Independent Check on Study of Leukaemia in Young Children Living near German Nuclear Power Plants

Sarah C Darby and Simon Read
University of Oxford, UK

Introduction

SSK Working Group invited SD & SR to visit IMBEI to perform independent check of analyses published in Kaatsch P, Spix C, et al. Int J Cancer 2008; 1220: 721-726.

Preparation for visit

SD & SR attended a meeting of the SSK Working Group at which the study was discussed.

They then prepared a Workplan for the visit.
It included:

1. **clarifying the methodology used by the Mainz team**
2. **repeating the main calculations in the paper**
3. **carrying out additional calculations to clarify results**

Results

1. Clarification of study methodology

Discussions with the investigators clarified all queries relating to the study methodology.

2. Repetition of main calculations

The calculations reported in Kaatsch et al. were repeated. All results agreed with those in the paper.

3. Additional clarifying calculations

Three categories:

a. ***Alternative analysis with different assumptions***
b. ***Further sensitivity analyses***
c. ***Additional analysis of place of residence***

a) Alternative analysis with different assumptions

Description:

- **“Acute leukaemia,” rather than “all leukaemia”, as this disease group used in hypothesis generating study**
- **Two-sided significance tests and confidence intervals rather than one-sided, to avoid false positives.**
- **Most analyses considered distance in non-overlapping categories (ie < 5, 5-9, 10+ km,), to avoid 1/distance model and reveal true relationship.**
- **Distance category with the largest numbers as baseline, to maximise power.**
- **Separate analyses for time-period used in earlier, hypothesis generating, study and later, hypothesis testing, period**

a) Alternative analysis with different assumptions

Results shown in next 4 tables:

Table 1. Analysis using conditional logistic regression model with continuous explanatory variable '1/(distance in km from nearest NPP)' for acute leukaemia at ages <5 years (see Table III of Kaatsch et al).

Diagnostic group	Regression coefficient (β)	95% confidence interval		P-value for test of no association (2-sided)	Number of cases	Number of controls
Acute leukaemia	1.70	(0.39,	3.02)	0.01	587	1748

Table 2. Analysis for acute leukaemia at ages <5 years for 6 categories of distance from nearest NPP (see Table IV of Kaatsch et al).

Distance from NPP (km)	Odds ratio	95% confidence interval	P-value for test of difference from 10-29 km (2-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	1039
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 of subjects				587	1748

*Baseline category

Table 3. Analysis for acute leukaemia at ages <5 years for 3 categories of distance from nearest NPP (see Table V of Kaatsch et al).

Distance from NPP (km)	Odds ratio	95% confidence interval	P-value for test of difference from 10+ km (2-sided)	Number of cases	Number of controls
<5	2.21	(1.42, 3.44)	0.0005	37	54
5-9	1.06	(0.76, 1.47)	0.73	57	170
10+*	1.00	-	-	493	1524
Total number of subjects				587	1748

*Baseline category

Table 4. Analysis for ages <5 years for <5 km from an NPP versus 5+ km, separately for hypothesis generating and hypothesis testing periods (see Table VI of Kaatsch et al).

Calendar period	Odds ratio < 5 versus 5+ km from NPP	95% confidence interval	P-value for test of difference between < 5 and 5+ km (2-sided)	Distance from nuclear power plant			
				< 5 km		5+ km	
				Number of cases	Number of controls	Number of cases	Number of controls
Hypothesis generating period							
1980-1990	3.00	(1.36, 6.62)	0.007	13	14	208	640
Hypothesis testing periods							
1991-1995	2.10	(0.91, 4.83)	0.08	10	15	140	432
1996-2003	1.78	(0.89, 3.57)	0.10	14	25	202	622
Total hypothesis testing periods							
1991-2003	1.90	(1.12, 3.25)	0.02	24	40	342	1054

a) Alternative analysis with different assumptions

Conclusions:

- **Table 1: original findings confirmed and change from 'all leukaemia' to 'acute leukaemia' has little effect**
- **Tables 2 and 3: increased risk entirely due to <5 km, with no increase at 5+ km**
- **Table 4: significant increase present for hypothesis testing period:**

odds ratio < 5 km *vs* 5+ km: 1.90 (95 % CI 1.12, 3.25; p-value: 0.02)

(b) Sensitivity analyses

Original investigators had already confirmed:
- **results not dependent on any individual power plant.**
- **results not strongly dependent on one or two children**

Additional sensitivity analysis:
- **excluded cases and controls in communities not complying fully with study, to avoid bias**
- **included all available controls requested from communities with full compliance (up to 6), to increase power**
- **considered "acute leukaemia"**
- **considered hypothesis generating and testing periods separately.**

Table 5. Analysis for ages <5 years for <5 km from an NPP versus 5+ km, separately for hypothesis generating and hypothesis testing periods. Extra controls from fully compliant areas included, and cases and controls from not fully compliant areas excluded

Calendar period	Odds ratio < 5 versus 5+ km from NPP	95% confidence interval	P-value for test of difference between < 5 and 5+ km (2-sided)	Distance from nuclear power plant			
				< 5 km		5+ km	
				Number of cases	Number of controls	Number of cases	Number of controls
Hypothesis generating period							
1980-1990	3.20	(1.56, 6.60)	0.002	13	26	177	1068
Hypothesis testing period							
1991-2003	1.74	(1.02, 2.96)	0.04	21	64	287	1733

(b) Sensitivity analyses

Conclusions:

•Sensitivity analyses carried out by original investigators confirmed.
•Odds ratio for acute leukaemia at <5 versus 5+ km from NPP is 1.74 (95% CI 1.02, 2.96; p-value: 0.04) during the hypothesis testing period (ie, 1991-2003)

(c) Additional analysis of place of residence

To gain insight into the causes of the association between childhood leukaemia and residence near an NPP, SD & SR inquired whether any additional variables summarizing attributes of the place of residence of the children were available. Each child's place of residence had been classified according to whether it was located in an urban area, in a rural area, or in an area that was a mixture of urban and rural. Further analyses of this variable were performed.

Results shown in next 4 tables

Table 6. Numbers of controls by distance from an NPP and urban/rural status

Urban/rural status	Distance from a nuclear power plant		
	<5 km	5+ km	Total
Rural	20 (22.2%)	437 (15.6%)	457 (15.8%)
Mixed	45 (50.0%)	1149 (41.0%)	1194 (41.3%)
Urban	25 (27.8%)	1215 (43.4%)	1240 (42.9%)
Total	90 (100%)	2801 (100%)	2891 (100%)

Table 7. Odds ratios for acute leukaemia at ages <5 years according to urban/rural status of place of residence, separately for hypothesis generating and hypothesis testing periods.

Urban/rural status	Odds ratio	95% confidence interval	P-value for test of difference from urban (2-sided)	Number of cases	Number of controls
Hypothesis generating period: 1980-1190					
Rural	1.23	(0.45, 3.39)	0.68	30	166
Mixed	0.88	(0.53, 1.45)	0.61	72	443
Urban	1.00*	-	-	88	485
Number of subjects				190	1094
Hypothesis generating period: 1991-2003					
Rural	2.22	(1.14, 4.34)	0.02	64	291
Mixed	1.07	(0.74, 1.54)	0.73	122	751
Urban	1.00*	-	-	122	755
Number of subjects				308	1797
Entire study period: 1980-2003					
Rural	1.85	(1.06, 3.23)	0.03	94	457
Mixed	0.99	(0.74, 1.34)	0.96	194	1194
Urban	1.00*	-	-	210	1240
Number of subjects				498	2891

*Baseline category

Table 9. Odds ratios for acute leukaemia at ages <5 years according to distance of place of residence from an NPP and urban/rural status, separately for hypothesis generating and hypothesis testing periods.

Distance from NPP and urban/rural status	Odds ratio	95% confidence interval	P-value for test of difference from 5+ km and mixed/urban (2-sided)	Number of cases	Number of controls
Hypothesis generating period: 1980-1990					
<5 km and rural	7.57	(1.70, 33.66)	0.008	6	5
5+ km and rural	1.14	(0.42, 3.07)	0.80	24	161
<5 km and mixed/urban	2.19	(0.88, 5.49)	0.09	7	21
5+ km and mixed/urban	1.00*	-	-	153	907
Number of subjects				190	1094
Hypothesis testing period: 1991-2003					
<5 km and rural	3.11	(0.83, 11.69)	0.09	4	15
5+ km and rural	2.18	(1.19, 4.00)	0.01	60	276
<5 km and mixed/urban	1.89	(1.04, 3.42)	0.04	17	49
5+ km and mixed/urban	1.00*	-	-	227	1457
Number of subjects				308	1797
Hypothesis testing period: 1980-2003					
<5 km and rural	5.14	(1.98, 13.29)	0.001	10	20
5+ km and rural	1.85	(1.11, 3.09)	0.02	84	437
<5 km and mixed/urban	1.96	(1.19, 3.23)	0.008	24	70
5+ km and mixed/urban	1.00*	- -	-	380	2364
Number of subjects				498	2891

*Baseline category

Table 8. Odds ratios for acute leukaemia at ages <5 years according to residence in a rural or a mixed/urban area, separately according to sex and age.

Sex and age group	Odds ratio rural versus mixed/urban	95% confidence interval	P-value for test of difference from mixed/urban (2-sided)	Rural		Mixed/urban	
				Number of cases	Number of controls	Number of cases	Number of controls
Boys aged 0-1	0.83	(0.21, 3.36)	0.79	13	73	53	307
Girls aged 0-1	1.13	(0.32, 4.03)	0.85	16	87	48	278
Boys aged 2-4	2.85	(1.23, 6.59)	0.01	41	191	166	1025
Girls aged 2-4	1.97	(0.83, 4.64)	0.12	24	106	137	824

(c) Additional analysis of place of residence

Conclusions

- **Table 6: Control children living <5 km from an NPP are more likely to live in rural or mixed area than in urban area**

- **Table 7: Children living in mixed areas had similar risk of acute leukaemia compared with children in urban areas but children living in rural areas had higher risk (odds ratio 1.85, 95% CI 1.06, 3.23; p-value: 0.03, based on 94 cases/ 457 controls in rural areas and 210 cases/1240 controls in urban areas).**

- **Table 7: Increase not attributable to selection bias from hypothesis generating study, as larger during hypothesis testing period than earlier hypothesis generating period. Odds ratios 1.23 (95% CI 0.45, 3.39) and 2.22 (95% CI 1.14, 4.34) respectively.**

- **Table 8: Increase entirely due to ages 2-4 years**

- **Table 9: Children living in rural areas at increased risk for both <5 and 5+ km from an NPP. Children in mixed/urban areas only at increased risk if also <5km from an NPP. Increases for <5km larger in hypothesis generating than in hypothesis testing, period.**

Overall Conclusion from Independent Check

•The calculations reported in Kaatsch P, Spix C, et al. Int J Cancer 2008; 1220: 721-726 are correct.

•Additional analyses with alternative assumptions and also an extra sensitivity analyses provide further evidence of the integrity of the original study.

•There is evidence of an increased incidence of acute leukaemia aged <5 years living < 5 km from an NPP. The best estimate of the odds ratio is 1.74 (95% CI 1.02, 2.96, see Table 5).

•The above estimate is based on 21 cases occurring in children living within 5 km of a plant over a 13-year period. Thus a total of 9 cases (ie 21 x 0.74/1.74) are attributable to the factor that is causing the increase, or just under one case per year.

•There is no evidence of any increase in the risk of acute leukaemia in children living > 5 km from an NPP.

Interpretation of the increase

SD & SR concluded that the increase is not causally related to radioactivity released by the power plants because:

•The reported releases of radioactivity from NPPs are very low, and there is no evidence of unreported releases.

•Other studies of individuals exposed to ionising radiation, where the doses are known, would suggest that the risks likely to occur near an NPP would be very small indeed

•Studies in both Germany and the UK of children in areas where NPPs were planned but were never built have found similar increases. This suggests that nuclear power plants tend to be built in areas where the risk of childhood leukaemia is already increased for some other, as yet unknown, reason.

Discussion of the increase

•The increased risk of childhood leukaemia in children living near both existing and planned NPPs in Germany, suggests that there is a causal factor that varies according to place of residence.

•As NPPs are in rural more often than urban areas, the possible role of the urban/rural status of the child's place of residence as a risk factor for leukaemia was investigated.

•Evidence was found of an increased risk of acute leukaemia in children living in rural areas, as opposed to an urban or mixed environment.

•The estimated odds ratio for living in a rural area was 1.85 (95% confidence interval 1.06, 3.23).

•The increased risk associated with living in a rural area did not account for the increased risk associated with living near an NPP. It is likely that there is another, but as yet unknown, causal factor that is responsible for both associations.

•In the present study there were 94 cases occurring over a 24-year period in children living in rural areas. Thus 43 cases (ie 94 x 0.85/1.85) are attributable to the causal factor, or just under 2 cases per year within the study population.

•This study included only a small proportion of the German population. If the causal factor were also present in other rural areas in Germany, or if it affected some children living in areas that are not rural (eg those living near nuclear power plants in mixed or urban areas), then the number of cases attributable to it could be many more than this.

Pointers for further investigation

•Further studies of the causes of childhood leukaemia that build on the finding of an increased risk associated with living in rural areas and areas where an NPP has been built or planned may be helpful.

•Several recent investigations of the causes of childhood leukaemia have been of limited value, as some parents of children in the study areas have not consented to participate in the study. To avoid bias, future studies need to be based on data for which parental consent is not required.

•The causal risk factor must be environmental (including a gene-environment interaction), rather than purely genetic, as rural and urban populations in Germany are genetically similar.

Acknowledgement

SD & SR would like to thank all the staff at IMBEI and the German Childhood Cancer Registry for their kind hospitality during our stay at Mainz. They welcomed us to their institute, provided us with full documentation of their study, gave us full access to their data, and answered our many questions with both patience and good humour. Working with them was indeed a pleasure.

Declaration regarding possible conflicts of interest

SD & SR are not aware of any possible conflicts of interest that might have affected their work. They accepted re-imbursement from the SSK for the expenses incurred in carrying it out, but refused the offer of payment. Rather they requested that any such money should be donated towards investigating the causes of childhood leukaemia in Germany.