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Assessment of the Epidemiological Study on Childhood Cancer in the Vicinity of Nuclear Power Plants (KiKK Study)

Statement of the Commission on Radiological Protection (SSK)

Approved at the 227th meeting of the Commission on Radiological Protection, held on 25/26 September 2008

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Bewertung der epidemiologischen Studie zu Kinderkrebs in der Umgebung von Kernkraftwerken (KiKK-Studie)

Stellungnahme der Strahlenschutzkommission

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In the event of any doubts about the meaning, the German original as published shall prevail.

Foreword

The study "Epidemiological Study on Childhood Cancer in the Vicinity of Nuclear Power Plants" ("Epidemiologische Studie zu Kinderkrebs in der Umgebung von Kernkraftwerken"; KiKK Study), which was presented to the public on 10 December 2007, found a statistical correlation between the proximity of a person's residence to the nearest nuclear power plant, at the time of diagnosis, and the person's risk of contracting cancer (or leukaemia) prior to his or her fifth birthday. Since, understandably, this result led to considerable public concern, the Federal Minister for the Environment, Nature Conservation and Nuclear Safety commissioned the Commission on Radiological Protection (SSK) to assess the KiKK Study and, especially, to answer the question of whether the radiation emitted by nuclear power plants could be responsible for the result found by the study.

To prepare for answering the questions listed in the advising order, the SSK appointed an interdisciplinary, international working group.

The members of the working group were as follows:

- Prof. Dr. Sarah Darby, University of Oxford, epidemiologist (corresponding member; led an independent check of the data)
- Dr. Peter Jacob, German Research Center for Environmental Health, Munich, risk analyst
- Prof. Dr. Rolf Michel, University of Hanover, radioecologist, Chairman of the SSK
- Prof. Dr. Wolfgang-Ulrich Müller, University of Essen, radiobiologist, Chairman of the Working Group
- Dr. Martin Röösli, University of Bern, epidemiologist
- Prof. Dr. Brigitte Stöver, Charité Berlin, children's radiologist
- Dr. Margot Tirmarche, IRSN; (Institute for Radiation Protection and Nuclear Safety), Paris, epidemiologist
- Prof. Dr. Dr. Heinz-Erich Wichmann, German Research Center for Environmental Health, Munich, epidemiologist.

To ensure that only scientific aspects entered into the assessment of the KiKK Study – and that no political influence of any sort was applied – only the members of the working group took part in the working group's meetings, and only the members of the SSK took part in the SSK's meetings. At the same time, the working group did invite guests to some of its meetings, with the aim of obtaining the most comprehensive picture possible:

23 January 2008, Bonn:	The authors of the KiKK Study
17 April 2008, Berlin:	Prof. Dr. Michael Atkinson/Dr. Michael Rosemann (molecular aspects)
17 April 2008, Berlin:	The group of experts that defined the specifications for the KiKK Study and followed the study
08 May 2008, Berlin:	Prof. Dr. Sarah Darby, Dr. Colin Muirhead, Simon Read (experience gained in the UK)
15 May 2008, Munich:	The Federal Office for Radiation Protection (BfS)

29 July 2008, Bonn: Prof. Dr. Sarah Darby and Simon Read (via videoconference).

The SSK considered the KiKK Study at its meetings on the following dates:

13 May, 3 July, 5 August, 4 and 25 September 2008.

Since the Federal Environment Minister expected the questions in the advising order to be answered as quickly as possible, it was clear from the outset that the SSK would be subject to enormous time pressure. In the course of relevant deliberations, it emerged that it would not be possible to complete both the SSK's statement of position and the pertinent scientific annex by the originally specified date (end of September 2008). For this reason, and in light of the extensive editorial work required for the scientific annex, it was decided, in agreement with the Federal Environment Ministry (BMU), to publish the scientific annex later, along with all pertinent details and all literature citations. The annex includes detailed positions regarding the numerous commentaries provided, outside of the SSK framework, with regard to the KiKK Study. Consequently, the KiKK Study will concern the SSK in further meetings of the SSK.

Anyone who has followed the discussion in connection with the KiKK Study should not be surprised that the SSK was also unable to answer the question regarding the cause of the result reported in the KiKK Study. The SSK has been able to conclude, however, that certain causes can be ruled out in light of knowledge available to date. In addition, the SSK has issued proposals for efforts that should be undertaken in future in order to clarify this matter.

Prof. Dr. R. Michel

Chairman of the
Commission on Radiological Protection
(SSK)

Prof. Dr. W.-U. Müller

Chairman of the working group

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1 Summary

On 10 December 2007, the study "Epidemiological Study on Childhood Cancer in the Vicinity of Nuclear Power Plants" ("Epidemiologische Studie zu Kinderkrebs in der Umgebung von Kernkraftwerken"; KiKK Study)[1] was presented to the public. The authors summarised the study's main finding as follows: "*Our study has confirmed that a correlation is observed in Germany between the proximity of a person's residence to the nearest nuclear power plant, at the time of a relevant diagnosis, and the person's risk of contracting cancer (or leukaemia) prior to his or her fifth birthday. This study cannot provide any information as to what biological risk factors might explain this correlation.*"

The results of the deliberations of the Commission on Radiological Protection (SSK; Strahlenschutzkommission) can be summarised as follows:

- The KiKK Study's new data confirm the results of earlier exploratory studies that found an increased risk of leukaemia, for children younger than five, within a 5 km radius around German nuclear power plants, relative to the risk in the outer areas around the relevant study areas. Studies carried out in other countries produced conflicting findings, however. It thus cannot be concluded with finality that there is any evidence for increased rates of leukaemia, in general, in the vicinity of nuclear power plants.
- By virtue of its design, the KiKK Study exhibits numerous methodological weaknesses with regard to determination of exposure and surveying of influencing factors. Consequently, the study should not have been carried out in the manner in which it was carried out. In spite of such weaknesses, the study's design is suitable for the task of analysing dependence on distance.
- The evidence for increased cancer rates in children is limited to areas that are no more than 5 km from the relevant nuclear power plant sites. There is thus no justification for using attributable risks to calculate hypothetical additional cancer cases for greater distances.
- The study is thus not suited to the task of establishing a correlation with exposure to radiation from nuclear power plants. All of the radioecological and risk-based circumstances reviewed by the SSK indicate that exposure to ionising radiation caused by nuclear power plants cannot explain the result found by the KiKK Study. The additional radiation exposure caused by nuclear power plants is lower, by a factor of considerably more than 1,000, than the radiation exposure that could cause the risks reported by the KiKK Study.
- The natural radiation exposure within the study area, and its fluctuations, are both greater, by several orders of magnitude, than the additional radiation exposure caused by the relevant nuclear power plants. If one assumes that the low radiation exposures caused by the nuclear power plants are responsible for the increased leukaemia risk for children, then, in light of current knowledge, one must calculate that leukaemias due to natural radiation exposure would be more common, by several orders of magnitude, than they are actually observed to be in Germany and elsewhere.

[1] Kaatsch, P.; Spix, C.; Schmiedel, S.; Schulze-Rath, R.; Mergenthaler, A.; Blettner, M.: Epidemiologische Studie zu Kinderkrebs in der Umgebung von Kernkraftwerken.
In addition, the findings of the KiKK Study were published in scientific journals:
Kaatsch et al., Int. J. Cancer: 1220, 721–726 (2008) and Spix et al., Eur J Cancer. 44, 275-284 (2008)

- The KiKK Study was unable to survey risk factors to a sufficient degree. For this reason, the KiKK Study cannot be used to help explain the causal reasons for the observed distance dependence of leukaemia rates.
- The reason for the increased leukaemia rate that the KiKK Study observed in children is unclear. Since leukaemia is caused by multiple factors, numerous influencing factors could have been responsible for the observed result. If the many relevant conflicting findings in the literature, and the finding of the KiKK Study, are to be understood, more extensive, interdisciplinary research into the causes and mechanisms of the development of leukaemias in children will have to be carried out.

2 The KiKK Study

2.1 Background

In about the year 1970, considerable controversy arose in the U.S. regarding the possibility of increased rates of infant mortality in the vicinity of nuclear facilities. Since then, it has been repeatedly suggested that nuclear power plants pose a threat to public health, and numerous relevant epidemiological studies, especially studies focussing on leukaemias in children, have been carried out. In general, no correlation has been found between nuclear power plants (i.e. power-generation facilities) and leukaemias in children. The situation is somewhat more open to debate with regard to nuclear facilities designed for purposes other than energy generation (such as reprocessing facilities). Some studies of nuclear power plants found higher rates in certain age and distance groups (i.e. groups of people within certain ranges of distance from nuclear power plants). This was the case, for example, for assessments carried out by the German Childhood Cancer Registry (GCCR) in Mainz in 1992 and 1997 for the group consisting of children younger than five and living no further than 5 km from a nuclear power plant.

The relevant correlations were examined by means of either "ecological studies" or "case-control studies". In ecological studies, different groups of persons are compared for which no individual data are available. Such studies can produce enormously erroneous conclusions. Case-control studies, by contrast, can be considerably more reliable, since their analyses are based on individual characteristics of cases of illness and of healthy control persons. In the following, these two groups are referred to as "cases" and "controls".

With such background in mind, the Federal Office for Radiation Protection (BfS) launched a case-control study in 2001, in an effort to obtain more reliable findings with regard to the relationship between children's cancer – especially leukaemias – and the vicinities of nuclear power plants. As part of this effort, a range of groups met in a "round-table" format. As a result of this work, a 12-member body of experts with epidemiological expertise then defined the type of study to be carried out and the pertinent questions to be considered. A call for proposals was then issued, as a result of which the German Childhood Cancer Registry (GCCR) in Mainz was commissioned to carry out the study. The study began in 2003.

2.2 Design of the KiKK Study

The "design" of a study is taken to mean the planning for a study, including the concepts to be applied in evaluating the study's results. The KiKK Study was set up to investigate

whether there is any correlation between residential distance to a nuclear power plant and the risk of contracting cancer by the age of five. In the process, distance was to serve as an approximation (proxy) for the radiation exposure caused by nuclear power plants (p. 29 of part 1 of the study). The KiKK evaluation plan states as follows in Chapter 3.3.1: "*The children's dose and exposure are estimated via the distance from the children's main residence at the time of diagnosis (in the case of controls: month in which the pertinent case is diagnosed) to the single nearest power reactor in an operational phase."*

Chapter 3.3.2 goes on to state as follows: "*From the hypothesis presented (Chapter 3.1), two basic requirements pertaining to modelling of the dose-impact relationship result: 1. The dose figures as a constant factor ("distance trend"); 2. The dose-effect relationship is assumed to be monotonous; i.e. if the risk depends on dose, then the risk increases with increasing dose ("negative distance trend")."*

The final report (KiKK Part 1, Chap. 2.5.2, p. 29) also explicitly formulates the relationship between dose and distance measure: "*In keeping with perspectives of radiation biology, epidemiology uses models of the type* ***relative risk (x) = 1+βx*** *(linear no threshold), where x is the cumulative radiation dose."* [2]

The study's main hypothesis was reviewed via a case-control study without any surveys of cases and controls (part 1 of the study). Another task consisted of identifying any possible "confounders", or disruptive factors. This was to be carried out in a second step, with the help of a survey of a sub-group of the population studied in part 1 of the study (part 2 of the study)[3].

2.3 Execution of the KiKK Study

The authors of the KiKK Study stuck closely to the pertinent operations manual and to the tasks prescribed in the evaluation plan.

The study regions corresponding to the 16 nuclear power plants included in the study were normally defined in terms of the rural district (Landkreis) in which the relevant nuclear power plant is located, the nearest neighbouring rural district and the nearest rural district to the east. In some cases, a fourth rural district was also included, to ensure complete coverage of areas covered by earlier studies.

In Part 1 of the KiKK Study, the study period began, in each case, one year after a reactor was commissioned at the pertinent location. In no instance did it begin earlier than 1 January 1980, however. The study period ended, in each case, 5 years after the last reactor at the pertinent location was decommissioned, or no later than 31 December 2003. The study period was divided into two partial periods, of which the first comprised the first 11 years of the relevant study period.

The cases consisted of all new tumours reported in the German Childhood Cancer Registry (GCCR) in Mainz, for the study region (place of residence at the time of diagnosis) and the study period, and classified as malignant pursuant to the International Classification of

[2] In case-control studes, the odds ratio (OR) is determined. Where the prevalence is low, the OR can serve as a good approximation for the relative risk, which is used here in the discussion following.

[3] Note: Where reference is made, in the following, to the "KiKK Study", then such reference always includes both parts of the study. Specific references to only one of the two parts are identified via the terms "KiKK Study Part 1" and "KiKK Study Part 2". In this connection, the publications Kaatsch et al., Int. J. Cancer: 1220, 721–726 (2008) and Spix et al., Eur J Cancer. 44, 275-284 (2008) should also be considered, in the interest of completeness.

Childhood Cancer (ICCC). Analyses were also carried out for the following sub-groups: Leukemias (ICCC: Ia-Ie), acute lymphatic leukaemias (Ia), acute myeloic leukaemias (Ib), tumours of the central nervous system (ZNS, IIIa-IIIf) and embryonic tumours[4] (IVa, V, VIa).

The controls agreed with the cases in terms of sex and year of birth, and they lived in the same relevant nuclear power plant region when they were of the ages at which the cases were diagnosed. In each case, the relevant municipalities were requested to provide a total of six control addresses. For each case, three of the reported control addresses were selected at random.

The distance to the oldest exhaust chimney at the relevant nuclear power plant site was determined for all residential addresses of cases and controls.

The KiKK Study hypothesis defined in advance by the body of experts (null hypothesis) was as follows: *"There is no correlation between residential proximity to a nuclear power plant and the risk of contracting cancer by the age of five. There is no negative distance trend for the risk of contracting cancer."* The alternative hypothesis was as follows: "*There is a negative distance trend. Cases tend to be more common in the vicinity of a nuclear power plant."*

The data (odds ratios as approximations for the relative risk) for matched cases and controls were evaluated both continuously and categorially, and the hypothesis was tested one-sidedly.

In continuous evaluation, the best estimate for a parameter β, pursuant to a relative risk model selected in accordance with radiobiological criteria, $(x) = 1 + \beta x$ with $x = 1/r$, was determined from the data for the matched cases and controls, and the lower one-sided 95 % confidence limit was determined. The null hypothesis was to be rejected if β proved to be significantly greater than zero.

In categorial evaluation, the data for the matched cases and controls were evaluated pursuant to the categories of "residences at a distance of up to 5 km" and "residences at a distance of more than 5 km". Analogous evaluation was carried out for categories with a distance boundary of 10 km. In addition, for each of these categories an odds ratio (OR) was estimated, as an approximation for the relative risk for the comparison of "within" and "outside of" the relevant distance boundaries, along with the lower one-sided 95 % confidence limit. The null hypothesis was to be rejected if an OR proved to be significantly greater than one.

Part 2 of the KiKK Study was to take account of possible risk factors that could function as confounders. Each of the case and control families was sent an informational flyer and a short questionnaire. It was indicated that the impacts of environmental and living conditions on occurrence of cancers in children were to be studied. Those families who did not respond, and whose child was not known to have died of cancer in the meantime, were contacted by phone where possible.

A computer-aided telephone interview was conducted with those families who were willing to cooperate. Wherever possible, the child's biological mother was interviewed.

[4] Embryonic tumours form during organ development, via tissue misdifferentiation. The embryonic tumours include, inter alia, Wilms' tumours, retinoblastomas and neuroblastomas.

2.4 Results of the KiKK Study

In Part 1 of the study, the distances from the residential communities to the nearest nuclear power plant were evaluated, in the period 1980 to 2003, for 1,592 cases of cancer in children younger than five reported in the vicinity of 16 German nuclear power plants. The distances were also evaluated for 4,735 control persons. For all cases of cancer, including leukaemia, the analysis found a significant result for the coefficient of the inverse distance from residential address, at the time of the cancer diagnosis, and the nearest nuclear power plant ($\beta = 1.18$; lower one-sided 95 % confidence limit: 0.46)[5]. In sub-period 1, the best estimate of the distance coefficient was 1.89 (lower one-sided confidence limit: 0.85), and in sub-period 2, it was 0.54 (lower one-sided confidence limit: -0.47) (Tab. 1). In light of the large statistical uncertainties involved, this difference is not significant, however. Within a 5 km radius around the nuclear power plants, the cancer risk for children younger than five was increased by a factor of 1.61 by comparison to the risk for the study area outside of the 5 km radius (lower one-sided 95 % confidence limit: 1.26, i.e. > 1).

Recruitment of controls was less successful in the inner vicinity of the nuclear power plants than it was in more distant regions, and this may have led to an overestimation of the mean distances of residential locations of control children. Confinement of the analysis to case-control data, which were provided for all controls, yielded a slight reduction of the distance coefficient (Tab. 1). Review also showed that erroneous addresses had been given for some cases and controls. Analysis of a random sample that excluded data for which address errors were found also showed a slight reduction of the distance coefficient. All in all, the sensitivity analyses carried out point to a lower distance coefficient than that obtained in the main analysis.

For leukaemias (593 cases, 1,766 controls), a larger distance coefficient was found than was found for all cancer cases ($\beta = 1.75$; lower one-sided 95 % confidence limit: 0.65). Within a 5 km radius around the nuclear power plants, the leukaemia risk for children younger than five was increased by a factor of 2.19 by comparison to the risk for the study area outside of the 5 km radius (lower one-sided 95 % confidence limit: 1.51).

[5] $\beta>0$ corresponds to an increasing risk as the distance to a nuclear power plant decreases.

Tab. 1: Compilation of some of the results of the KiKK Study for the regression coefficient (best estimate and lower one-sided 95 % confidence limit) of the dependence of the cancer risks, for children younger than five, on the inverse distance from the place of residence to the nearest nuclear power plant. A positive value corresponds to a decreasing risk as the distance increases. Sub-period 1 corresponds to the first half of the relevant reactor's operational phase; sub-period 2 corresponds to the second half

Cancers	Restriction of the study group	Number of incidences of cancer	Regression coefficient	
			Best estimate*)	Lower confidence limit
All cancer disorders	**None**	**1592**	**1.18**	**0.46**
	Sub-period 1	698	1.89	0.85
	Sub-period 2	894	0.54	-0.47
	Addresses for all control persons available	1310	1.01	0.47
	Addresses are correct	1132	1.05	0.59
Leukaemias	**None**	**593**	**1.75**	**0.65**
	Participation in telephone interview	273	0.44	-1.86
	Participants in Part 2 have addresses in the study area	230	0.33	-2.19
Acute lymphatic leukaemias	None	512	1.63	0.39
Acute myeloic leukaemias	None	75	1.99	-0.41
CNS tumours	None	242	-1.02	-3.40
Embryonic tumours	None	486	0.52	-0.83

*) The value is significant if the lower confidence limit > 0.

For acute lymphatic leukaemias, the best estimate of the distance coefficient was somewhat lower than that for all leukaemias, while for acute myeloic leukaemias the best estimate of the distance coefficient was somewhat higher than that for all leukaemias (Tab.

1). No statistical correlation was found between the risk of contracting CNS tumours and embryonic tumours and the distance to the nearest nuclear power plant.

At the request of the Commission on Radiation Protection (Strahlenschutzkommission), Sarah Darby and Simon Read carried out an independent analysis of the raw data of the KiKK Study (cf. Chap. 4Tab. 2 shows the analysis result for a categorial evaluation with no overlapping of the various categories. A significant increase was observed only at a distance of less than 5 km.

Tab. 2: Estimated odds ratios (relative risks) for acute leukaemias (n=587) in children younger than five, for 6 categories of distance from place of residence to the nearest nuclear power plant (S. Darby and S. Read 2008)

Distance from nuclear power plant in km	Odds ratio*)	95% confidence interval	P value for test for difference from the 10-29 km zone (two-sided)	Number of cases	Number of controls
< 5	2.27	(1.45 - 3.56)	0.0003	37	54
5-9	1.09	(0.78 - 1.52)	0.62	57	170
10-29	1.00	-	-	327	1,039
30-49	1.12	(0.87 - 1.43)	0.38	135	385
50-69	0.95	(0.56 - 1.61)	0.85	27	89
70+	1.11	(0.34 - 3.63)	0.86	4	11
Total number				587	1,748

*) The value is significant if the lower limit of the confidence interval > 1.

During the observation period, considerable numbers of people moved into the study regions. On average, the net influx into the regions around the various nuclear power plants amounted to several thousand people per year.

In Part 2 of the study, it was found that parents of cases in the vicinity of nuclear power plants responded considerably less frequently to questions put to them than did parents of controls. Analysis of leukaemia data for persons who participated in the telephone interview found a slight, non-significant distance coefficient ($\beta = 0.44$). Due to the large difference seen with regard to the results of Part 1 of the study, the authors did not rely on Part 2 of the study in interpreting the results of Part 1 of the study with regard to confounders (possible disruptive factors).

The analyses of possible influences of confounders that were carried out nevertheless were inconclusive.

The group of test persons also included persons who had never lived in the study area prior to the relevant sample day (and who therefore should never have been included in the study). When these participants were excluded, and the mean distance of places of residence during the observation period was used (i.e. instead of the distance of the places of residence at the time of diagnosis), the resulting distance coefficient was smaller than that for all participants in Part 2 of the study.

2.5 Additional publication in Deutsches Ärzteblatt 2008

In a supplementary effort (Kaatsch et al. 2008 in the journal Deutsches Ärzteblatt, in print), the following additional considerations of the authors of the KiKK Study were published:

In the KiKK Study, the relative risks for childhood leukaemia and cancer were calculated on the basis of participating cases and controls (which were not always considered completely). In the present work, additionally standardised incidence ratios (SIR) for leukaemias were calculated on the basis of the complete data of the German Childhood Cancer Registry (GCCR) in Mainz. These standardised incidence ratios show the

relationship between the number of observed cases and the number of expected cases. The expected cases are calculated from the number of inhabitants younger than five in the region studied and from the incidence rate observed nationwide during the same period. The following results were obtained:

- For the entire KiKK Study region (41 rural districts), an SIR of 0.99 resulted (confidence interval, CI: 0.92-1.07), which is practically identical to SIR=1, i.e. to the incidence expected on a national average.
- For the 15 groups of rural districts assigned to the various nuclear power plants, the SIR varied non-significantly between 0.85 and 1.21.
- For the 5 km zone, an SIR of 1.41 resulted (CI 0.98-1.97).
- The incidences for municipalities whose centres are further than 5 km from the nearest nuclear power plant (5-10, 10-30, 30-50, 50-70, over 70 km) lie between 0.85 and 1.00.
- When the municipalities with centres within the 5 km zone are considered separately by area type, the SIR for the rural area type is 1.81, that for the mixed area type is 1.18 and that for the urban area type is 1.71. None of these SIR is statistically significantly high, and no trend is apparent. What is more, the estimates for the 5 km zones around nuclear power plants were not affected by these figures at all, and thus the fact that nuclear power plants tend to be located in rural regions cannot explain the correlation between the power plants' locations and incidence of leukaemia.

In the discussion, the authors concluded that the KiKK Study – like nearly all empirical, non-experimental studies – exhibits potential distortions and limitations. They included the following points among such aspects:

- The data for the KiKK Study are not independent of the data of the two previous studies of the German Childhood Cancer Registry (GCCR) in Mainz. The KiKK Study thus does not constitute an independent confirmation of the results of earlier studies.
- Since the relevant municipalities' willingness to cooperate varied by distance to the relevant nuclear power plant, sensitivity analyses were carried out, and these showed that the problems in recruiting controls may well have led to a slight overestimation of the effect in question.
- The KiKK Study was unable to take account of confounders, because it was unable to obtain the necessary information for such consideration.
- For determination of the relevant distances, only the residential addresses at the time of diagnosis were available; no individual residential histories were available. The precision achieved in determination of individual distances may thus be a pseudo-precision with regard to "exposure" caused by the nuclear power plants.
- It is problematic to use the distance as a measure of radiation exposure. No data on actual radiation exposure were available, and no background radiation exposure was taken into account. The variation in such radiation exposure is several times greater than the variation in the radiation exposure around a nuclear power plant during normal operation.
- While there are statistical advantages in modelling a continuous distance curve, such modelling also presents a number of disadvantages. For this reason, it makes sense to calculate attributable cases only for the distance zone in which the effects are truly pronounced. (It should be noted that use of the distance measure 1/r was justified by reference to the proposal of the United Nations Scientific Committee on the Effects of

Atomic Radiation (UNSCEAR; relevant United Nations expert group) in which the extent of radiation exposure was estimated in this manner as a function of the distance from a relevant point source.)

- The authors find it unlikely that there is any causal relationship with exposure to ionising radiation from nuclear power plants, since the radiation exposure resulting from a nuclear power plant in normal operation is lower, by a factor of at least 1,000, than the natural radiation exposure in Germany.
- This view was shared by international experts present at the ICNIRP/WHO/BfS workshop "Risk factors to childhood leukaemia", which was held in Berlin in 2008. The Berlin workshop also showed that numerous different factors could conceivably be responsible for leukaemias in children, and that a combination of different factors is probably involved in leukaemia etiology.

3 What is known at present

3.1 Biological and epidemiological findings relative to development of childhood leukaemia

At present, there are still extraordinarily many gaps in our scientific understanding of how leukaemias develop in childhood. The reasons for this include the fact that past research has tended to be concentrated on other disorders, since childhood leukaemia is an extremely rare disease: about five cases occur per year in Germany per 100,000 children no older than 15; for children younger than 1, the rate is about 4 cases per 100,000 children per year, and for children at the ages of 1 to 4, the rate is about 9 cases per 100,000 children per year. The corresponding figures in other countries are about the same. Even when all cancers in children up to the age of 15 are taken into account, the rates of all incidence are still very low; about 15 cases per 100,000 children per year are observed[6]. It is striking that children, in contrast to adults, contract almost solely the acute forms of leukaemia; they almost never contract chronic forms.

In the blood cells of relatively many newborn children, one finds genetic anomalies (for example, chromosomal translocations, amplifications) that are considered relevant for leukaemia development. Only a small fraction of the children with such anomalies in their blood cells actually develop leukaemia, however (for example, the pertinent number is smaller than the entire number of children in the group by a factor of 100 in the case of fusion of the genes *TEL* and *AML1*). From this fact, it is concluded that initiation takes place during pregnancy, and that initiation is not by itself able to cause leukaemia. This indicates that additional factors must also play a role, factors that continue a process that has already been initiated. Epidemiological studies have identified numerous factors that could be involved in such continuation, via extremely complex processes. The primary reasons why the epidemiological findings are so inconclusive in many areas are that a range of factors are involved in leukaemia development, and that the relevant factors may need to interact in order to cause the disease. What is more, individual factors' contributions are difficult to identify.

Many different factors are suspected of triggering childhood leukaemia, of continuing leukaemias triggered by other factors, or of preventing leukaemia formation (these factors

[6] Figures provided by the German Childhood Cancer Registry (GCCR) in Mainz; http://info.imsd.uni-mainz.de/K_Krebsregister/

are discussed in detail in the scientific annex). It is unquestioned that childhood leukaemias can be triggered by ionising radiation. And radiation-dosage strength plays a central role in the possibility of such triggering. Other factors that are at least suspected to trigger or support leukaemias include various chemicals (such as benzene and other hydrocarbons, pesticides, chemotherapeutic agents); magnetic fields (although no biological mechanism has been found to date that could explain pertinent findings, which not all relevant studies have produced); social status (this factor has recently again been the subject of controversy; previously, it had been considered reliably established that children from families with high social status have higher leukaemia risks); weight at birth (increased risk in children weighing less than 2.5 kg or more than 4 kg); genetic predispositions (for example, children with Down's syndrome have 10 to 20 times the leukaemia risk of comparable children without the syndrome); and infections.

The factor "infections", in particular, has proven to be extremely complex, since there are indications that infections can both trigger/support leukaemias and protect against leukaemias. The immune system plays a key role in this context. At present, the search for clear answers in this area is still being hampered by the immune system's complexity, as well as by great gaps in our understanding of immunological mechanisms. As a result, many of the relevant conclusions that have been advanced are highly speculative. With regard to nuclear power plants and immunology, it is conceivable that microbial exposure from cooling towers or rivers may be a risk factor.

3.2 Occurrence of children leukaemias in the vicinity of nuclear power plants

In 1983, it was reported that an increased incidence of leukaemias in persons up to the age of 24 had been observed in the vicinity of the Sellafield reprocessing facility in England. Since then, many different studies have been carried out in an effort to determine whether the leukaemia rates in the vicinity of nuclear facilities are higher, in general, than the normally expected rate. These studies are described individually in the Annex. The relevant German studies reported the following events:

In 1992, a study of the German Childhood Cancer Registry (GCCR) in Mainz was published that compared the incidences of childhood leukaemia, in the period 1980 to 1990, in the vicinity of 20 nuclear power plants in the western German Länder. In its design, that study was oriented strongly to a study carried out in England and Wales, with the purpose of reviewing that study's finding with respect to Germany. For that reason, for children aged 0 to 14, that study compared new incidences within a 15 km radius around each nuclear power plant site with incidences within control regions. That study found no increased risk. On the other hand, an additional analysis that considered the youngest age group (0 to 5 years), within a 5 km radius, did find a significantly higher risk. And the result remained when the focus was restricted to the period 1991-95.

In 1992, a study of the incidence of childhood leukaemia in the vicinity of the three nuclear reactor sites in the new German Länder was published. That study also used 15 km-radius zones and focussed on the age group 0 to 14. The time period considered was 1961 to 1988. No statistical correlations emerged, even for 5 km-radius zones.

In the period 1990 to 1996, an increased incidence of childhood leukaemia occurred in the vicinity of the Krümmel nuclear power plant and of the GKSS Research Centre in Geesthacht. A significantly increased incidence was observed within a 10 km radius during this period, and the incidence remained high in later years. In spite of intensive study of possible causes, including chromosomal studies, and analysis of monitoring documents and

internal operational documents of the Krümmel nuclear power plant, no proof was found of any causal relationship between the observed increased incidence of leukaemia and the emissions of these facilities.

In 1994, an increased leukaemia incidence in adults (of ages 15 to 64) within a 5 km radius of the Krümmel nuclear power plant was reported for the period 1984-93. A review of this finding that was then carried out for the vicinities of four northern German power reactors, within the framework of a case-control study (Northern German Leukaemia and Lymphoma Study – Norddeutsche Leukämie- und Lymphomstudie) that conducted surveys to take account of key risk factors and that used a mathematical spreading model to quantify exposure, found no increased risk from the nuclear power plants.

Extensive studies of the same topic have also been carried out in other countries:

The COMARE 10 study explored the possible dependency of childhood-leukaemia frequency on distance to nuclear facilities in the UK. That study observed no increase in the frequency of childhood leukaemias in the vicinity of nuclear power plants. In a new look at that study's data, the analysis was adapted, as far as possible, to the conditions prevailing in the KiKK Study. For example, reported cases of acute leukaemia in children younger than five were studied. No evidence was found that the rate of incidence in the various relevant wards depended on distance to the nearest nuclear power plant.

A more recent study considered the possible relationship between childhood leukaemia in the vicinity of nuclear facilities in France and bone-marrow doses, which were calculated from data for releases of radioactivity via exhaust air. The study area consisted of 40 km × 40 km areas around a total of 24 nuclear facilities, including 19 nuclear power plants and the reprocessing facility in La Hague. The 2,107 municipalities within the study area were grouped into five categories defined by annual effective dose (<0.045, -0.072, -0.316, -1.0, >1.0 μSv/year). In the period 1990 to 2001, the French national registry of childhood leukaemia and lymphomas registered a total of 750 acute cases of leukaemia in the study area in children younger than 15. The pertinent leukaemia rate was lower than the average rage for the country as a whole. At the same time, the relevant difference had only borderline significance (a standardised incidence ratio (SIR) of 0.94, with a 95 % confidence interval ranging from 0.88 to 1.01). In none of the five dose categories studied was the SIR significantly increased. In none of the age groups studied, i.e. including the group of children younger than five, was there evidence that the SIR depended on dose.

In 2007, Baker et al. published a meta analysis of childhood leukaemias and proximity to nuclear power plants. That study considered a total of 136 facilities. Separate models, based on mortality and incidence data, were calculated for studies. Effect estimates were calculated separately for the age groups 0-9 and 0-25, as well as for the distance ranges <16 km and 0-25 km. All models yielded increased risks. The increases lay within the range +2 % to +25 %, and in most cases they were statistically significant. There were no indications that the authors applied any publication bias. At the same time, the authors found no evidence for a hypothesis that could explain the additional risk: in light of studies that have derived dose-impact relationships, it is implausible that the slight additional ionising radiation generated by nuclear power plants can explain the increased risk. As a possible alternative explanation, the authors mentioned a hypothesis of Gibson and Wheldon to the effect that there could be synergistic effects between ionising radiation and exposure to chemical pollutants. The authors cited a range of studies that found no changes in leukaemia rates when nuclear power plants were commissioned or decommissioned. Other studies found increased risks in planning regions of nuclear power plants. It was thus speculated that an exposure other than the exposure to ionising radiation is responsible for

the observed increased risks. To date, no such factor has been identified. The possibility of "population mixing" was also discussed, which could be linked to changes in the concentration and/or the occurrence of pathogens. No likely pathogen (virus, bacteria) has yet been identified, however. The methods used in the meta-analysis of Baker et al have been criticised. The primary objections raised by such criticism are that the analysis did not explain the criteria via which studies were selected for inclusion, and that there are indications that negative studies are underrepresented.

In overall assessment of the German studies and of other studies – from the UK, France, Spain, the U.S., Canada and Japan – a number of problems arise that limit the studies' comparability:

- Differences between the types of reference populations selected (total population; comparative region)
- Differences in definition of "vicinity" (concentric circles; administrative units)
- Differences in selection of the youngest age group (0-5 years, 0-14 years, 0-24 years)
- Differences in selection of disease groups (individual forms of leukaemia, all leukaemias, leukaemias and lymphomas, all childhood cancers)
- Differences in target events (new incidences, mortality)
- Failures to publish additional studies (publication bias).

Nevertheless, in sum it can be concluded that a slight increase of leukaemia incidence is observed in the vicinity of nuclear facilities, and that the increase appears in the relevant youngest age group in the nearest vicinity of the facilities. Almost all authors agree in the assessment that estimates of the population's exposure indicate that any assumption of a causal relationship with radioactive emissions from the nuclear facilities could not be reconciled with current scientific findings. A number of studies analyse, or at least discuss, possible alternative explanations. On the whole, such efforts do not yield any consistent picture, however.

3.3 Radiation exposure

To describe the radiation exposure for a population in the vicinity of nuclear power plants comprehensively, one must take account of all contributions to such radiation exposure. In the following, such contributions are listed and briefly explained.

Note: both here and in general, figures for radiation exposure for the population are given as organ equivalent doses or as effective doses, both in mSv. Pursuant to recommendations of the ICRP, in risk estimates radiation exposure should be considered in energy-dose units, expressed as mGy. In consideration of organ doses, use of mSv produces more conservative results than does mGy, since a quality factor of 20 is used for alpha emitters, with the result that the dose in mSv is higher than the corresponding energy dose. In consideration of effective dose, applicable weighting factors for tissue make it necessary to review, in individual cases, whether the resulting figures are meaningful in the proper context and are usable in risk considerations. In the present assessment, the relevant organ dose is used in such cases.

3.3.1 Natural radiation exposure

The effective dose from natural radiation in Germany averages 2.1 mSv per year. Individual doses vary, in a 95 % frequency range, from 1.2 mSv to 4.6 mSv per year. The

natural radiation exposure consists of contributions of external radiation exposure, including cosmic and terrestrial radiation, inhalation of radon and radon decay products and ingestion of natural radionuclides.

Radiation exposure via inhalation of radon and radon decay products in houses is the main source of variability in the natural radiation exposure. The mean effective dose from radon amounts to 1.1 mSv per year (95 % frequency range of 0.3 mSv to 3.6 mSv per year). Inhalation of radon and radon decay products leads to an organ dose for red bone marrow, with an effective dose coefficient of 0.3 mSv per year and per 100 Bq/m³ of radon concentration in the air within the living area.

In Germany, the external radiation exposure via cosmic radiation and terrestrial radiation averages 0.7 mSv per year, with a 95 % frequency range of 0.5 mSv to 1.2 mSv per year. The structural materials used in buildings influence the external radiation exposure. On the whole, the effective dose in buildings is higher than it is outdoors. The differences between the natural external radiation exposure outdoors and the natural external radiation exposure indoors average about 0.1 mSv per year, assuming in each case that a person remains in the relevant area (indoors or outdoors) for the entire year. Depending on the structural materials used, the external radiation exposure in houses can differ, from house to house, by more than a factor of 6.

The radiation exposure from ingestion, which averages 0.3 mSv per year and has a 95 % frequency range of 0.2 to 0.4 mSv per year, is relatively constant.

3.3.2 Medical radiation exposure

Individual radiation exposures per diagnostic application vary from 0.01 mSv to about 20 mSv. For the year 2006, the Federal Government's report to the Parliament (Parliamentary Report) places the average medical diagnostic radiation exposure in Germany at 1.9 mSv per person per year (this figure also includes those persons who received no medical diagnostic radiation exposure). The average medical diagnostic radiation exposure was lower in the past. In 1972, it was given as 0.5 mSv per person per year.

3.3.3 Radiation exposure from tests of nuclear weapons

In 1963, the effective doses caused in Germany via fallout from above-ground tests of nuclear weapons reached a peak value of about 0.15 mSv per year. In subsequent years, they then declined sharply. In 2000, they were still at a level of 0.005 mSv per year. When the relevant figures are integrated over 50 years, and over all exposure pathways, a total of about 1.2 mSv results as the effective dose from fallout from testing of nuclear weapons.

In the study period covered by the KiKK Study, the main contributions to radiation exposure came from the long-lived radionuclides H-3 (tritium), C-14, Sr-90 and Cs-137. In the Federal Government's Parliamentary Reports, the annual radiation exposures from these sources are given as < 0.01 mSv per year.

In the 1960s, above-ground nuclear explosions brought about a doubling of natural specific activity in atmospheric carbon, and they increased the natural specific activity of atmospheric hydrogen by 3 orders of magnitude. These peak values of C-14 and H-3 contamination led to maximum radiation exposures of about 0.01 mSv per year for each substance. By 2000, radiation exposure as a result of nuclear-testing fallout of C-14 had declined to about 0.002 mSv per year, while exposure via H-3 of similar origin amounted to less than 0.00001 mSv per year.

3.3.4 Radiation exposure as a result of the Chernobyl disaster

Fallout from the reactor accident in Chernobyl caused radiation exposure in Germany. In keeping with the nonhomogeneity of the fallout, a range of 0.5 mSv to 2.2 mSv must be assumed for the relevant effective doses, integrated over 50 years.

In Germany in 1986, the pertinent mean annual effective doses, summed over all exposure pathways, amounted to about 0.11 mSv. By 1990, they had dropped to about 0.025 mSv, and since 2000 they have been lower than 0.015 mSv.

3.3.5 Public radiation exposure from nuclear facilities

Systems for monitoring emissions from German nuclear power plants are combined systems for monitoring emissions and immissions. They make it possible to assess the radiation exposure for people that results from discharges of radioactive substances via air and water, and they make it possible to control compliance with dose limits.

In light of the environmental contaminations resulting from factors such as above-ground nuclear explosions and fallout from the Chernobyl disaster, emissions measurements are better than immissions measurements as a basis for determining doses in the vicinity of nuclear power plants.

Nonetheless, in the framework of the system for remote monitoring of nuclear reactors (Kernreaktorfernüberwachungssystem; KFÜ) pursuant to the Directive on Emission and Immission Monitoring (Richtlinie für die Emissions- und Immissionsüberwachung; REI), and via the Integrated Measurement and Information System (integriertes Mess- und Informationssystem; IMIS), immissions are also monitored. In Germany, the required performance of monitoring systems is defined in terms of required detection limits. Compliance with the required detection limits for measurement programmes ensures that radiation exposures of 0.001 mSv per year would be detected.

The Federal Office for Radiation Protection (BfS) provided the Commission on Radiological Protection (SSK) with detailed information on annual discharges of radioactive substances from nuclear power plants for the plants' entire operational periods. In combination with weather statistics, these data would make it possible to calculate the additional radiation exposure for the population that is caused by nuclear power plants.

The Parliamentary Reports have always given the radiation exposure for the population that results from discharges of radioactive substances via exhaust air or wastewater from nuclear power plants as < 0.01 mSv per year. For individual nuclear power plants, values between < 0.0001 mSv and 0.02 mSv per year were given for various years of the study period covered by the KiKK Study.

Such figures refer to the potential radiation exposure for a reference person, and they were calculated on the basis of the general administrative provision (Allgemeine Verwaltungsvorschrift (AVV) for Section 47 of the Radiological Protection Ordinance (StrlSchV)). For the various relevant exposure pathways (external radiation from the cloud, from radioactive substances deposited on the ground, and from inhalation and ingestion), the AVV model calculates the maximum activity concentrations in the air, on the ground, in foods and in drinking water. In addition, it assumes, in each case, that the reference person is located at the most unfavourable impact point for the relevant exposure pathway and obtains his or her food and drinking water solely from the most unfavourable relevant impact points. The assumptions regarding the duration of the reference person's stay in the relevant location and the quantities of food and water the person ingests are as specified by the Radiological Protection Ordinance. While such assumptions provide complete

coverage of the relevant frame of reference, they are unrealistically high by comparison to the behaviour of any real persons. These parameters have been so conservatively chosen that they enable the competent authority, in licensing procedures, to assume conformance, pursuant to Section 47 of the Radiological Protection Ordinance, with the dose limits for members of the general public, if the parameters have been used for calculating the potential radiation exposure pursuant to the general administrative provision for Section 47 of the Radiological Protection Ordinance.

In calculation of the reference persons' radiation-exposure levels given in the Parliamentary Reports, the actual emissions of relevant nuclear facilities and the actual weather conditions at the relevant sites are taken into account. Otherwise, the conservative approach of the general administrative provision is retained.

In the estimation of the Commission on Radiation Protection (Strahlenschutzkommission), the Parliamentary Reports' values for a reference person's radiation exposure from discharges of radioactive substances from nuclear power plants may be used as a conservative upper boundary for the actual radiation exposure of individual persons in the vicinities of nuclear power plants.

3.3.6 Radiation exposure via other and diffuse anthropogenic radiation sources

Radiation exposure also results from air travel, for example. A person travelling on the North Atlantic route receives radiation exposure of about 0.006 mSv per hour from cosmic radiation. That level of expected radiation exposure per hour of flying time is on the order of the annual radiation exposure for a reference person in the vicinity of a nuclear power plant. With respect to a considerable number of nuclear power plants and observation periods, it is even markedly higher than such annual exposure.

The possibility of receiving radiation exposure from relatives or acquaintances who have undergone therapeutic nuclear-medical measures must also be mentioned. For activity levels of 400 MBq I-131 upon discharge, and for conformance with proper relevant behaviour, the EU estimates (RP97) that radiation exposure for children younger than two could lie between 0.8 mSv and 1.6 mSv. In Germany, such exposure is limited via the directive "Radiation Protection in Medicine" ("Strahlenschutz in der Medizin"), pursuant to which the radiation exposure for individual persons of the population located at a distance of two meters from the relevant source must not exceed 1 mSv in a calendar year.

To date, diffuse sources of anthropogenic radionuclides, such as atmospheric Kr-85 activity, fallout of I-129 from reprocessing facilities, and excretions from nuclear-medical patients (especially I-131), have caused only negligible radiation exposure in Germany.

3.3.7 Radiation exposure in the workplace

Parents' workplace radiation exposure could be of relevance for the children covered by the KiKK Study. Figures for distribution of workplace radiation exposure in Germany are provided by the Parliamentary Reports. Pertinent detailed data on exposure levels for individual persons can be determined.

Conclusion:

A wealth of experience regarding the radiation exposure resulting for humans via environmental radioactivity has been gained via experience with natural radioactivity and radiation, with above-ground explosions of nuclear weapons, with the Chernobyl disaster, and with a great many other events and circumstances. This experience covers all of the radionuclides (H-3, C-14, fission and activation products, radioactive noble gases,

actinides) that are relevant to the issue of the additional radiation exposure resulting from nuclear power plants. In particular, the experience gained in connection with above-ground nuclear-weapons testing and with the Chernobyl disaster supports the conclusion that any additional environmental radioactivity that causes radiation exposure with annual doses of more than 0.01 mSv will leave such clear traces in the environment that it can be reliably detected with instruments.

3.4 Quantitative estimation of childhood leukaemia and cancer risks (all types of cancer) following low-dose radiation exposure

The Oxford Survey of Childhood Cancers (OSCC) is far and away the largest case-control study on childhood cancers (all types of cancer). That study considered the effects of *in utero* radiation exposure via x-ray examinations of mothers. For the period 1953 to 1981, the study included a total of 15,276 cancer deaths of persons younger than 16, along with a corresponding number of control persons. About 16 % of the cases, and 12 % of the control persons, had experienced x-ray examinations *in utero*. Over 90 % of the relevant x-ray examinations took place in the third trimester of pregnancy, and thus the OSCC's results referred primarily to exposures during that period of pregnancy.

The OSCC is also the largest of all studies carried out to date with regard to childhood leukaemias following *in utero* x-ray examinations. In 1975, Bithell and Stewart analysed data for children younger than 16, and for the period 1953-1967, including a total of 4,771 cases of leukaemia / lymphoma mortalities, and with a corresponding number of control children. A total of 661 of the cases (13.8 %) and 483 of the controls (10.1 %) had *in utero* exposures resulting from x-ray examinations of their mothers.

The OSCC's main results refer to incidences of cancer in persons younger than 16. By contrast, the KiKK Study considered incidences in children younger than five. In 1989, Muirhead and Kneale analysed the age-dependence of the relative childhood-cancer risk seen in the OSCC data. They found that the relative risk for children younger than five is about 10 % higher than the relative risk throughout the entire age group of persons younger than 16. Consequently, the relative risk for children younger than five is only slightly higher than the mean risk levels – which are relatively well-founded – for children of all ages.

In sum, the analyses of the OSCC data yielded a relative-risk estimate of about 1.4, both for leukaemia and for all types of cancer, for children younger than five, following *in utero* x-ray examinations with a fetus dose of 10 mGy. The upper limit of the relevant confidence interval for a worst-case estimate is about 1.8.

The validity of the OSCC has been intensively discussed in the pertinent scientific literature. Overall, arguments in support of the study's reliability predominate. In particular, the OSCC's results relative to cancer and leukaemia have been confirmed via a large number of case-control studies. While cohort studies tended to find lower risks, their results, within the framework of relevant uncertainties, were compatible with the OSCC results.

The OSCC's results refer to exposures with low LET radiation, with fetus doses of several milligrays or more. There is no evidence that additional risks result from exposures with fetus doses of 1 mGy or less.

Less is known regarding childhood leukaemia or cancer risks following postnatal exposures than is known about such risks following *in utero* exposures. All in all, however,

there are indications that the risk following postnatal exposure is lower than that following *in utero* exposure.

Along with low LET radiation, alpha radiation caused by nuclear power plants also contributes to radiation exposure, although that contribution is much smaller. At the same time, it must be noted that the natural alpha radiation emitted by radon and radon decay products causes exposures that are higher, by several orders of magnitude. No reliable information is available regarding the relative risk for childhood leukaemias and cancers resulting from exposure to alpha radiation. No evidence is available that would preclude use of the value 20 for the relative biological effectiveness of alpha radiation, the value recommended by the International Commission on Radiological Protection (ICRP).

Comparison with the risks reported by the KiKK Study

The KiKK Study's best estimates for the relative risk for children younger than five, within a 5 km radius around a nuclear power plant, and in comparison to the study area outside of the 5 km radius zone, were 1.61 for all types of cancer and 2.19 for leukaemias. These reported risks are thus similarly high to, and in some cases higher than, the risks observed in the OSCC for *in utero* radiation exposure with doses of 10 mGy. Higher doses would be needed to bring about such risks via exposure in childhood. There are no indications that lower doses cause higher or comparable risks. Consequently, if one wishes to adduce radiation exposure to explain the KiKK Study's results, one must assume that the cumulative dose within the 5-km radius zone differed from that outside of the 5-km-radius zone by at least 10 mGy.

4 Independent new analysis of the KiKK Study's data

British epidemiologists have conducted a new analysis of the data used in Part 1 of the KiKK Study (cf. the report by Sarah Darby and Simon Read (2008) in the scientific annex). Their analyses have confirmed the KiKK Study's main conclusions and provided a number of additional findings.

The additional findings were obtained by analysing the data for acute leukaemias. The relevant significance tests were carried out two-sidedly. In categorial evaluation, the distance interval with the largest number of cases (10-29 km) was chosen as the reference point. Non-overlapping distance intervals were studied. In addition, separate analysis was carried out of the data used for hypothesis generation (1980-1990) and for hypothesis testing (1991-2003).

A restriction to acute leukaemias led to exclusion of a total of six cases of leukaemia. In complete agreement with the KiKK Study's pertinent result, a distance coefficient of 1.70 was obtained (95 %-CI: 0.39; 3.02). The result is significant ($p = 0.01$).

For the 5-km radius zones around the nuclear power plants, a relative risk of childhood leukaemia of 2.27 was obtained (95 %-CI: 1.45; 3.56). This result is highly significant ($p = 0.0003$). Outside of the 5-km-radius zones, no significantly higher risk was found for any distance category (Fig. 1). The best estimates obtained lay between 0.95 (50-69 km radii) and 1.12 (30-49 km radii).

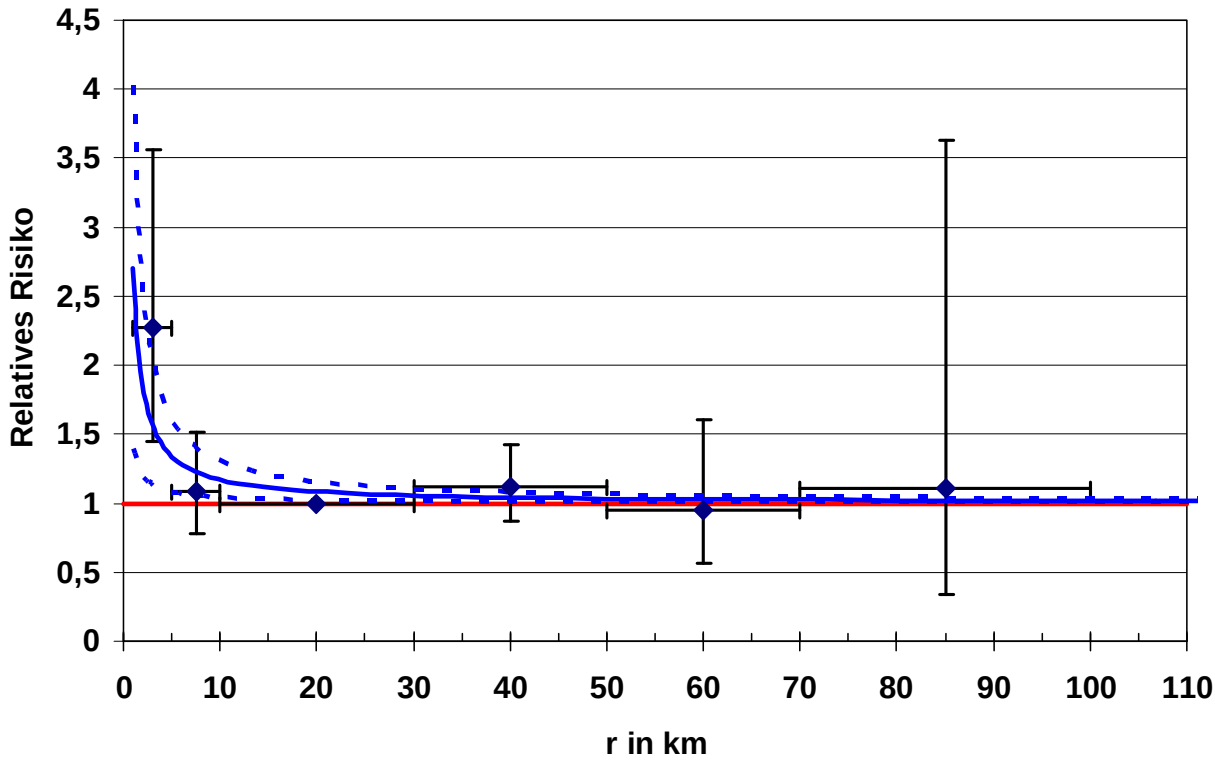

Fig. 1: Result of categorial evaluation (points) and continuous evaluation (lines) carried out by Sarah Darby and Simon Read (2008) for acute leukaemias in children younger than five (relative risk from Table 2 of the 2008 report of Sarah Darby and Simon Read. The bounded straight lines along the x axis show the breadth of the relevant regions, while the bounded straight lines along the y axis show the 95 % confidence intervals of the odds ratios. The unbroken line corresponds to an RR(x)=1+βx model with x = 1/r and β = 1.7; the broken lines correspond to the β values for the limits of the two-sided 95% confidence interval; β = 0.39 and β = 3.02). [y-axis = relative risk]

The risk in the 5-km-radius zones, in comparison to that in the study area outside of the 5-km-radius zones, was significant both for the hypothesis-generation period and for the hypothesis-testing period (cf. also 5.4.3). With exclusion of case-control groups for which complete information was not available for all controls, a relative risk of 1.74 was obtained (95 %-CI: 1.02; 2.96). This estimate is based on 21 childhood incidences that occurred within the 5-km-radius zones around the nuclear power plants in 13 years. This means that a total of 9 cases must be assigned to those influencing factors that are responsible for this increase. Such assignment, in turn, translates into a rate of nearly one case per year.

The leukaemia risk was higher in rural areas than it was in urban regions. The relative risk in the former areas was 1.85 (95 %-CI: 1.06; 3.23). A separate analysis of rural and mixed/urban regions found, in both cases, a significantly higher risk within the 5-km-radius zones in comparison to the risk in the study area outside of the 5-km-radius zones.

The authors of the report on the comparative calculations conclude that there is an increased risk for childhood acute leukaemia within the 5-km-radius zones around the nuclear power plants. The relevant causes are unknown. The analysis indicates that triggering factors could be related to living conditions in rural areas around the nuclear power plants.

5 Assessment of the KiKK Study

5.1 Assessment of the design of the KiKK Study

5.1.1 Exposure determination, and radioecological aspects

The KiKK Study uses the distance to the nearest nuclear power plant as a proxy for exposure to ionising radiation. The exposure measure selected, 1/distance, is justified by appeal to a simplified, averaged, theoretical model of spreading. In the following, with regard to exposure determination, the degree to which the distance to the nearest nuclear power plant reflects exposure to ionising radiation is discussed separately, from a radioecological perspective. Subsequently, the study's use of such distance dependency is discussed.

Distance to the nearest nuclear power plant as a surrogate for exposure

Use of the distance measure does not take account of the fact that the emissions of the different facilities studied differ widely and vary over time. From power plant to power plant, and from year (considered) to year (considered), the exposures for small children (the reference persons) can differ by a factor of about 100. This fact does not impair the analysis, however, since each case was "matched" to three control children with regard to facility location and time of diagnosis. Greater difficulty arises in that meteorological circumstances suggest that spreading will be clearly direction-dependent. The isotropic model of spreading fails to take account of this fact, and this leads to erroneous classification of exposure. At the same time, it is unlikely that such erroneous classification would cause an association to be observed where none actually exists. The same can be said for radiation exposure via wastewater discharges, which occur at other geographical locations and which the distance measure also fails to take into account. On the other hand, such exposures, in comparison to those from discharges via exhaust air, are of subordinate importance with regard to the population's exposure.

The main problem in the exposure estimation used is that the relevant radiation exposures from natural and other civilisation-related sources (including medical sources) were not determined. The exposures from such other sources are greater, by orders of magnitude, than the radiation exposures that can be attributed to nuclear power plants. What is more, they show no dependence on distance. In addition, the fluctuation ranges of exposures from such sources are considerably greater than the radiation doses delivered by nuclear power plants. For these reasons, distance cannot serve as a measure for individual radiation exposure.

By focussing exclusively on the distance to the nearest nuclear power plant, the KiKK Study provides a completely inadequate picture of the overall radiation exposure of the affected persons. With this approach, the study failed to make use of the wealth of information that has been gathered, over the past five decades, about natural and civilisation-related radiation exposure for the population; about discharges from nuclear power plants and the related radiation exposures; and about other civilisation-related radiation exposures. It also failed to make use of available relevant radioecological findings. Furthermore, unlike the approach used by a comparable French study, the study made no attempt to calculate the radiation exposures resulting from nuclear power plants. In the view of the Commission on Radiation Protection (Strahlenschutzkommission), the KiKK Study would have been able to carry out such modelling of radiation exposure, with similar effort and expense, and such modelling would have yielded useful additional findings.

Categorial or continuous evaluation

In statistical evaluation, one can divide the data into categories for evaluation, or one can seek to fit a continuous function to the data. Both approaches have advantages and disadvantages. In categorial evaluation, no assumptions have to be made with regard to the sort of curve that fits the exposure-effect relationship. On the other hand, evaluation using a continuous exposure measure tends to have greater statistical power than does categorial evaluation. Fitting of a continuous exposure measure to a continuous function entails the risk, however, that significant effects in one or more categories can make the entire curve seem significantly raised, even though the other categories lack such effects. An important problem in the continuous function selected (1/r) is that it is a non-linear transformation of the distance measure. As a result, observations made at small distances to the nuclear power plant have a greater influence on estimation of the distance coefficient than do observations at large distances. This "leverage" is shown graphically in Figure 2. The cases' and controls' distances to the relevant nuclear power plants, as determined in the KiKK Study, lay between 1 km and 92 km. With the distance measure x = 1/r, this means that all values lay within the interval 1/km to 0.01/km. Distances smaller than 5 km account for a total of 80 % of this interval [1/km, 0.2/km]. As Figure 2 shows, a linear regression with 1/distance as the explanatory variable almost has to become significant if the result for the innermost category differs from those for the other categories, even though only a small percentage of all cases and controls are found in the innermost category. For this reason, the Commission on Radiation Protection (Strahlenschutzkommission) maintains that categorial evaluation would be the more suitable approach.

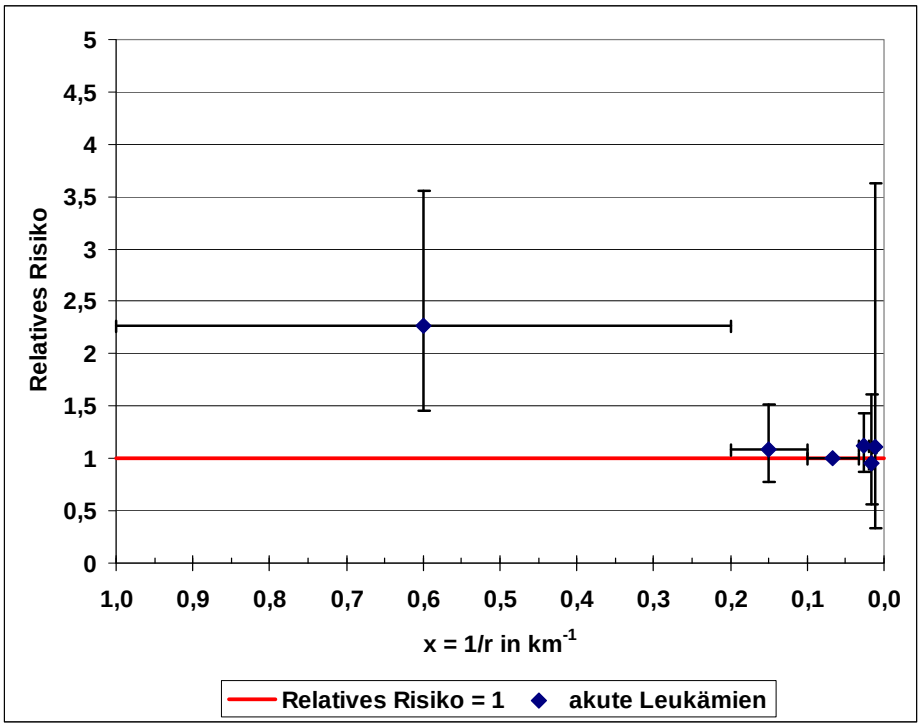

Fig. 2: Result of the categorial evaluation (points) for acute leukaemias in children younger than 5 vs. 1/distance. The bounded straight lines along the x axis show the breadth of the relevant regions, while the bounded straight lines along the y axis show the 95 % confidence intervals of the odds ratios. The graph is similar to that in Fig. 1; only the x axes are different (Fig. 1: x = r in km, Fig. 2: x = 1/r in km^{-1})[y axis = Relative risk]

5.1.2 Selection of study areas

The study areas were selected on the basis of rural districts. Rural districts differ widely in their forms, however. As a result, in some cases persons living relatively far away were included, while persons located in closer areas (between the included persons' areas and the sources) could not be included. What is more, large cities at middle distances had to be excluded, since otherwise the distance-distribution imbalance that was already present would have been even more pronounced. But since cases and controls were taken from the same areas, it is unlikely that this constraint falsified the study's result.

5.1.3 Place of residence at the time of diagnosis

Development of childhood leukaemias must be assumed to include latent periods of several months to several years. If one also takes account of the great likelihood that radiation-triggered leukaemias in very young children are triggered during embryonic / fetal development, then the place of residence at the time of diagnosis is not particularly relevant. If one assumes that exposure to radiation (or other noxa) during pregnancy is a critical factor, then the question arises as to whether cases (prior to diagnosis) and controls differ in their moving histories (changes of residence):

a) If moving behaviour of cases differs from that of controls, selection of a reference time for exposure determination introduces a systematic error (bias). For example, if (future) cases showed a greater frequency of moving into the vicinity of a nuclear power plant, that would suffice to explain the observed study result.

b) If the groups' moving behaviours (behaviour in changing residences) do not differ, the place of residence at the time of diagnosis introduces a random error into exposure estimation. If an exposure-effect relationship truly exists, that error would probably cause the relevant risk to be underestimated. If no exposure-effect relationship exists, then it is highly likely that no erroneous exposure-effect relationship will be observed. There is no way to review these possibilities without any knowledge of the pertinent individual residence histories. The moving frequencies were highly similar for about one-third of the cases and controls that participated in the second part of the study (Tab.3.7, Part 2). It remains to be seen whether this level of agreement also applies for the entire group that participated in the first part of the study.

5.1.4 Places of residence and main locations

The place where a child lives does not necessarily have to be the location where the child spends most of his or her time. Even small children do not spend all of their time in their home (they also spend time with their grandparents, with their day-care nannies, in day-care centres...). In this light, use of the place of residence as a proxy for exposure would introduce an erroneous classification, along with the implications described under point 5.1.3. For estimation of the real exposure-effect relationship, it would then be relevant to know how erroneous the erroneous classification is and whether the classification differs systematically between cases and controls.

5.1.5 Alternative locations

The KiKK Study chose only nuclear power plants as the centres of the study regions. It would have been useful for the study to review planning sites for nuclear power plants, or other industrial sites – in the manner applied in past efforts. Such review was not part of the task that the KiKK Study's authors were commissioned to carry out, however.

5.2 Assessment of the execution of the KiKK Study

The KiKK Study was carried out in accordance with the principles for good epidemiological practice. In the process, the authors stuck closely to the specifications for the evaluation plan. Only in calculating the attributable risk did they exceed the bounds of what was prescribed in the evaluation plan. Neither the Commission on Radiological Protection (SSK), nor Darby and Read (in their review), discovered any errors in execution. In fact, the study results were confirmed. Ultimately, the SSK's assessment of the KiKK Study's weaknesses was similar to that presented by the study's authors themselves, in a subsequent publication in the journal Deutsches Ärzteblatt.

5.2.1 Consideration of confounders

In the context of epidemiological studies, a "confounder" is a disruptive factor that has a distortional influence on an exposure-effect relationship. For a confounder to function in this manner, two conditions have to be fulfilled: the confounder has to have an effect that is independent of the real association in question, and the confounder has to be related to the real association in question. Epidemiological experience has shown that a significant distortional influence can normally be statistically proven only in cases in which the confounder is large and the confounder has a pronounced relationship with the association in question.

In part 2 of the KiKK Study, the attempt was made, via a survey of a sub-population of the study participants, to identify possible confounders that have an influence on leukaemia development and that also could be associated with proximity to nuclear power plants. Because the relevant group exhibited insufficient overall willingness to participate in the survey, and, especially, because cases and controls differed in their willingness to participate, it was not possible to take potential confounders into account. As the study itself also noted, there are a great many potential risk factors for childhood leukaemia that could function as confounders even if they were associated with proximity to nuclear power plants. Specifically, the following factors would be pertinent candidates: pollution from pesticide use in agriculture; chemical or microbial pollution from nearby rivers or cooling towers; low-frequency magnetic fields; radiation exposure of parents; socio-economic factors, such as social interaction and related exposure for the immune system (for example, migration; small children's attendance at day-care centres). It must also be remembered that locations of nuclear power plants tend to have certain types of geographic features in common, features that could be associated with environmental risk or other, unknown risks. For example, all German nuclear power plants are located along rivers of considerable size.

None of the aforementioned potential risk factors is considered well-established, however, and it may be assumed that such risks are relatively small (relative risk < 2). It is thus unlikely that a single factor, even one correlating very strongly with distance to a relevant nuclear power plant, could explain the results of the analysis. At present, the question of whether interaction of different confounders could explain the result of the study must be left unanswered.

5.2.2 Problems in recruiting controls

In control selection, four problems arose whose effects were then reviewed with the help of sensitivity analyses:

1. Municipalities in the vicinity of nuclear power plants tended to refuse to provide addresses of controls more frequently than did other municipalities. In order to check whether the distance to the nuclear power plant was being systematically underestimated for controls, a sensitivity analysis was carried out in which all cases and controls from municipalities which had provided no control addresses were excluded. For both leukaemias and all tumours, the distance coefficients decreased slightly (leukaemias, $\beta = 1.73$, instead of $\beta = 1.75$; all tumours: $\beta = 1.01$ instead of $\beta = 1.18$).
2. Not all municipalities selected controls from the diagnosis years for the corresponding cases. In 26 % of the cases, the sample date was different (usually, it was then 31 December, and not the time of diagnosis). In 5 % of the cases, the controls were known to have been selected from the current residential population, and in an additional 5 % of the cases, the controls were presumed to have been so selected. Selection of controls from the current residential population, rather than from the residential population at the time in question, results in exclusion of persons who have moved away in the meantime, and such persons' moving away may be correlated with disease status.
3. Correct addresses were available for only 1,132 (of 1,592) cancer patients and the relevant associated control persons. Analysis of this data showed a slightly reduced distance coefficient ($\beta = 1.05$ instead of $\beta = 1.18$).

4. In Part 2, it was found that only 230 of the 273 cancer patients and associated control persons who participated in the telephone interview had a residential address within the study area. When the mean distances of the relevant places of residence within the study period were taken into account, the distance coefficient for leukaemia was reduced ($\beta = 0.33$ instead of $\beta = 0.44$).

All in all, the distance dependency suggested by the sensitivity analyses is weaker than that suggested by the main analysis of the study. This finding is confirmed by calculation of the leukaemia risk for children younger than 5, in areas nearer than 5 km to the nearest nuclear power plant, in relation to the risk in Germany: The age-standardised relative risk is 1.41, with a lower 95% confidence limit of 0.98.

5.2.3 Population fluctuation

Although the annex for Part 1 of the study lists numerous figures that document migration – in some cases, considerable – of persons into the vicinity of nuclear power plants, population fluctuations were not taken into account. In addition, large numbers of outsiders enter the power-plant regions regularly in connection with maintenance work. In the UK, considerable migration of outsiders into a previously rather isolated area has been tied to an increase in childhood leukaemias. At the same time, the population density in the relevant power-plant regions in the UK was considerably lower than the population density in the relevant regions in Germany. If regions around nuclear power plants were isolated enough to meet criteria for the so-called "Kinlen Hypothesis", then an explanation for an increased leukaemia risk for children in the vicinity of nuclear power plants would be available. The Kinlen Hypothesis states that an increase in leukaemia cases is expected in previously isolated regions that experience large migratory influxes.

5.2.4 Consideration of total radiation exposure

The study did not determine radiation exposure of natural and civilisation-related (including medical) origins, although such exposure is larger, by orders of magnitude, than the radiation exposure that can be attributed to nuclear power plants. In addition, the fluctuation ranges of natural radiation exposure are considerably greater than the radiation doses delivered by nuclear power plants. This fact was also not taken into account.

5.3 Assessment of the results of the KiKK Study

The study provides evidence for an increased incidence of acute leukaemias in children who live within a 5 km-radius zone around a nuclear power plant. An independent review by British epidemiologists, carried out on the basis of the original data, confirmed the findings of the KiKK Study.

Studies have been carried out, in Germany and the UK, that found an increased leukaemia risk for children who lived in areas in which nuclear power plants were planned but never built. In its nature and strength, this risk was similar to that found in the vicinity of existing nuclear power plants. From this, one can conclude that nuclear power plants may tend to be built in areas which, for reasons that have not yet been understood, have a higher risk for childhood leukaemias.

The Commission on Radiological Protection (SSK) concluded that such higher risk is not causally related to the radioactivity emitted by nuclear power plants. Although ionising radiation, in principle, can present a risk for development of leukaemias, radioactive

emissions from nuclear power plants are too low, by several orders of magnitude, to explain the risks observed in the KiKK Study.

An additional evaluation of the KiKK Study's data, carried out by Darby and Read, provides a clear indication of the presence of a causal environmental factor that varies as a function of the children's residential location: in rural regions, the leukaemia risk was significantly increased, to a level of 1.85, in comparison to the corresponding risk in urban or mixed regions. Although nuclear power plants tend to be built in rural regions, the increased risk of childhood leukaemia in rural regions does not explain the higher risk in the vicinity of nuclear power plants (cf. the section on the Darby study). In any case, it is likely that rural life is not a causal factor per se; it is likely that the higher risk is associated with causal factors that are still unknown to date.

5.4 Assessment of the KiKK Study's interpretations

5.4.1 Assessment with regard to exposure

In a background paper published in the Internet[7], the Federal Office for Radiation Protection (BfS) found, with regard to exposure: "*It was not possible to take the radiation exposure into account, since neither are measurements available for the over 6,000 children in the relevant home municipalities nor is it possible to model the radiation exposure in a useful way. The distance between the residence and the reactor was used as a substitute for the radiation exposure, which cannot be determined directly.*"

In connection with its assessment of the KiKK Study, the Commission on Radiological Protection (SSK) reviewed the following:

- All sources of radiation exposure for the children of the KiKK Study,
- All nuclear power plants' emissions data, throughout the plants' entire operational periods,
- The immissions data from the system for remote monitoring of nuclear reactors (Kernreaktorfernüberwachungssystem; KFÜ), from the framework of the Directive on Emission and Immission Monitoring (Richtlinie für die Emissions- und Immissionsüberwachung; REI) and from the Integrated Measurement and Information System (integriertes Mess- und Informationssystem; IMIS),
- The potential radiation exposure of reference persons, throughout the entire operational periods of nuclear power plants, and
- Childhood cancer and – in particular – leukaemia risks, studied for children who had undergone low levels of radiation exposure *in utero* or during childhood.

The SSK drew the following conclusions from this review:

- For the nuclear power plants of the KiKK Study, and for the study periods (in each case, the starting date of the study period, minus 5 years), complete data was available on discharges via exhaust air and wastewater. Calculations of the radiation exposure of reference persons are available with regard to discharges of radioactive substances via exhaust air and wastewater.
- The SSK considers the Parliamentary Reports' figures for radiation exposure of reference persons, from nuclear facilities, to be highly conservative. Such figures, so

[7] http://www.bfs.de/de/kerntechnik/kinderkrebs/hintergrund_kikk.pdf

the SSK, can be considered a reliable upper boundary for the radiation exposure caused by nuclear power plants.

- In the SSK's assessment, determinations of radiation exposure for reference persons, from discharges of radioactive substances from nuclear power plants, conform to relevant needs and fulfil the legal requirement pertaining to reporting of the radiation exposure for the population in the Federal Republic of Germany.
- The radiation exposures for reference persons, from discharges of radioactive substances from nuclear power plants, vary from power-plant location to power-plant location, as well as from year (considered) to year (considered) for individual nuclear power plants, by a factor of up to 100.
- Immissions measurements carried out within the framework remote monitoring of nuclear reactors (KFÜ), of the Directive on Emission and Immission Monitoring (REI), and of the Integrated Measurement and Information System (IMIS) are able, on the basis of required detection limits, to detect radiation exposures of 0.001 mSv per year. The immissions data provide no indications of exposures higher than those calculated for reference persons with regard to discharges of radioactive substances from nuclear power plants.
- In the SSK's assessment, the natural radiation exposure levels for the people of the KiKK Study were higher, by a factor of at least 1,000, than the exposure levels calculated for reference persons with regard to discharges of radioactive substances from nuclear power plants. Simply the differences in the effective terrestrial doses, throughout the various power-plant locations, are several times higher than the radiation exposures for such reference persons from discharges of radioactive substances from nuclear power plants. The variability in natural radiation exposure, resulting from such factors as structural techniques used in houses, radon concentrations in residences, and individual eating habits, is higher, by orders of magnitude, than the highest levels of radiation exposure from discharges of radioactive substances from nuclear power plants.
- If one assumes that the low radiation exposures caused by the nuclear power plants are responsible for the increased risk of childhood leukaemia, then one must calculate that leukaemias due to natural radiation exposure would be more common, by several orders of magnitude, than they are actually observed to be in Germany and elsewhere.
- Other possible civilisation-related, additional contributions to the radiation exposure for children of the KiKK Study – for example, contributions from medical examinations – are also higher (also by orders of magnitude) than the radiation exposure resulting from discharges of radioactive substances from nuclear power plants.

The radiation exposure for reference persons that results from discharges of radioactive substances from nuclear power plants is so low – even though the pertinent estimates are highly conservative – that it cannot explain the observed increased relative risks for leukaemia within the 5 km-radius zones of the nuclear power plants of the KiKK Study.

With regard to the possibility of a causal relationship between the radiation exposure caused by the nuclear power plants and the increased relative risk for childhood leukaemia observed within the 5 km-radius zones around the nuclear power plants, the SSK maintains that the Bradford Hill criteria (cf. Section B5 of Chapter 6) are not fulfilled.

5.4.2 Independence of the statistical analyses

It must be noted that about two-thirds of the data came from an older analysis (and, significantly, also provided the basis for generating the relevant hypothesis). With regard to this "old" data, it was thus known that increased incidences of leukaemia had been observed in children younger than 5 within the 5 km-radius zones around nuclear power plants. Consequently, the present KiKK Study is "independent" only in the sense that it used different methods for data analysis. While this fact has no implications for the study results, it does have implications for interpretation of the results within a global context.

5.4.3 Statistical test procedure

The KiKK Study tested one-sidedly. Use of one-sided testing is justified in confirmatory studies. But the data used to generate the hypothesis may then not also be used for testing the hypothesis.

Since the authors decided to include the old data in the analyses, however, the data, for statistical purposes, cannot be considered hypothesis-generating. Therefore, two-sided testing would have been adequate.

In general, this does not change any aspects of the significance of the result, however. Two-sided testing would lead to larger confidence intervals and p values. The authors consider their evaluation to be confirmatory, but that view is not tenable in light of the inclusion of the "old" cases.

5.4.4 Problems connected to continuous evaluation and use of the attributable risk

The KiKK Study looked at the question of whether there is a correlation between childhood cancers and residential proximity to a nuclear power plant. For this, the attempt was made, via a regression analysis, to fit the data to the continuous function 1/distance. The advantage of a continuous function is that it has greater statistical power. This advantage is offset by a number of problems. In the first place, the quality of the model fit must be taken into account. If agreement between the continuous function and the observed data is poor, the overall result may be driven by only part of the data. Another problem arises in defining the model's validity range. For this, one needs additional criteria, since it certainly does not make sense to analyse the relevant association at an arbitrarily large distance. Furthermore, use of the function 1/distance tends to strongly weight the incidence figures for smaller distances.

In addition to analysing the possible association between residential proximity to the nuclear power plant and the cancer risk, the KiKK Study also calculated the attributable risk. It is formally possible to calculate the attributable risk, i.e. to convert the relative risk with regard to the affected population group. However, such calculation should be carried out only when the causal relationship between exposure and effect is solidly established. Where this is not the case, the attributable risk can suggest that an uncertain exposure has effects on a population group, an exposure whose scientific basis has not been adequately established. Relevant remarks are provided in the scientific annex.

Furthermore, categorial evaluation showed that the increased risk is found only within the 5 km-radius zone (cf. Chap. 4). It is thus also not permissible to calculate fictive incidence figures, on the basis of a continuous function for larger distances beyond the 5 km-radius zone, and to express those figures as an attributable risk.

In general, it seems more suitable to consider the association with distance categorially and to downplay the 1/distance calculations strongly. The attributable risk should be calculated only for categories that truly show an increased relative risk.

6 The advising order

The Federal Ministry for the Environment, Nature Conservation and Nuclear Safety (BMU) presented the SSK with an extensive catalogue of questions relative to the study concept and to the causality of the KiKK Study's finding.

In the following section, the questions posed within the advising order are answered. (Note: The questions posed within the BMU's advising order are printed in italics. Unavoidably, this leads to repetitions of certain aspects that were already discussed in Chapters 5.1 through5.4.)

A. Study concept

A1 Do the data collection, data retention, and data quality conform to requirements for good epidemiological practice?

The study's execution conforms to requirements for good epidemiological practice. This was reviewed, and confirmed, in the framework of two audits. In addition, an independent review was carried out in Mainz, by Sarah Darby and Simon Read, from 23 to 27 June 2008. For this review, full access to all raw data was provided. The reviewers were not charged with commenting on the quality of the pertinent raw data. The final report that emerged from that review is part of the scientific annex of the SSK's present statement.

A2 Were the cases and controls determined in an adequate manner, or was there any statistical distortion of these data?

The study took account of all children younger than 5 who, between 1980 and 2003, were reported to the German Childhood Cancer Registry (GCCR) in Mainz as having contracted cancer and who lived in the study region at the time of the pertinent diagnosis. The German Childhood Cancer Registry (GCCR) in Mainz has a long tradition, and it is highly complete (it records more than 95 % of all incidences of leukaemia). Of a total of 1,633 cases, only 41 had to be excluded from the analysis for understandable criteria. Apart from those cases, case recruitment is not likely to have distorted the study result in any way.

The controls were identified via "two stage random sampling". In a first step, the home municipality for a control was selected at random. This was achieved via weighting of all municipalities by age/sex/year, in keeping with the relevant percentages in their populations (at the time of diagnosis of the corresponding case). In a second step, the municipality was requested to provide a control address. In providing a database for control selection, the municipalities had to take account of their populations at the times at which the corresponding cases were diagnosed. In each case, the two steps were carried out six times, with the aim, ideally, of generating six controls for each case child. In principle, this methodological approach is correct.

The following problems occurred, however: (i) Municipalities in the vicinity of nuclear power plants tended to refuse to provide addresses of controls more frequently than did other municipalities. (ii) Not all municipalities selected controls from the diagnosis years for the corresponding cases. (iii) The addresses provided for a considerable number of control persons (or for cases to which controls were allocated) were incorrect. (iv) Some of

the control persons (or cases to which controls were allocated) should not have been included in the study, since they had not been residents of the study area at the time of sampling. Relevant sensitivity analyses yielded smaller risk coefficients (in some cases, only slightly smaller) for the various factors. Although it was not possible to estimate the total influence of these factors, the SSK assumes that the risk within the 5 km-radius zone is significantly increased independently of these disruptive factors.

A2.1 Were the statistical methods that were used adequate?

The data were modelled by means of conditional logistic regression. That is considered to be the standard procedure for a "matched" case-control study. It was decided, a priori, to carry out an analysis with continuous distance data (1/distance) and an analysis with distance categories. The categories were defined prior to the start of the analysis (5 km-radius zones). All important analyses were replicated by an additional statistician, from the Coordination Center for Clinical Trials (KKS) in Mainz.

In epidemiological procedures, it is customary to give (two-sided) 95 % frequency intervals. The aspect that needs to be discussed is one-sided hypothesis testing, i.e. calculation of a one-sided 95 % confidence interval. In light of the developments leading up to the study, while one-sided hypothesis testing is acceptable, in a rigorous approach the old cases that were known prior to the commencement of the (later) study should have been excluded. If the old data are to be included, two-sided testing would be the more suitable approach.

Overall, the statistical analyses were carried out properly and correctly. There are no indications of any undeclared post-hoc analyses aimed at creating statistical significances – for example, by adapting the definition of the distance categories to the observed case distribution.

A2.2 Is the study's design – in particular, its use of 1/r dependency – adequate?

The 1/r dependency describes the distance to the nuclear power plant. It is not suitable for use as a proxy for radiation exposure (cf. A 4.2). The data distribution seen does not provide a basis for any robust conclusions regarding the distance dependency outside of the 5 km-radius zone.

This was confirmed by the assessment carried out by Sarah Darby and Simon Read, which clearly showed that the association found was limited to the 5 km-radius zones around the nuclear power plants (cf. Tab. 2 in Chap. 2.4 and Chap. 4).

For this reason, all conclusions should refer only to the results of categorial analysis. In particular, it is off the mark to use the 1/r dependency to calculate, for the area outside the 5 km-radius, attributable risks and the numbers of sick children who should be associated with the relevant nuclear power plants. As described in detail in the scientific annex, that approach yields hypothetical incidence figures that – solely for mathematical reasons – grow larger with increasing distance from the nuclear power plants, without providing any information about the real risks involved.

A3 To what extent was the residential history of the affected persons taken into account? What influence, if any, does such history have, i.e. how long did the children, or their parents, live in the community or region (rural district) prior to the relevant incidence of cancer?

The distances from the case families' and control families' places of residence to the nearest nuclear power plants (i.e. in each case, to the nearest nuclear power plant) were

determined with great care and effort. At the same time, in the main study only the place of residence at the time of diagnosis was selected. And yet the exposure at the time at which an incidence of cancer is diagnosed cannot be the cause of the incidence of cancer. As a rule, considerable time passes between the time at which the responsible exposure occurs and the time at which the resulting incidence of cancer is diagnosed (latency period). For an analysis of a possible association between a) the distance from a possible exposure site (= place of residence) to the nearest nuclear power plant and b) an incidence of cancer, therefore, it would be necessary to consider the relevant residential history from the beginning of the pertinent pregnancy until the pertinent incidence is diagnosed.

The residential-history evaluation carried out in the second part of the study failed to consider places of residence outside of the study area. It resulted that about one-third of all case families, and about one-third of all control families, moved during the period from the beginning of the pertinent pregnancy until the pertinent incidence of cancer was diagnosed.

All in all, it is impossible to rule out the possibility that the failure to take account of residential history, i.e. in particular, the failure to take account of the latency period from the time of possible exposure until the time of diagnosis, led to a distortion of the results.

A4 How high was the radiation exposure – including natural radiation exposure – of the affected persons?

This question was answered in detail in Chap. 5.4.1. The following table (Tab. 3) summarises the various possible contributions to the individual radiation exposure of the affected persons.

In any consideration of a radiation risk, one must always consider the total natural and anthropogenic radiation exposure of the persons concerned. The additional radiation exposure caused by nuclear power plants is lower, by a factor of at least 1,000, than the natural radiation exposure. It is also lower, by orders of magnitude, than the variability of the natural radiation exposure at the locations of the various nuclear power plants. In addition, such consideration must also take account of other anthropogenic exposures.

A4.1 Did the study take account of potential individual risks for the children (such as frequent examinations with radioactive substances or ionising radiation; radiation therapy)?

In reaching its findings, part 1 of the study did not take account of such individual risks. Originally, it was planned to take such risks into account in part 2 of the study. That plan proved unfeasible, however, due to the varying willingness of surveyed parents of cases and controls to complete relevant questionnaires.

A4.2 Can any conclusions regarding dose be drawn from the distance?

No, no conclusions regarding dose can be drawn from the distance. In the study period, the discharges of radioactive substances from nuclear power plants, via exhaust air, varied by a factor of more than 100 from plant site to plant site, and, over time, at the individual plant sites.

In the total radiation exposure for the KiKK Study children, the natural, highly variable radiation exposure predominates to such an extent that any significant dependency of total radiation exposure from the distance to the nearest nuclear power plant can be ruled out. Furthermore, potential civilisation-related radiation exposures, which can also be considerably higher than the radiation exposure caused by nuclear power plants, cannot be expected to depend on distance from the nuclear power plants.

The largest problem, however, is that the differences in the nuclear power plants' emissions are not taken into account. As a result, the proxy gains uncertainties of several orders of magnitude with regard to different nuclear power plants and different years. For consideration of the manner in which immissions decrease with distance, this point is inconsequential, however, since if immissions decrease with distance for each individual nuclear power plant, they decrease with distance for all nuclear power plants taken together. That relationship, in turn, would mean that the search for the possible cause of the incidences should focus not on the absolute power-plant-related exposures, but solely on the differences between cases' exposures and controls' exposures as a result of differences in distance to nuclear power plants. By nature, such differences in exposures are considerably smaller than the absolute exposures.

Tab. 3: Possible contributions to individual radiation exposure of members of the population

Exposure	**Effective dose or area**	**Persons affected**
Natural radiation exposure	2.1 mSv per year (95 % frequency range 1.2 mSv – 4.6 mSv per year)	all
Nuclear weapons testing*)	1963: 0.15 mSv per year 2000: 0.005 mSv per year	
Effects of the Chernobyl disaster in Germany**)	Mean value for all of Germany: 1986: 0.11 mSv per year 1990: 0.025 mSv per year Since 2000: < 0.02 mSv per year	
Radiation exposure from medical diagnosis; mean for the population of Germany	1972: 0.5 mSv per year 2006: 1.9 mSv per year	Hypothetical "average" person
Radiation exposure from medical diagnosis	0.01 mSv – 20 mSv per application	Only directly affected persons
Exposure via close relatives, following nuclear-medical treatments	< 1 mSv per year	
Air travel	0.006 mSv per h (North Atlantic route)	
Maximum radiation exposure for all age groups, at the most unfavourable impact points in the vicinity of nuclear power plants	< 0.01 mSv per year (global conclusion in the Parliamentary Reports) Individual nuclear power plant covered by the KiKK Study, in various years: < 0.0001 mSv – 0.02 mSv per year	Hypothetical reference persons
Real exposure of members of the public in the vicinity of nuclear power plants, as a result of discharges	<<< 0.01 mSv per year	Only directly affected persons

**) effective dose, integrated over 50 years: 1.2 mSv*
***) effective dose (since 1986), integrated over 50 years: 0.5 mSv – 2.2 mSv*

A4.3 Are there uncertainties in determination of doses for the children?

The KiKK Study did not determine any radiation doses for the children. The study did not look at potential exposures, nor did it attempt to determine the various contributions to the radiation exposure for the children or for their parents.

A5 Has a similar distance-correlated cancer / leukaemia rate become known or been found for other industrial facilities (if applicable, also facilities in other countries), and, if so, has such a rate been scientifically established?

Distance-correlated cancer / leukaemia rates have also been found for other industrial facilities. For example, Knox and Gilman have reported increased risks in the vicinity of various types of industrial sites (including oil refineries, automobile plants, automobile repair shops, solvent production plants). In addition, ecological studies have been carried out that have found increased rates of childhood leukaemias in the vicinity of planning areas for nuclear power plants (cf. the following answer to question A5.1).

A5.1 Can similar findings be expected for nuclear power plants, or planned sites of nuclear power plants, that have not yet been studied in this regard?

This question cannot be answered before a relevant analysis is carried out. In the past, (ecological) studies have shown that frequencies of leukaemia (and other types of cancer) in the vicinity of planned sites of nuclear power plants were similar to those in the vicinity of operational nuclear power plants.

As described in detail in Chapter 3.2, in 2007, Baker et al. published a meta analysis of childhood leukaemias and proximity to nuclear power plants. In that work, the authors cited a range of studies that found no changes in leukaemia rates when nuclear power plants were commissioned or decommissioned. Other studies found increased risks in planning regions of nuclear power plants. It was thus speculated that an exposure other than the exposure to ionising radiation is responsible for the observed increased risks. To date, no such factor has been identified. The possibility of "population mixing", which could be linked to changes in the concentration and/or the occurrence of pathogens, was also discussed. No likely pathogen (virus, bacteria) has yet been identified, however.

A6 Can the findings be applied to adults?

In light of the considerable body of evidence that the relevant etiology for children differs from that for adults, it cannot be said whether the increased leukaemia incidence in children younger than 5 within the 5 km-radius zone points to an increased corresponding risk for adults. As a result, it is not possible to answer the question of whether the findings can be applied to adults.

On the other hand, ecological studies that found no increased leukaemia risk for persons from the ages of 5 to 15 indicate that it is at least unlikely that an increased risk would be found for adults. In addition, the North German Leukaemia and Lymphoma Study found no indication that adults could be affected by emissions from nuclear power plants.

North German Leukaemia and Lymphoma Study

The North German Leukaemia and Lymphoma Study (Norddeutsche Leukämie- und Lymphomstudie; NLL) is a population-based case-control study of the causes and risk factors for incident leukaemias, malignant lymphomas and related disorders in the 1986 – 1998 age cohorts in six rural districts in Schleswig-Holstein and Lower Saxony. One of its main hypotheses has to do with exposures to radioactive emissions from nuclear facilities

in normal operation. Lifelong exposure determination within the NLL was based on standardised, personal, computer-aided interviews with 71.5 % of all cases (N=1,430) and 54.5 % (N=3041) of all controls.

The pertinent analyses took account of all relevant sources of radiation exposure for the general population. To quantify exposures with regard to emissions from nuclear facilities in normal operation, the spreading model used in the framework of remote monitoring of nuclear reactors (general administrative provision for Section 45 of the Radiological Protection Ordinance) was used to carry out quantitative calculations of the ingestion dose for various food groups (leafy greens, other plant products, meat and milk), and relevant total levels for inhalation and external radiation were applied to the NLL test persons' lifelong places of residence and work.

No systematically increased risks from radionuclide exposure, resulting from emissions from nuclear facilities in normal operation, were found for any of the disease entities studied.

Significantly, the NLL was carried out because a study of the incidences of leukaemias, lymphomas and myelomas within a 5 km-radius zone around the nuclear facilities in Geesthacht (Krümmel and GKSS) had found a significantly increased leukaemia rate. For the same group of patients, in the same region, the NLL found no increased risk. At the same time, the NLL took account of the individual risks of the patients and of a control group, and it quantified the exposure more effectively, using exposure variables based on the aforementioned general administrative provision.

In principle, the exposure quantification method used for the NLL, and based on the spreading model from the aforementioned general administrative provision, would also have been available for the KiKK Study.

B. Causality

B1 Are there any radiobiological findings that could plausibly explain the results?

Findings regarding development of leukaemia in children

Childhood leukaemias are not a homogeneous group of disorders. Leukaemias fall into numerous sub-groups that are characterised by factors such as differential gene expression, antigens and chromosomal and molecular abnormalities. There are strong indications that more than one relevant event has to take place for a childhood leukaemia to occur. In one common understanding, genetic mutations are first induced during fetal development (for example, fusion of the *TEL* gene onto chromosome 12, and fusion of the *AML1* gene onto chromosome 21, presumably as a result of faulty repair of breaks in the DNA double helix). During childhood, leukaemia can then develop as the result of additional genetic changes. In both steps, infections, chemicals, ionising radiation or other, still unknown, environmental factors could be involved.

Implausibility of a causal correlation

As explained in the section "What is known at present" (Chap. 3.4), the ionising-radiation doses received within and outside of the 5 km-radius zone around a nuclear power plant would have to differ by at least 10 mGy if doses of such radiation were to be used to explain the relative risks reported by the KiKK Study. But the real radiation exposures occurring via emissions from nuclear power plants are lower, by a factor of at least 1,000 (cf. Tab. 3 in A4). Consequently, it is not plausible, from a radiobiological perspective, to adduce the ionising radiation emitted by nuclear power plants to explain the KiKK Study's

finding. From a radiobiological perspective, factors other than ionising radiation must provide the explanation for the KiKK Study's finding.

B2 What detection limits apply with regard to the transferability of the radiobiological findings mentioned under point B1 to small children?

Small children are known to have a higher radiation risk than adults have. But, as described under point B1, radiobiological findings indicate that a causal role for ionising radiation does not provide a plausible explanation for the KiKK Study's findings with regard to small children. Consequently, it is not necessary to rely on data for adults or for older children to determine the radiation risk for small children. An analysis of OSCC data, for example, found that the cancer risk for children younger than 5, following *in utero* radiation exposure, did not differ significantly from the risk throughout all of childhood. Findings of other studies in which these two age groups were analysed separately are consistent with this result.

A special aspect with regard to small children is that some hereditary diseases entail a significantly increased risk of developing childhood leukaemia (for example, Down's syndrome, Fanconi anemia, Ataxia teleangiectatica). Some of these hereditary diseases also entail a heightened sensitivity to radiation (for example, Ataxia telangiectasia) and thus can be expected to further increase the already greater radiation sensitivity of small children. There are no findings that indicate whether there are sub-populations of small children who have no hereditary disease and yet do have significantly increased radiation sensitivity. If such sub-populations exist, they could not explain the KiKK Study's findings, however, since they would be much more likely to develop leukaemia via natural radiation exposure than via exposure to emissions from nuclear power plants.

B3 Are there other factors that could explain the leukaemia rates found?

Numerous factors have been cited that are suspected of triggering childhood leukaemias or at least of being involved in such triggering. At the same time, there is virtually no factor, apart from ionising radiation, that would not be open to controversy in this regard. There are strong indications that leukaemia development is a multifactorial process, and that the contributions of the various individual factors are each so small as to be impossible to detect. The factors that have been discussed in this regard, in addition to ionising radiation, include many different chemicals; infections; magnetic fields; social status; characteristics at birth (weight at birth, order of birth, breastfeeding); and others.

B4 Can the findings of this study be used to derive a causality, via application of causality criteria – such as those pursuant to Bradford Hill?

In 1965, Sir Austin Bradford Hill published nine different criteria for evaluating causation in epidemiological associations. For a causality to be present, the criterion of timeliness must be fulfilled. All of the other criteria do not necessarily have to be fulfilled. In the following section, the nine criteria are discussed with regard to the KiKK Study. For some criteria, and for the overall assessment, a differentiation is made between distance-dependency and dependency on the radiation exposures caused by nuclear power plants.

a) **Consistency:** For fulfilment of this criterion, different scientists must have achieved comparable results, using different study approaches. **Evaluation:** Increased cancer risks around nuclear power plants were also observed in some other, earlier studies. Their results are not consistent, however. On the one hand, it is unclear how strongly the results were influenced by publication bias. On the other hand, some studies were initiated after a conspicuously large number of

incidences were seen in a given area. More recent studies carried out in France and the UK found no dependency of childhood leukaemia / cancer risks on distance to the nearest nuclear power plant. On the whole, the studies carried out in other countries found only slight evidence – when they found any evidence at all – for increased cancer / leukaemia risks, in children up to the age of 5, in the vicinity of nuclear power plants (at distances of up to 5 km). Only the recent French study explored a possible direct relationship to radiation exposure caused by nuclear power plants. That study found no correlation with cancer / leukaemia incidence rates among children.

b) **Strength of the association:** An association is strong if it can be demonstrated with a small probability of error after all potential distortions have been taken into account. **Evaluation:** For childhood leukaemias, a doubling of the risk within the 5-km-radius zone was found (OR=2.19; lower confidence limit: 1.51); for all incidences of cancer, the risk was increased by 60 % (OR=1.61; lower confidence limit: 1.26). These results are significant. In light of the uncertainties as to whether data gaps and other disruptive factors are causing distortions, the strength of the association must be questioned, however. It is true that sensitivity analyses carried out for individual factors showed only small influences on results. All key sensitivity analyses showed a reduction of the effect, however. The overall effect of all disruptive factors cannot be estimated. Nonetheless, the evidence for a statistical correlation between residential proximity to the nuclear power plants considered in the study and children's risks of contracting cancer – especially leukaemia – predominates. The study is thus not suited to the task of establishing a correlation with exposure to radiation from nuclear power plants.

c) **Dose-effect relationship / biological gradient:** A biological gradient is considered to be present if the strength of the relevant effect increases, in a continuously comparable manner, with increasing exposure or increasing total dose. **Evaluation:** From a statistical standpoint, a clear dose-effect relationship emerges if one uses the linearity model with 1/distance as a basis. The analysis of the distance categories detected only an increased risk within the 5-km-radius zone, however. With regard to exposure via ionising radiation, the dose-effect relationship cannot be assessed, since the total radiation exposure is not expected to correlate with the distance measure. In light of the fact that emissions of nuclear power plants account for an extremely small contribution to total radiation exposure, a dose-effect relationship with regard to exposure via ionising radiation is highly unlikely.

d) **Timeliness:** Fulfilment of this criterion means that the proper chronological sequence is present (exposure first, and then effect). **Evaluation:** The analyses took account of the times at which the facilities were commissioned; where necessary, they also took account of the times at which the facilities were decommissioned. On the other hand, the exposure variable selected was the distance of the place of residence to the nearest nuclear power plant at the time of diagnosis, and not at the time at which the disease occurred or developed. Pursuant to the data from the second part of the study, about one-third of all case / control families moved at least once after the study was conceived. To take adequate account of the timeliness of the etiology, and to be able to identify potentially critical time windows for exposure, the study should have reconstructed the residential histories for these study participants until the time at which the study was conceived.

e) **Biological plausibility / coherence:** Findings should not conflict with biological or pathophysiological findings. **Evaluation:** No factors are known that correlate with

distance to nuclear power plants and that can cause a risk as high as that reported by the KiKK Study. It is indeed unquestioned that ionising radiation can lead to cancer and, especially, to leukaemias. On the other hand, nuclear power plants cause only very low levels of additional exposure via ionising radiation, in comparison to the natural background radiation. The increased risks found cannot be explained in terms of the customary dose-effects models.

f) **Specificity:** A correlation between a specific exposure and highly specific, typical disease phenomena is an indication of causality. **Evaluation:** Specificity is not expected in the present case. Cancer disorders are influenced by many different factors, and thus other factors could also be part of the explanation in any given case.

g) **Experiments / animal testing:** The presumed relationships should be reproducible in experiments or animal models. **Evaluation:** No experiments or animal testing relative to the dependency of radiation effects on proximity to the nearest nuclear power plant have been carried out. It is true that comparable disorders can be induced in animal models via ionising radiation (although the disorders in question are primarily solid tumours, since the available animal models have considerable limitations with regard to demonstration of leukaemia development). For doses as low as those received by the population via emissions from German nuclear power plants, no experimental data are known that show effects, however.

h) **Lack of plausible alternative explanations:** The case for causality is strengthened by a lack of alternative explanations for the associations that have been found. **Evaluation:** The distance to the nearest nuclear power plant is only a proxy for the risk factors linked with the nuclear power plant's site. No such risk factors are known. For this reason, the present review discusses only alternatives to the explanation whereby the increased risk is the result of radiation exposures caused by nuclear power plants. The authors of the study offer three alternative explanations: confounders, statistical chance and selection bias. For a single confounder to be able to explain the observed association, it would have to be a strong risk factor for childhood leukaemia and also show a strong correlation with the distance to nuclear power plants. No such factor is known, and it seems unlikely any could be found. At the same time, it cannot be ruled out that interaction of different confounders led to the observed association. The literature describes numerous possible factors whose correlations with proximity to nuclear power plants are not known (cf. for example, the answer to question B3; this aspect is discussed in detail in the scientific annex). All of those factors could be moderate risk factors for childhood leukaemia and could be correlated with proximity to nuclear power plants.

   Statistical chance can always explain effects in epidemiological studies. For this reason, a statistical significance level was defined in advance: 5 %. Chance findings must still be considered possible, to a certain extent, even when this level is complied with. The effect of a possible selection bias was evaluated via sensitivity analyses. While that evaluation showed that it was plausible that selection bias could lead to a certain overestimation of the association, it also showed that it is highly unlikely that all of the increased risk is due to selection bias.

   All in all, the question of alternative explanations cannot be answered conclusively.

i) **Analogy:** Any similar examples can be useful in assessing causality. **Evaluation:** In the past, similar studies were carried out, of planned sites of nuclear power

plants, that also found increased relative risks. The KiKK Study did not consider planned sites.

All in all, it is highly unlikely that radioactive emissions from nuclear power plants are causally associated with childhood leukaemia. None of the Bradford Hill criteria, with the exception of the criterion of "timeliness", which is borderline positive, returned a positive result (cf. Tab. 4). The emissions in question are considerably too weak, in light of current radiobiological findings, to be able to account for the observed increased risk. Since the KiKK Study did not take account of individual radiation exposure, the study provides no information regarding the question of whether a correlation with radiation exposure was observed.

On the other hand, there is some evidence for a causal relationship between residential proximity and childhood leukaemia within a 5-km-radius zone. With the exception of the criteria "biological plausibility", "experiments / animal testing" and "lack of plausible alternative explanations", the Bradford Hill criteria return either positive results or no results. Consequently, the question arises as to the cause or causes for what was observed. Without any consideration of individual influencing factors, in the manner originally planned for second part of the KiKK Study, that question cannot be answered.

Tab. 4: Overview of assessment of causality criteria, pursuant to Bradford Hill, with regard to the distance-dependency or dependency on the radiation exposure caused by nuclear power plants: '+' stands for evidence for causality, '0' stands for inconclusive, and '-' stands for evidence against causality.

Explanatory variable	Causality criterion pursuant to Bradford Hill									Overall assessment
	a)	b)	c)	d)	e)	f)	g)	h)	i)	
Unknown factor that correlates with distance from the nuclear power plant: continuous evaluation	+/0	0/-	0	+/0	0/-	0	0/-	0/-	0	The balance is tipped against a causal relationship
Unknown factor that correlates with distance from the nuclear power plant: categorial evaluation	+/0	+	0	+/0	0/-	0	0/-	0/-	0	The balance is tipped in favour of a causal relationship
Radiation exposure via nuclear power plants	-	0	0	+/0	-	0	0/-	0/-	0	The balance is tipped strongly against a causal relationship

B5 What additional studies are needed in order to clarify the matter?

1 Collection of additional data, to supplement the KiKK Study data

1.1 Survey of the mobility behaviour of the population, including seasonal workers (maintenance personnel, agricultural workers) within the area covered by the KiKK Study.

1.2 Study of the potential changes in the immunological situation in the vicinity of nuclear power plants – for example, using the frequency of the occurrence of infectious diseases as an indicator – in order to determine whether accompanying circumstances that occur at sites of nuclear power plants could be responsible for the increase in leukaemia incidence.

2 Intensified promotion of interdisciplinary basic research aimed at illuminating the causes and mechanisms of leukaemia incidence in children

As the explanation provided in Chap. 3.1 of the SSK's statement shows, the causes of childhood leukaemia are still largely not understood. If this matter is to be clarified, study of the causes and biological mechanisms of leukaemia incidence will have to be intensified. Ideally, to have a chance of succeeding, such efforts should entail co-operation between researchers working in different relevant fields (especially epidemiology, genetics, immunology, molecular biology, and radiobiology).

3 Epidemiological studies

Since childhood leukaemias are extremely rare (in Germany, about 4 to 5 cases occur per year per 100,000 children), many of the epidemiological studies conducted in the past have lacked the power to have even a chance of detecting relevant effects and the causes of such effects. For this reason, intensive consideration needs to be given to designing and financing international studies in ways that can overcome such difficulties.

Such major international epidemiological studies should gather information about environmental exposure and genetic information, with the aim of exploring possible gene-environment interactions.

In the process, they should study a broad spectrum of industrial facilities (for example, steel-processing plants, coal-fired power plants, chemical factories, solar parks and sites with large numbers of wind turbines).

The epidemiological research carried out to date has relied to some degree on case-control studies, which require co-operation by study participants. Since it is impossible to achieve a 100-percent rate of such co-operation, and since cases and healthy persons typically differ in their willingness to co-operate, such studies entail a selection bias that can distort results. Future epidemiological studies should thus be designed in different ways.