiKK study are discussed below.

It must be realized that the data of the most recent study are not independent from the data of the two preceding studies by the German Childhood Cancer Registry and do not constitute independent confirmation of the findings of earlier German studies. Increased incidence in the immediate vicinity of power reactors leads both to an increased SIR for communities in the area concerned (the approach of the first two incidence studies and the new analysis in *table 5*) and to an increased OR in the case-control design. Thus, the OR of 3.00 for 1980 to 1990 *(table 3)* corresponds to the almost identical relative risk from the first NPP study (RR = 3.01) (8). The limitation of the study to children under 5 years of age and the determination of the predefined subsidiary issues for investigation with regard to the 5-km zone and the subgroup of leukemia were based on the corresponding findings of the first NPP study (10, 11). The OR values in *table 3* show a slightly decreasing tendency for the two periods after 1980 to 1990, to which the region around the NPP Krümmel made an essential contribution.

In case-control studies the nonresponse problem can lead to distortion of the results. Thus, in the most recent study the authors depended on the assistance of local authorities to recruit controls. Not all of them cooperated, the willingness to help varying according to the distance from the NPP. The consequences of this incomplete and sometimes error-prone recruitment of controls were, as far as possible with the available data, described in detail in sensitivity analyses in the concluding report (9). These problems with control recruitment may have led to slight overestimation of the effect.

The decision to base the study region on the boundaries of administrative districts led to anomalies. For instance, any town that constituted its own administrative unit rather than being part of a district was not included, regardless of its proximity to the NPP concerned. Administrative districts have irregular boundaries, leading to inclusion of some communities very far from an NPP and exclusion of other communities that were much closer.

In none of the three NPP studies could confounders be taken into account. In the incidence studies, only the type of community was considered as potential influencing factor. The most recent study stratified individually by age, sex, year, and NPP area. A supplementary analysis also examined the influence of community type. Consideration of other potential confounders (e.g., social status) was categorically excluded in the earlier studies, and they were also not investigated in the KiKK study, for the reasons detailed in the concluding report (9).

In both study types (incidence studies, case-control study), only the residential address at the time of diagnosis was used to determine distance; previous addresses were disregarded. Moreover, no information is available as to whether or for how long the children actually resided at that address before the onset of illness (extended visits to grandparents, time spent in crèches, with child minders, in kindergarten, on holiday, etc.). However accurate the individual distance determination, it may therefore not reflect the true "exposure" to the NPP.

The problem of interpreting distance as a measure of radiation exposure is shared by all three NPP studies. No data on radiation exposure were available; in particular, the natural background exposure was not taken into account. The variation in natural radiation exposure in Germany is many times higher than the radiation exposure from an NPP in normal operation.

The modeling of a constant distance curve has statistical advantages over categorical models (18, 19). On the other hand, it carries the inherent risk that a function will be fitted that only partly reflects the true trend of the data. This holds particularly when the distribution of the exposed probands tends to be uneven. Furthermore, certain basic assumptions cannot be disregarded in the

TABLE 3

Odds ratios (OR) with lower limit of one-sided 95% confidence interval (CI) for leukemias and assignment to the category of "Krümmel cases," by period*1

	< 5 years				< 15 years
Period*1	OR*3	OR*3 without the 30 cases from the Krümmel area	KiKK study patients from the whole Krümmel area*4	KiKK study patients from the Krümmel 5-km zone*5	Cases forming the known "Krümmel cluster"*5
1980–1990	3.00*2 (1.54)	2.78*2 (1.42)	9	1	4
1991–1995	2.10*2 (1.04)	1.79 (0.76)	9	4	5
1996–2003	1.78 (0.99)	1.52 (0.81)	12	3	5
1980–2003	2.19*2 (1.51)	1.96*2 (1.31)	30	8	14

*1 Analogous to the study periods of the three NPP studies carried out with data from the German Childhood Cancer Registry
*2 Significant at 5% level, one-sided
*3 Residential address within 5 km or over 5 km (in parentheses, lower limit of CI)
*4 "Kruemmel cases" from the "KiKK administrative districts" (Duchy of Lauenburg, Harburg, and Lueneburg)
*5 From the communities of Geesthacht and Elbmarsch

modeling. It is particularly important to ensure that the observed data, by definition, do not include any "non-exposed" probands. In other words, the curve assigns an "exposure-dependent risk" to every individual, regardless of distance. It therefore makes sense, for example, to calculate attributable cases only for the range of distance with a genuinely clear effect. Attributable cases are cases that—assuming causality—could be put down to residing in the vicinity of an NPP. Derivation from the complete fitted curve is mathematically feasible, but implies the assumption that a quantitatively relevant "effect" persists right to the outer margin of the study area. This cannot be substantiated by the categorical analyses. These aspects were not taken into consideration in the critical discussion of the authors' evaluation of the study, a theme also taken up in the pages of Deutsches Ärzteblatt (20).

Not unexpectedly, in view of the topic, the public discussion has been heated and emotional (21). Thus, opinions differ as to whether the results indicate a causal relationship with the exposure to ionizing radiation from NPP. Based on the findings of radiation research such a connection seems implausible, because the radiation emitted by an NPP in normal operation is at least 1000 times lower than "background radiation," i.e., the 1.4 mSv of natural radiation to which the average German is exposed in a year (22). This comparison is based on a report commissioned by the European Union (23), which gives cumulative lifetime exposure of 0.0003200 to 0.0000019 mSv for a 50-year-old person living within 5 km of a German NPP. In their interpretation of the data, the authors assume normal operation of the NPP. The authors do not know to what extent incidents involving leakage of radiation may have occurred. No major incidents in Germany are known.

In May 2008 an international workshop on the causes of childhood leukemia, co-organized by the Federal Office for Radiation Protection, was held in Berlin. Participants emphasized that many different factors are involved in the etiology and that a simple monocausal interpretation of the present study's findings is not permissible (6, 24). Unfortunately, it cannot currently be ascertained whether several such factors occur together in the vicinity of German NPP, thus determining the study's findings. The authors' analyses show that living in a rural area is associated with a higher risk of leukemia, but this has no decisive influence on the main conclusion of the study.

After publication of the recent study, the authors were constantly approached by concerned citizens wanting to know whether it was dangerous to live in the area of an NPP and whether they should perhaps consider moving away. The SIR calculations for the KiKK study, presented here for the first time, are therefore of particular interest. For the whole study region they show almost exact agreement with the national incidence rate. The disease rates in the individual NPP areas fluctuate randomly above or below the national average, but the observed SIR values all lie within the statistical range of fluctuation. While one approach yields a striking result for the 5-km zone (OR = 2.19 *[table 1]*), the other approach gives a result which, though also increased, is not statistically significant (SIR = 1.41 *[table 5]*). Since the determination of distance using the central point of the community was much less exact than using individual residential addresses, as in the case-control study, a correspondingly less clear measure of effect was to be expected. In this respect the two approaches are not contradictory. Nevertheless, the disease rates, both for the individual NPP sites in the KiKK study with their

TABLE 4

Observed and expected numbers of cases of leukemia and standardized incidence ratios (SIR) with 95% confidence intervals (CI)—whole study region*1

Region Name of nuclear power plant	Observed*2	Expected*2, 3	SIR	Lower limit of 95% CI	Upper limit of 95% CI
Whole study region	619	623.67	0.99	0.92	1.07
Administrative district groups (15 NPP sites)					
Brunsbüttel	33	38.16	0.86	0.60	1.21
Brokdorf	58	49.72	1.17	0.89	1.51
Krümmel	40	40.56	0.99	0.70	1.34
Stade	67	57.10	1.17	0.91	1.49
Unterweser	34	34.51	0.99	0.68	1.38
Lingen/Emsland	55	56.11	0.97	0.73	1.26
Grohnde	49	42.14	1.16	0.86	1.54
Würgassen	40	42.16	0.95	0.68	1.29
Grafenrheinfeld	24	21.26	1.13	0.72	1.68
Biblis	51	60.20	0.85	0.63	1.11
Obrigheim	31	33.96	0.91	0.62	1.30
Neckarwestheim	121	120.96	1.00	0.83	1.20
Philippsburg	111	104.95	1.06	0.87	1.27
Isar	31	25.54	1.21	0.82	1.70
Gundremmingen	38	42.00	0.90	0.64	1.24

*1 For the whole study region and for the 15 groups of administrative districts assigned to the individual NPP sites (95% CI corresponds to two-sided test at 5% level)
*2 Leukemias in children under 5 years old
*3 Expected incidence based on known incidence for whole of Germany

TABLE 5

Observed and expected numbers of cases of leukemia and standardized incidence ratios (SIR) with 95% confidence intervals (CI)—by distance to nuclear power plant*1

Zone	Observed*2	Expected*2, 3	SIR	Lower limit of 95% CI	Upper limit of 95% CI
< 5 km	34	24.09	1.41	0.98	1.97
5 to < 10 km	61	62.89	0.97	0.74	1.25
10 to < 30 km	356	364.20	0.98	0.88	1.08
30 to < 50 km	140	140.39	1.00	0.84	1.18
50 to < 70 km	23	27.08	0.85	0.54	1.27
≥ 70 km	5	5.02	1.00	0.32	2.32

*1 By distance of central point of each community in the study region to nearest NPP (95% CI corresponds to two-sided test at 5% level)
*2 Leukemias in children under 5 years
*3Expected incidence based on known incidence for whole of Germany

associated groups of administrative districts and for the whole study region with all 16 NPP, were unremarkable *(table 4)*. The central 5-km zones represent only a small fraction (<5%) of the total study region.

Acknowledgement
Thanks are due to all those who engaged themselves constructively and critically with the study and its conduct and supported the authors. Gratitude is owed to the authors' colleagues, the parents involved in the study's survey component, the local authority registration offices and data centers for providing addresses, and the Society for Paediatric Oncology and Haematology (GPOH) and its clinical studies, without which the high quality of the data in the German Childhood Cancer Registry would not be assured. The authors are particularly grateful to the Federal Ministry for the Environment, Nature Conservation and Nuclear Safety and the Federal Office for Radiation Protection (BfS) for financing the KiKK study (project no. StSch 4334) and to the Expert Commission of the BfS. The authors thank the Robert Koch Institute for conducting the study audit suggested by the Expert Commission and the Coordinating Center for Clinical Studies (KKS) of the Faculty of Medicine, University of Mainz, for checking their calculations. The authors expressly thank the following individuals: J. Michaelis and J. Schüz für scientific advice; the research assistants A. Mergenthaler, E. Münster, S. Schmiedel, and R. Schulze-Rath; the project assistants M. Kaiser, S. Kleinefeld, and C. Trübenbach; the student assistants J. Albrecht, C. Hornbach, and S.Weinand; and the interviewers A. Becht, B. Grossmann, B. Haupt, B. Krey, L. Krille, F. Müller, P. Quetsch, R. Schmunk, R. Tekie, and C. Varlik. They thank M. Ressing for looking through the manuscript and for constructive suggestions.

Conflict of interest statement
The authors declare that no conflict of interest exists according to the guidelines of the International Committee of Medical Journal Editors.

Manuscript received on 23 July 2008, revised version accepted on 18 September 2008.

Translated from the original German by David Roseveare.

REFERENCES

1. Kaatsch P, Spix J: Jahresbericht 2006/07 (1980–2006) des Deutschen Kinderkrebsregisters. www.kinderkrebsregister.de. Institut für Medizinische Biometrie, Epidemiologie und Informatik, Universität Mainz 2008.
2. Kaatsch P, Steliarova-Foucher E, Crocetti E, Magnani C, Spix C, Zambon P: Time trends of cancer incidence in European children (1978–1997): report from the ACCIS project. Eur J Cancer 2006; 42: 1961–71.
3. Spix C, Eletr D, Blettner M, Kaatsch P: Temporal trends in the incidence rate of childhood cancer in Germany 1987–2004. Int J Cancer 2008; 122: 1859–67.
4. Alexander FE, Boyle P, Carli PM, Coebergh JW, Draper GJ, Ekbom A et al.: Spatial temporal patterns in childhood leukaemia: further evidence for an infectious origin: EUROCLUS project. Br J Cancer 1998; 77: 812–7.
5. Greaves MF, Alexander FE: An infectious etiology for common acute lymphoblastic leukemia in childhood? Leukemia 1993; 7: 349–60.
6. Schüz J, Blettner M, Michaelis J, Kaatsch P: Ursachen von Leukämien im Kindesalter: Resümee einer Fallkontrollstudie des Deutschen Kinderkrebsregisters. Dtsch Arztebl 2005; 102(38): A 2557–64.
7. Spix C, Schmiedel S, Kaatsch P, Schulze-Rath R, Blettner M: Case-control study on childhood cancer in the vicinity of nuclear power plants in Germany 1980–2003. Eur J Cancer 2007; 44: 275–84.
8. Kaatsch P, Spix C, Schulze-Rath R, Schmiedel S, Blettner M: Leukaemia in young children living in the vicinity of German nuclear power plants. Int J Cancer 2008; 122: 721–6.
9. Kaatsch P, Spix C, Schmiedel S, Schulze-Rath R, Mergenthaler A, Blettner M: Epidemiologische Studie zu Kinderkrebs in der Umgebung von Kernkraftwerken (KiKK-Studie) – Abschlussbericht. Umweltforschungsplan des Bundesumweltministeriums (UFOPLAN) – Reaktorsicherheit und Strahlenschutz. Bundesamt für Strahlenschutz. Salzgitter 2007.
10. Michaelis J, Keller B, Haaf G, Kaatsch P: Incidence of childhood malignancies in the vicinity of West German nuclear power plants. Cancer Causes Control 1992; 3: 255–63.
11. Michaelis J, Haaf G, Kaatsch P, Keller B: Krebserkrankungen im Kindesalter in der Umgebung westdeutscher kerntechnischer Anlagen. Dtsch Arztebl 1992; 89(30): A 2538–44 .
12. Kaatsch P, Kaletsch U, Meinert R, Michaelis J: An extended study on childhood malignancies in the vicinity of German nuclear power plants. Cancer Causes Control 1998; 9: 529–33.
13. Michaelis J, Kaatsch P, Kaletsch U: Leukämien im Kindesalter – Epidemiologische Untersuchungen des Deutschen Kinderkrebsregisters. Dtsch Arztebl 1999; 96(14): A 918–24.
14. Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P: International Classification of Childhood Cancer, Third Edition. Cancer 2005; 103: 457–67.
15. Kaatsch P: Deutsches Kinderkrebsregister – Eine international angesehene Datenquelle. Dtsch Arztebl 2005; 102(20): A 1421–2.

16. United Nations Scientific Committee on the effects of atomic radiation (UNSCEAR). Sources and effects of ionizing radiation; Report 2000; Vol. I Sources, Annex A: Dose assessment methodologies, Chapter III „Atmospheric dispersion from a near-surface release". New York, United Nations 2000.
17. Schulze-Rath R, Kaatsch P, Schmiedel S, Spix C, Blettner M: Krebs bei Kindern in der Umgebung von Kernkraftwerken: Bericht zu einer laufenden epidemiologischen Studie. Umweltmed Forsch Prax 2006; 11: 20–6.
18. Lagakos SW: Effects of mismodelling and mismeasuring explanatory variables on tests of their association with a response variable. Stat Med 1988; 7: 257–74.
19. Greenland S: Dose-response and trend analysis in epidemiology: alternatives to categorical analysis. Epidemiology 1995; 6: 356–65.
20. Richter-Kuhlmann E: Streit um Kausalzusammenhang. Dtsch Arztebl 2008; 105(20): A 1052–3.
21. Kaatsch P: Empfehlungen für eine gute Risikokommunikation – Erfahrungen anhand deutscher Studien zu Krebs bei Kindern und Wohnortnähe zu Kernkraftwerken. Umweltmed Forsch Prax 2006; 11: 27–31.
22. Bundesamt für Strahlenschutz, Umweltradioaktivität und Strahlenbelastung: Jahresbericht 2005. Bundesministerium für Umwelt, Naturschutz und Reaktorsicherheit 2006.
23. Smith JG, Bexon A, Boyer FHC, Harvey M, Jones AL, Kindler T et al.: Assessment of the radiological impact on the population of the European Union from European Union nuclear sites between 1987 and 1996. Luxembourg. Office for Official Publications of the European Communities 2002.
24. International Commission on Non-Ionizing Radiation Protection (ICNIRP). Risk factors to childhood leukemia. Proceedings of the International ICNIRP/WHO/BfS Workshop. Berlin, 5–7 May 2008. Radiat Prot Dosimetry, Special Issue, in press.

Corresponding author
Dr. rer. physiol. Peter Kaatsch
Institut für medizinische Biometrie, Epidemiologie und Informatik
Klinikum der Johannes Gutenberg-Universität Mainz
Obere Zahlbacher Str. 69
55131 Mainz, Germany
kaatsch@imbei.uni-mainz.de