

Childhood leukemia around French nuclear power plants – the Geocap study, 2002-2007

Claire Sermage-Faure^{1,2}, Dominique Laurier⁴, Stéphanie Goujon-Bellec^{1,2,3}, Michel Chartier⁴, Aurélie Guyot-Goubin^{1,2,3}, Jérémie Rudant^{1,2,3}, Denis Hémon^{1,2}, Jacqueline Clavel^{1,2,3}.

CESP Equipe 6, Inserm U1018; 16 av. Paul Vaillant-Couturier, F-94807 VILLEJUIF CEDEX

¹ Inserm, CESP Center for research in Epidemiology and Population Health, U1018, Environmental epidemiology of cancer Team, F-94807, Villejuif, France

² Univ Paris-Sud, UMRS 1018, F-94807, Villejuif, France

³ French National Registry of Childhood Hematological malignancies (NRCH), Villejuif, France

⁴ Institute of Radiological Protection and Nuclear Safety, IRSN/DRPH/SRBE F-92262, Fontenay-aux-Roses, France

⁵ Institute of Radiological Protection and Nuclear Safety, IRSN/DRPH/SER, F-92262, Fontenay-aux-Roses, France

Short title: Childhood leukemia around French nuclear power plants

Correspondence to:

Jacqueline CLAVEL, MD, PhD

CESP Equipe 6, Inserm U1018

16 av. Paul Vaillant-Couturier, F-94807 VILLEJUIF CEDEX

Tel: +33 1 45 59 50 37 / Fax: +33 1 45 59 51 51

Mail: Jacqueline.Clavel@inserm.fr

Keywords: Childhood leukemia; epidemiology; incidence; case-control; nuclear reactors

Financial disclosure: The authors declare that there is no potential conflict of interest.

Abbreviations and definitions:

AL: childhood acute leukemia

ALL: childhood acute lymphoblastic leukemia

AML: childhood acute myeloblastic leukemia

DBGZ: Dose Based Geographic Zoning

IGN: National Geographic Institute

IRSN: National Institute of Radiological Protection and Nuclear Safety

NPP: Nuclear Power Plant

NRCH: French National Registry of Childhood Hematopoietic Malignancies

O (resp. E): Observed (resp. expected) number of cases

OR: Odds Ratio

SIR: Standardized Incidence Ratio

Submission for a research article

The very good representativeness of our sample relative to the source population, the careful and precise geocoding, and the use of dose-based geographic zoning are the major assets of the study.

Abstract

To study the risk of childhood acute leukemia (AL) around French nuclear power plants (NPPs).

The nationwide Geocap case-control study included the 2,753 cases diagnosed in mainland France over 2002-2007 and 30,000 contemporaneous population controls. The last addresses were geocoded and located around the 19 NPPs. The study used distance to NPPs and a dose-based geographic zoning (DBGZ), based on the estimated dose to bone marrow related to NPP gaseous discharges.

An odds ratio (OR) of 1.9 [1.0-3.3], based on 14 cases, was evidenced for children living within 5 km of NPPs, compared to those living 20 km or further away, and a very similar association was observed in the concomitant incidence study (standardized incidence ratio (SIR) = 1.9 [1.0-3.2]). These results were similar for all the 5-year age groups. They persisted after stratification for several contextual characteristics of the municipalities of residence. Conversely, using the DBGZ resulted in OR and SIR close to one in all of the dose categories. There was no increase in AL incidence over 1990-2001 and over the entire 1990-2007 period. The results suggest a possible excess risk of AL in the close vicinity of French NPPs in 2002-2007. The absence of any association with the DBGZ may indicate that the association is not explained by NPP gaseous discharges. Overall, the findings call for investigation for potential risk factors related to the vicinity of NPP, and collaborative analysis of multisite studies conducted in various countries.

1. INTRODUCTION

The risk of childhood leukemia around nuclear power plants has given rise to considerable debate. Several epidemiological studies have analyzed the incidence of childhood leukemia around nuclear sites¹⁻⁵ and, more specifically, nuclear power plants⁶⁻¹³. In general, no excess risk has been evidenced by the multisite studies although persistent localized excesses of childhood acute leukemia (AL) have been reported around a few specific sites: the Sellafield¹⁴⁻¹⁶ and Dounreay^{17; 18} nuclear fuel reprocessing plants in the United Kingdom, and the Krummel nuclear power plant in Germany^{10; 19; 20}. Given the low radiation levels measured near the sites, the hypothesis that local population mixing related to the installation of the sites might ease the spread of a leukemogenic agent was raised²¹⁻²³ and appeared consistent with some further observations in the village of Seascale close to the Sellafield nuclear site²⁴. Seascale underwent a period of intensive population mixing and most of the observed excess appeared primarily related to this factor. Recently, the German KiKK population-based case-control study showed an association between leukemia in children less than 5 years old and living less than 5 km from a nuclear power plant (NPP)²⁵⁻²⁸. In France, a national geographic study of the period 1990-1998 was carried out^{12; 29} but found no association between the incidence of childhood AL and distance from nuclear sites. No association was demonstrated by an extended 1990-2001 study that used geographic zoning based on gaseous discharge dose estimates to assess radiation exposure in the municipalities near the sites³⁰.

The aim of the present study was to provide updated results on the risk of childhood leukemia near French NPPs, using a case-control design in addition to the usual geographic incidence approach. All the cases of childhood AL for the period 2002-2007 and a set of contemporaneous population controls were individually located and categorized in terms of

their distance from the 19 French NPPs and dose-based geographic zoning (DBGZ). The updated incidence study (1990-2007) is also presented.

2. MATERIAL AND METHODS

The Geocap case-control study, 2002-2007

The case-control study included all the 2,753 French childhood leukemia cases aged up to 15 years at the end of the year of diagnosis, diagnosed between 2002 and 2007, and residing in metropolitan France. The cases were obtained from the French National Registry of Childhood Hematopoietic Malignancies (NRCH)³¹.

A set of 30,000 control addresses, 5,000 each year for the period 2002-2007, representative of the French pediatric population for those years, was randomly sampled from the pediatric population of mainland France, by the National Institute for Statistics and Economic Studies (INSEE) using the income and council tax databases. The sample was stratified on the *Département* administrative unit. The control sample was closely representative of its source population in terms of age and number of children in the household, and in terms of contextual socioeconomic and demographic variables: size of the urban unit, median income, proportion of blue-collar workers, proportion of subjects who successfully completed high school, and proportion of homeowners in the municipality of residence (table 1).

The age available in the INSEE databases was the age at the end of the year (i.e. based on the year of birth) and that age variable was therefore also used for the cases. The INSEE database did not specify child gender.

The age distribution of the cases included in the study showed the expected peak of incidence, between 2 and 4 years old. The cases were closely comparable to the controls in terms of the contextual socio-demographic variables (table 1).

Incidence studies: 1990-2001, 2002-2007 and 1990-2007

The incidence studies performed at the Commune level (the smallest French administrative unit) for the same period 2002-2007 as the case-control study, for the preceding period 1990-2001, and for the complete period 1990-2007. The cases consisted in all children diagnosed with AL before the age of 15 years and registered in the NRCH during the periods. The annual national incidence rates of AL estimated by the NRCH were taken as reference rates.

The estimates of *Commune* populations by year of age were directly provided by the INSEE for the census years: 1990, 1999, 2006 and 2007. For the other years, the estimates were interpolated from the census data and the yearly estimates provided by the INSEE for the 96 French mainland *Départements*. Person-years and expected numbers of AL cases were then computed for each year of the 1990-2007 period by *Commune* and five-year age group.

Geocoding of addresses, 2002-2007

The addresses of the cases and controls were geocoded by the GEOCIBLE company using the geographic information system MAPINFO, the NAVTEQ street databases and detailed vectorized maps from the National Geographic Institute (IGN). The process resulted in the location of the addresses with an uncertainty of at most 100 meters for 92% of the cases and 96% of the controls, and with an uncertainty of 15 meters for 67% of the cases and 76% of the controls. Only 3% of the cases and 1% of the controls were only located by their *Commune* of residence, and were thus allocated the coordinates of the town hall of their *Commune*.

The geocoding uncertainties were small compared to the range of distances considered in the analysis. All the cases and controls were located in the 5 categories of distance ([0-5 km[, [5-10 km[, [10-15 km[, [15-20 km[, ≥ 20 km) from NPPs without any uncertainty.

NPP characteristics

There are 19 NPPs in France (additional table 1), all but two (*Chooz and Civaux*) having been commissioned before 1990. The majority of the NPPs are located near a river, but 4 of them are coastal. The NPPs *Cattenom*, *Chooz* and *Fessenheim*, are located less than 20 km from the border with Luxembourg, Belgium and Germany, respectively. The nuclear electrical power generated ranges from 1,800 to 5,400 MW.

Distance from the nearest NPP

In the Geocap case-control study the distance between the residence and the nearest NPP was derived from the geocoding. The 32,753 subjects included in the case-control study were located in 5-km wide rings within 20 km of the NPP or outside of the area. In the incidence studies, the *Communes* were positioned by the coordinates of the town hall, and assigned to the areas defined above around the nearest NPP.

Dose-based geographic zoning (DBGZ)

DBGZ had been developed by the National Institute of Radiological Protection and Nuclear Safety (IRSN) for the authors' previous analysis³². It used estimated bone marrow doses associated with gaseous radioactive discharges from the NPPs to classify the exposures at the town halls of the *Communes* located less than 20 km from the nuclear sites. The *Communes* close to more than one NPP or to another nuclear site included in the previous analysis were allocated the sum of the doses estimated for each of the neighboring installations. This was the case for the *Flamanville* NPP, which is close to the *La Hague* nuclear site, and for the *Cruas* and *Tricastin* NPPs, which are close to the *Pierrelatte* nuclear site. For the analyses stratified by NPP the *Communes* close to more than one NPP were assigned to the NPP for which the estimated dose was the highest.

In the case-control study, the cases and controls were allocated the dose estimated at the town hall of the *Commune* of residence. The cutoffs were chosen so as to obtain the same distribution of expected cases as that obtained by dividing the area around the NPPs into rings 5 km wide, i.e. approximately 10%, 20%, 30% and 40% of the expected cases.

Statistical Analysis

All the statistical analyses were performed using the SAS software package (version 9; SAS Institute Inc., Cary, NC, USA). The analyses were conducted on all the NPPs and all the cases, and by age group (0-4, 5-9, 10-14 years), AL subtype: lymphoblastic (ALL) and myeloblastic (AML), NPP and year of study.

In the case-control study, the odds ratios (OR) and their 95% confidence intervals (CI) were estimated by unconditional logistic regression adjusted for age (5-year age groups) and *Département*.

In the incidence studies, the relative risk of AL was estimated by the standardized incidence ratio (SIR), defined as the ratio of the observed (O) and expected (E) numbers of cases. The 95% CI was calculated using Byar's approximation³³. The statistical distribution of the number of cases observed yearly around each NPP was compared to that obtained under the hypothesis of a Poisson distribution and no statistically or quantitatively significant departure was observed. Additionally our previous analyses evidenced no quantitatively significant over-dispersion at the *Commune*³⁴ or *Département*³⁵ scale in France.

The heterogeneity of the SIRs by year or NPP was tested using Pearson's chi-square statistic, with external (national rates) and internal (rates within 20 km around NPPs) references. Since small numbers might have impaired the validity of the tests, the statistical significance levels of the tests were estimated by simulation. In all, 50,000 distributions of the cases in the *Communes* were generated under the null hypothesis of a Poisson distribution with the

corresponding expected number of cases and the observed statistics were compared to the distribution of the 50,000 simulated statistics.

Analyses were also performed after excluding the subjects living further than 50km from a NPP in the case-control study and computing the incidence between 20 and 50 km.

Stratified analyses were conducted by NPP characteristic, i.e. electrical power, coastal location and border location in the 2002-2007 case-control study and in the 1990-2007 incidence study. In order to account for potential confounders, the analyses were repeated after stratification or adjustment for several contextual variables in the models. The contextual variables were extracted from the 1999 census data and consisted in the urban status of the *Commune* (rural, semi-urban or urban), the median income of the households, the proportion of blue-collar workers and the proportion of baccalaureate holders. The latter variables were used separately as well as jointly to take spatial socioeconomic heterogeneity into account.. The data were also analyzed after exclusion of the cases and controls who lived less than 200 meters from a high-voltage power line and those who lived less than 600 meters from a power line, since an association between the proximity of power lines and the risk of AL has been suggested^{36; 37}. Sensitivity analyses were performed by excluding, in turn, each year or each NPP, or by using a 6-year sliding window over the 1990-2007 period. The analyses with dose estimates were replicated using cutoffs based on the quartiles of the distribution in the controls.

To test for the existence of a trend in the incidence of AL with the distance from a NPP, the inverse distance function was considered. A test for linearity based on a log-likelihood ratio statistic was performed, considering the categorical variable derived from the 2-km-wide rings. The inverse distance was then included in the regression model as a continuous independent variable. The significance of the regression parameters was evaluated using 10,000 replications of the datasets. For the case-control analysis, 10,000 permutations of the

case-control status of all the children were made, by *Département* and independently of the distance from the NPPs. In the incidence studies, the 10,000 replicated datasets were built under the hypothesis of a Poisson distribution of the cases in the *Communes*.

Power of the studies

In the Geocap study using a one-sided test at the 5% level, the power to detect an OR of two for living less than 5 km from a NPP (compared to living more than 20 km), was equal to 43% for the 0-4 year age group and 70% for the 0-14 year age group. For the incidence studies, using an exact one-sided Poisson test at the 5% level and the approximation suggested by Breslow and Day³³, the power to detect a SIR of two for living less than 5 km from a NPP (compared to living more than 20 km), was very close to that of the Geocap study for the period 2002-2007 and greater than 80% for the 1990-2001 and 1990-2007 periods .

3. RESULTS

Childhood AL risk and proximity of NPP

Geocap case-control study (2002-2007)

Among the 2,753 cases included in the case-control study, 99 were living less than 20 km from a NPP. AL was significantly associated with living less than 5 km from a NPP (OR = 1.9 [1.0-3.2]) and ORs close to unity were observed for all the areas farther from the sites (table 2). When the cases and controls were located in rings 2 km wide instead of 5 km wide, the logarithm of the odds ratio tended to increase slightly with the inverse of the distance from the nearest NPP (additional figure 1), although this trend was not statistically significant when the inverse distance was considered a continuous variable in the regression model ($p_{\text{one-sided}} = 0.18$). For children less than 5 years old, the OR observed in the closest area was of the same

order of magnitude as that for the whole group, although not significant (OR = 1.6 [0.7- 4.1]). Very similar patterns were obtained for the 5-9 and 10-14 year age groups (data not shown).

The cases living in each of the 5 km rings around the NPPs presented with the usual age, gender and neoplastic cell characteristics (table 3). The number of AML cases was very small (17 cases within 20 km, none within 5 km). The results for ALL were very similar to those for all AL, the OR associated with living less than 5 km from a NPP being 2.4 [1.3-4.2] (additional table 2).

Incidence study, 2002-2007

Over the same period, 2002-2007, the incidence study included 2,831 AL cases less than 15 years old. The SIRs were very close to the OR of the contemporaneous case-control study for all the age groups and distance categories (table 2). The logarithm of the SIR increased slightly with the inverse distance from the nearest NPP (additional figure 1), but this trend was not statistically significant in the continuous model ($p_{\text{one-sided}} = 0.25$).

For the 1,159 subjects who lived within 20 km of the nearest NPP, the distances from NPP based on the coordinates of the *Commune* town hall used in the incidence study, and on the individual coordinates used in the case-control study, were highly correlated ($r = +0.97$). This finding is connected to the fact that most French NPPs are located in rural areas in which most of the dwellings are located close to the town hall.

Incidence study, 1990-2001

In the preceding period, 1990-2001, already covered by a previous analysis³⁰, 5,356 AL cases less than 15 years old were registered in the NRCH. Among the cases, 173 lived less than 20 km from a NPP (table 2). The SIR did not differ from one for any of the four 5-km rings around the NPPs.

Incidence study 1990-2007

Over the whole period, 1990-2007, 272 of the 8,187 cases registered by the NRCH lived less than 20 km, and 24 less than 5 km, from a NPP. The SIR were 1.0 [0.9-1.1] and 1.1 [0.7-1.7], respectively (table 2). The SIR for the closest area was slightly but not significantly higher for the 0-4 year age group (1.4 [0.8-2.3]; $p_{\text{one-sided}} = 0.15$).

Subgroup analyses, control of confounders and sensitivity analyses

The results were unchanged when the subjects living further than 50 km from a NPP were excluded from the case-control analysis. The SIR was very close to one (SIR=1.05[0.96-1.15]) for residences between 20 and 50 km from a NPP. The stratified analyses showed that the association between AL and living within 5 km of a NPP did not vary substantially with the power of the NPP, with location on a coast or border, or with the urban/rural status of the *Commune* (table 4). The increased risk with living less than 5 km from a NPP appeared more marked, although not significantly so, in *Communes* with the lowest median income or lowest proportion of baccalaureate holders than in other *Communes*.

Adjustments for the contextual variables either separately and jointly and for the deprivation index did not change the estimates. No case and 5 controls lived less than 5 km from a NPP and less than 200 m from a high-voltage power line, and excluding them did not substantially modify the association with proximity to NPP (OR=2.0 [1.1;3.6]). Considering children living less than 600 m from the lines did not change the association with NPP either (OR=2.1

[0.7;6.4] <600 m and OR=1.8 [0.9;3.5] further). Using the distance between the municipality and NPP rather than individual distances led to very similar OR and SIR.

The small numbers hampered the detailed analyses by NPP or year. No specific association with living less than 5 km from a given NPP was evidenced. When each NPP was excluded, in turn, from the case-control and incidence analyses, the OR/SIR estimated on the 18 remaining NPPs was very similar to that for the 19 NPPs (additional table 3). There was no heterogeneity of the SIRs estimated by NPP ($p = 0.13$) and the test of the hypothesis that they were all equal to one was on the borderline of statistical significance ($p = 0.07$).

Over the period, 2002-2007, AL cases living less than 5 km from a NPP were mostly diagnosed in 2003, 2006 and 2007 (table 4). However, the results remained similar when each year of observation was excluded, in turn, from the case-control and incidence analyses. For the whole period, 1990-2007, no significant heterogeneity of the annual SIRs was evidenced ($p = 0.12$), but the test of the hypothesis that the SIRs were all equal to one was on the borderline of significance ($p = 0.06$). When the incidence analyses were restricted to successive 6-year sliding windows over the whole 1990-2007 period, 2002-2007 was the only period for which an association with living less than 5 km from a NPP was observed. The use of simulations resulted in similar values of the statistics and the same conclusions.

Childhood AL and DBGZ

The estimated bone marrow doses related to radioactive gaseous discharge did not result in the same categorization of the cases and controls (table 5): 40% of the controls in the highest exposure category ($> 0.72 \mu\text{Sv}$) were in the 0-4.99 km ring, 44% in the 5-9.99 km ring, 11% in the 10-14.99 km ring and 4% in the 15-19.99 km ring.

No association between AL and DBGZ was observed in the case-control study or in the 2002-2007 incidence study (table 6). The SIRs and ORs were close to one for all the DBGZ categories. The results were the same when the DBGZ categories were based on the quartiles of the control exposure distribution (not shown). Exclusion of the NPPs close to other nuclear sites did not change the results. There was no association between AL and DBGZ for the whole period, 1990-2007 (table 6).

4. DISCUSSION

The Geocap case-control study evidenced an association between childhood AL and living less than 5 km from a NPP for the 2002-2007 period. The association was also observed in the contemporaneous incidence study, but not for the previous period, 1990-2001. Using the DBGZ yielded very different results, with SIRs and ORs close to one for all the DBGZ categories. The association observed for 2002-2007 was not specific to any age group, NPP or year.

One strength of the study resides in the fact that the cases were identified by the NRCH, which has covered the entire country since 1990. The NCRH relies on about three independent notifications per case on average. Its exhaustiveness has been estimated to be 99.4%³⁸. A further strength consists in the fact that the controls were selected from the nearly exhaustive database of taxpayer households with children. As illustrated by table 1, the controls in the Geocap study were highly representative of the source population. Another strength of the Geocap study is the precise geocoding of the cases' and controls' residences. The two complementary approaches used are sensitive to different potential sources of biases, selection of controls for the case-control study, and estimates of expected number of cases for the ecological study based on incidence data aggregated at the *Commune* level. The fact that both approaches resulted in almost identical findings is a strong argument in favour of the validity of the ORs and SIRs.

Adjustment for, and stratification on, age and the socioeconomic and demographic characteristics of the Commune of residence were assumed to cancel out a number of potential contextual confounders.

A limitation of the present study is that the data did not enable adjustment for individual potential risk factors such as birth order, breastfeeding, day-care attendance, or pesticide exposure. However, there is no obvious reason for these factors to differ within and outside the 5 km rings close to the NPPs conditionally on rural/urban status or other socioeconomic or demographic variables, which were taken into account. Data on parental employment at the NPPs was not available in the Geocap study, but an impact of parental employment on childhood leukemia is not supported by the literature³⁹. Also, population mixing could not be evaluated in this study. However, the Geocap study allowed to account for adjustment on the proximity of high-voltage power lines.

Like most studies of childhood leukemia in the neighborhood of NPPs, the Geocap study did not have access to complete residential histories, which is an important limitation for the evaluation of the true exposure to radiation or any factor related to the proximity of NPPs. However, neither the Finnish study which collected complete residential history and computed the distance from a NPP weighted by the time spent in the house⁹, nor the Swiss study which used the addresses at birth and diagnosis⁶ revealed an association with past or cumulative proximity to NPP.

Restricting the analyses to children aged less than 5 years, who are less likely to have moved house since birth than older children, resulted in similar ORs and SIRs. Three NPPs are located close to a French border, but only the French part of the 20-km radius was considered. However, excluding the three NPPs did not markedly change the results. None of the NPPs in neighboring countries was less than 20 km from the French border.

The method used to estimate the dose of radiation delivered to bone marrow by the NPPs was based on the average annual gaseous discharge levels, discharge composition and local meteorological parameters especially prevailing winds which influence the dispersion of

radionuclides. Due to the lack of data on real discharge rates, the discharge rates for carbon 14 were based on the regulatory limits. The contribution of carbon 14 to the radiation dose may therefore have been overestimated. However, the method was the same for all the NPPs. In consequence, the *Communes* are likely to have been correctly ranked within a given NPP area in terms of exposure despite the potential errors in dose estimates. Contrary to a classic assumption, table 5 clearly illustrates that the distribution of the population in terms of the dispersion of radionuclides released into the atmosphere cannot be represented by a simple function of the distance from the NPP. The use of the innovative DBGZ appears to be one step toward overcoming the limitations of studies using conventional circular zoning⁴⁰. The model did not take into account liquid discharges, although their contribution to the total radiation exposure related to NPP activity may have been of the same order of magnitude as that of the gaseous discharges. The radiation doses due to liquid discharges are mainly determined by individual behaviors (food consumption and water use) and are therefore not expected to comply with geographic zoning around NPPs. Furthermore, in many situations the doses are not expected to decrease smoothly with distance from the NPP. In addition, although the NPPs located on a coast or river may be expected to differ with regard to doses from liquid discharges, in the stratified analyses the associations with AL were similar. Overall, the estimated doses due to NPPs were very low compared to the doses due to natural radiation sources. Such doses are not expected to result in an observable excess risk on the basis of the available evidence⁴¹. Compared to other studies, the use of DBGZ constitutes in the authors' opinion, a major improvement. The approach used to derive DBGZ is already quite elaborated (consideration of a broad spectrum of 12 radionuclides, use of real average discharge data and local climate data, calculation of the dose to the pertinent organ, etc.). In future developments, DBGZ could be refined by including real discharge data for carbon 14 in the models for gaseous discharges and by accounting for the impact of liquid discharges in

the determination of dose levels. Also, DBGZ could provide estimates at the place of residence rather than at the town hall. However, while DBGZ could gain in accuracy and precision, the estimates are not expected to increase to the dose ranges that could exert a noticeable effect on leukemia risk according to predictive models.

In the authors' previous multisite incidence studies^{29; 30} no association between proximity to NPPs and AL was observed. This was in line with most multisite studies^{1; 2; 8; 12}, and is also in line with the results of the authors' incidence analysis over the whole period, 1990-2007. In Germany, the KiKK case-control study of children aged less than 5 years evidenced an association between AL and NPP proximity²⁵. However, there are several important differences between those results and the results of the present study. The German incidence study showed that incidence rates were higher specifically in the 0-4 year age group⁴², which was not the case in this study. Also, in the German study, the risk estimates obtained in the incidence analysis²⁶ appeared to be lower than those obtained with the case-control approach²⁵, while in this study, the estimates obtained with the two approaches were very similar. In the German study, the estimated risk in the 5 km ring was highly sensitive to whether or not the Krummel NPP was included⁸, while no noteworthy difference between the NPPs was observed in this study. A reassessment of the KiKK results showed the marked impact of the urban/rural status of the residence area on the estimated risk⁴³, while no noteworthy difference was observed in the present study. In the KiKK study, an increasing trend with the inverse distance from the sites, considered as a continuous variable, was reported; the trend was not detected when the distance was categorical²⁵. In the Geocap study, a slight but non-significant increasing trend of the OR and SIR with inverse distance was observed.

Overall, the results suggest a possible excess risk of AL in the close vicinity of French NPPs in 2002-2007. The increased incidence observed at less than 5 km from the NPPs in the Geocap study only partially supports the recent German findings since the increase was limited to recent years and was not specific to the youngest children. The absence of any association with DBGZ, which is assumed to reflect the distribution of gaseous radiation discharged from NPPs, may indicate that the association observed with distance <5 km over 2002-2007 and particularly in 2006-2007, is not explained by NPP gaseous discharges. Overall, the results suggest a potential excess risk over 2002-2007 that may be due to unknown factors related to the proximity of NPPs. Among the potential factors are population mixing and exposures to physical agents, including natural or man-made exposures to radiation not modeled by the DBGZ. Overall, the findings call for investigation for potential risk factors related to the vicinity of NPP, and collaborative analysis of all the evidence available from multisite studies conducted in various countries.

Acknowledgments:

This work was supported by the *Institut de Veille Sanitaire (InVS)*, *Agence Nationale de Sécurité Sanitaire de l'Alimentation, de l'Environnement et du Travail (ANSES)*, *Association pour la Recherche sur le Cancer (ARC)*, *Fondation Pfizer*, *Institut National du Cancer (INCa)* and *Agence Nationale de la Recherche (ANR)*.

The authors are particularly grateful to Olivier LAMY and Mathieu CARRÈRE (GEOCIBLE), who carefully ensured all the geocoding, and *Institut Géographique National (IGN)*, which made precise maps available for the whole country. The authors are also grateful to Magda TOMASINI and Laurent AUZET (INSEE), who conducted the control sampling, Aline MORIN (IRSN), who conducted the dose-based geographic zoning, all the NRCH research assistants who collected the cases' addresses and the pediatric oncology teams for their help in data collection.

References

- [1] Bithell JF, Keegan TJ, Kroll ME, Murphy MFG & Vincent TJ. Childhood leukaemia near British nuclear installations: methodological issues and recent results. *Radiat Prot Dosimetry* 2008; **132**: 191-197.
- [2] Laurier D, Jacob S, Bernier MO, Leuraud K, Metz C, Samson E & Laloi P. Epidemiological studies of leukaemia in children and young adults around nuclear facilities: a critical review. *Radiat Prot Dosimetry* 2008; **132**: 182-190.
- [3] Committee on Medical Aspects of Radiation in the Environment (COMARE). Tenth report. the incidence of childhood cancer around nuclear installations in Great Britain. *J Radiol Prot* 2005; **25(3)**: 335-336.
- [4] Michaelis J, Keller B, Haaf G & Kaatsch P. Incidence of childhood malignancies in the vicinity of west German nuclear power plants. *Cancer Causes Control* 1992; **3**: 255-263.
- [5] McLaughlin JR, Clarke EA, Nishri ED & Anderson TW. Childhood leukemia in the vicinity of Canadian nuclear facilities. *Cancer Causes Control* 1993; **4**: 51-58.
- [6] Spycher BD, Feller M, Zwahlen M, Rösli M, von der Weid NX, Hengartner H, Egger M & Kuehni CE. Childhood cancer and nuclear power plants in Switzerland: a census-based cohort study. *Int J Epidemiol* 2011; **40**: 1247-1260.
- [7] Jablon S, Hrubec Z & Boice JDJ. Cancer in populations living near nuclear facilities. A survey of mortality nationwide and incidence in two states. *JAMA* 1991; **265**: 1403-1408.
- [8] Committee on Medical Aspects of Radiation in the Environment (COMARE). Fourteenth report. Further consideration of the incidence of childhood leukaemia around nuclear power plants in Great Britain. health protection agency. chilton 2011.
- [9] Heinävaara S, Toikkanen S, Pasanen K, Verkasalo PK, Kurtio P & Auvinen A. Cancer incidence in the vicinity of Finnish nuclear power plants: an emphasis on childhood leukemia. *Cancer Causes Control* 2010; **21**: 587-595.
- [10] Kaatsch P, Kaletsch U, Meinert R & Michaelis J. An extended study on childhood malignancies in the vicinity of German nuclear power plants. *Cancer Causes Control* 1998; **9**: 529-533.
- [11] Mangano JJ, Sherman J, Chang C, Dave A, Feinberg E & Frimer M. Elevated childhood cancer incidence proximate to U.S. nuclear power plants. *Arch Environ Health* 2003; **58**: 74-82.
- [12] Laurier D, Hémon D & Clavel J. Childhood leukaemia incidence below the age of 5 years near French nuclear power plants. *J Radiol Prot* 2008; **28**: 401-403.
- [13] Waller LA, Turnbull BW, Gustafsson G, Hjalmar U & Andersson B. Detection and assessment of clusters of disease: an application to nuclear power plant facilities and childhood leukaemia in Sweden. *Stat Med* 1995; **14**: 3-16.
- [14] Goldsmith JR. Nuclear installations and childhood cancer in the UK: mortality and incidence for 0-9-year-old children, 1971-1980. *Sci Total Environ* 1992; **127**: 13-35, 43-55.
- [15] Sharp L, Black RJ, Harkness EF & McKinney PA. Incidence of childhood leukaemia and non-Hodgkin's lymphoma in the vicinity of nuclear sites in Scotland, 1968-93. *Occup Environ Med* 1996; **53**: 823-831.
- [16] Bithell JF, Dutton SJ, Draper GJ & Neary NM. Distribution of childhood leukaemias and non-Hodgkin's lymphomas near nuclear installations in England and Wales. *BMJ* 1994; **309**: 501-505.
- [17] Heasman M, Kemp I, Urquhart J & Black R. Childhood leukaemia in northern Scotland. *Lancet* 1986; **1**: 266.

- [18] Black RJ, Sharp L, Harkness EF & McKinney PA. Leukaemia and non-Hodgkin's lymphoma: incidence in children and young adults resident in the Dounreay area of Caithness, Scotland in 1968-91. *J Epidemiol Community Health* 1994; **48**: 232-236.
- [19] Hoffmann W, Dieckmann H, Dieckmann H & Schmitz-Feuerhake I. A cluster of childhood leukemia near a nuclear reactor in northern Germany. *Arch Environ Health* 1997; **52**: 275-280.
- [20] Hoffmann W, Terschueren C & Richardson DB. Childhood leukemia in the vicinity of the Geesthacht nuclear establishments near Hamburg, Germany. *Environ Health Perspect* 2007; **115**: 947-952.
- [21] Kinlen L. Childhood leukaemia, nuclear sites, and population mixing. *Br J Cancer* 2011; **104**: 12-18.
- [22] Kinlen L. Epidemiological evidence for an infective basis in childhood leukaemia. *Br J Cancer* 1995; **71**: 1-5.
- [23] Kinlen LJ, Dickson M & Stiller CA. Childhood leukaemia and non-Hodgkin's lymphoma near large rural construction sites, with a comparison with Sellafield nuclear site. *BMJ* 1995; **310**: 763-768.
- [24] Dickinson HO & Parker L. Quantifying the effect of population mixing on childhood leukaemia risk: the Seascale cluster. *Br J Cancer* (1999) **81**: pp. 144-151.
- [25] Kaatsch P, Spix C, Schulze-Rath R, Schmiedel S & Blettner M. Leukaemia in young children living in the vicinity of German nuclear power plants. *Int J Cancer* 2008; **122**: 721-726.
- [26] Kaatsch P, Spix C, Jung I & Blettner M. Childhood leukemia in the vicinity of nuclear power plants in Germany. *Dtsch Arztebl Int* 2008; **105**: 725-732.
- [27] Spix C, Schmiedel S, Kaatsch P, Schulze-Rath R & Blettner M. Case-control study on childhood cancer in the vicinity of nuclear power plants in Germany 1980-2003. *Eur J Cancer* 2008; **44**: 275-284.
- [28] Kinlen L. A German storm affecting Britain: childhood leukaemia and nuclear power plants. *J Radiol Prot* 2011; **31**: 279-284.
- [29] White-Koning ML, Hémon D, Laurier D, Tirmarche M, Jouglu E, Goubin A & Clavel J. Incidence of childhood leukaemia in the vicinity of nuclear sites in France, 1990-1998. *Br J Cancer* 2004; **91**: 916-922.
- [30] Evrard A, Hémon D, Morin A, Laurier D, Tirmarche M, Backe J, Chartier M & Clavel J. Childhood leukaemia incidence around French nuclear installations using geographic zoning based on gaseous discharge dose estimates.. *Br J Cancer* 2006; **94**: 1342-1347.
- [31] Lacour B, Guyot-Goubin A, Guissou S, Bellec S, Désandes E & Clavel J. Incidence of childhood cancer in France: national children cancer registries, 2000-2004. *Eur J Cancer Prev* 2010; **19**: 173-181.
- [32] Morin A & Backe J. Programme environnement et santé 1999. Une estimation de l'exposition du public due aux rejets radioactifs des centrales nucléaires. *Note Technique SEGR/SAER/02-51 Indice 1. Institut de Radioprotection et de Sécurité Nucléaire, Fontenay-aux-Roses, Juillet 2002.*
- [33] Breslow NE & Day NE. Statistical methods in cancer research. Volume ii--The design and analysis of cohort studies. *IARC Sci Publ* 1987 : 1-406.
- [34] Bellec S, Baccaïni B, Goubin A, Rudant J, Ripert M, Hémon D & Clavel J. Childhood leukaemia and population movements in France, 1990-2003. *Br J Cancer* 2008; **98**: 225-231.
- [35] Faure C, Mollié A, Bellec S, Guyot-Goubin A, Clavel J & Hémon D. Geographical variations in the incidence of childhood acute leukaemia in France over the period 1990-2004. *Eur J Cancer Prev* 2009; **18**: 267-279.

- [36] Greenland S, Sheppard AR, Kaune WT, Poole C & Kelsh MA. A pooled analysis of magnetic fields, wire codes, and childhood leukemia. childhood leukemia-EMF study group. *Epidemiology* 2000; **11**: 624-634.
- [37] Ahlbom A, Day N, Feychting M, Roman E, Skinner J, Dockerty J, Linet M, McBride M, Michaelis J, Olsen JH, Tynes T & Verkasalo PK. A pooled analysis of magnetic fields and childhood leukaemia. *Br J Cancer* 2000; **83**: 692-698.
- [38] Clavel J, Goubin A, Auclerc MF, Auvrignon A, Waterkeyn C, Patte C, Baruchel A, Leverger G, Nelken B, Philippe N, Sommelet D, Vilmer E et al.. Incidence of childhood leukaemia and non-Hodgkin's lymphoma in France: national registry of childhood leukaemia and lymphoma, 1990-1999. *Eur J Cancer Prev* 2004; **13**: 97-103.
- [39] Committee on Medical Aspects of Radiation in the Environment (COMARE). Seventh report. Parents occupationally exposed to radiation prior to the conception of their children. A review of the evidence concerning the incidence of cancer in their children (chairman: professor b a bridges obe). *National Radiological Protection Board* (2002).
- [40] Wing S, Richardson DB & Hoffmann W. Cancer risks near nuclear facilities: the importance of research design and explicit study hypotheses. *Environ Health Perspect* 2011; **119**: 417-421.
- [41] United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR). Exposure from natural radiation sources. In: UNSCEAR: sources and effects of ionizing radiation. 2000; **Volume I: Sources, Annex B. New-York: United Nations, 133.**
- [42] Grosche B. The 'kinderkrebs in der umgebung von kernkraftwerken' study: results put into perspective. *Radiat Prot Dosimetry* 2008; **132**: 198-201.
- [43] Strahlenschutzkommission (SSK). Bewertung der epidemiologischen studie zu kinderkrebs in der umgebung von kernkraftwerken (KiKK study). *Bundesministerium für Umwelt, Naturschutz und Reaktorsicherheit, Heft* 2009; **58.**

Table 1: Comparability of the Geocap controls with their source population by individual and contextual socioeconomic and demographic variables – 2002-2007, mainland France, and distribution of 2002-2007 cases by the same individual or contextual variables.

	Source population %	Geocap controls %	Geocap cases
Individual characteristics			
Age at the end of the year			
0	6.2%	6.1%	2.5%
1	6.6%	6.3%	6.4%
2	6.7%	6.9%	12.3%
3	6.7%	6.7%	14.1%
4	6.7%	6.4%	11.6%
5	6.7%	6.9%	8.5%
6	6.7%	6.7%	6.9%
7	6.7%	6.8%	6.1%
8	6.6%	6.5%	5.1%
9	6.6%	6.9%	4.9%
10	6.6%	6.6%	4.4%
11	6.7%	6.7%	4.2%
12	6.7%	6.8%	4.1%
13	6.8%	6.9%	4.1%
14	6.9%	7.0%	5.0%
Number of children in the household			
1	29.7%	29.4%	NA
2	42.9%	43.1%	NA
3	19.8%	20.0%	NA
≥ 4	7.7%	7.5%	NA
Contextual variables			
Size of the urban unit^a of the <i>Commune</i> of residence			
Rural unit	26.1%	25.8%	26.7%
< 5,000 inhabitants	6.3%	6.3%	5.9%
5,000-9,999 inhabitants	5.5%	5.5%	5.4%
10,000-19,999 inhabitants	5.0%	5.0%	5.0%
20,000-49,999 inhabitants	6.0%	6.0%	6.1%
50,000-99,999 inhabitants	6.6%	6.5%	6.5%
100,000-199,999 inhabitants	5.0%	5.1%	5.5%
200,000-1,999,999 inhabitants	21.7%	21.9%	22.6%
Paris urban unit	17.9%	17.9%	16.4%
Median annual income of the <i>Commune</i> (€)			
<12,864	25.0%	24.4%	24.3%
12,864-14,332	25.0%	25.6%	24.9%
14,333-16,429	25.0%	24.8%	26.1%
>16,429	25.0%	25.2%	24.7%
Proportion of blue-collar workers in the <i>Commune</i>			
< 20%	25.0%	25.3%	25.3%
20-26.5%	25.0%	25.1%	25.2%
26.6-34.2%	25.0%	24.7%	24.6%
>34.2%	25.0%	24.9%	24.9%
Proportion of baccalaureate holders in the <i>Commune</i>			
< 19.2%	25.0%	24.7%	24.6%
19.2-24.5%	25.0%	25.3%	25.8%
24.6-30.6%	25.0%	24.8%	25.3%
>30.6%	25.0%	25.2%	24.3%
Proportion of homeowners in the <i>Commune</i>			
<42.8%	25.0%	25.2%	23.7%
42.8-60.1%	25.0%	24.7%	25.5%
60.2-76.0%	25.0%	24.9%	25.6%
>76.0%	25.0%	25.2%	25.2%

^aThe urban unit is defined by the INSEE (National Institute of Statistics and Economic Studies) as a group of *Communes* in which the distance between dwellings is not more than 200 m.

Table 2: Distance to the nearest French nuclear power plant (NPP) and childhood acute leukemia - Geocap case-control study and incidence studies.

	Geocap study, 2002-2007 ^a					Incidence study, 2002-2007 ^b					Incidence study, 1990-2001 ^b					Incidence study, 1990-2007 ^b				
	(distance: residence-nearest NPP)					(distance: municipality-nearest NPP)					(distance: municipality-nearest NPP)					(distance: municipality-nearest NPP)				
	Cases	Controls	OR	95%CI	p	O	E	SIR	95%CI	p	O	E	SIR	95%CI	p	O	E	SIR	95%CI	p
Age < 15 years^c																				
0-4.99 km	14	80	1.9	[1.0-3.3]	*	14	7.4	1.9	[1.0-3.2]	*	10	13.6	0.7	[0.4-1.4]		24	21.0	1.1	[0.7-1.7]	
5-9.99 km	17	213	0.9	[0.5-1.5]		19	20.6	0.9	[0.6-1.4]		40	39.2	1.0	[0.7-1.4]		59	59.8	1.0	[0.8-1.3]	
10-14.99 km	27	320	0.9	[0.6-1.4]		30	25.4	1.2	[0.8-1.7]		50	48.5	1.0	[0.8-1.4]		80	73.9	1.1	[0.9-1.4]	
15-19.99 km	41	447	1.0	[0.7-1.4]		36	42.4	0.9	[0.6-1.2]		73	81.5	0.9	[0.7-1.1]		109	124.0	0.9	[0.7-1.1]	
≥ 20 km	2654	28940	1.0																	
<20 km	99	1060	1.0	[0.8-1.3]		99	95.7	1.0	[0.8-1.3]		173	182.9	0.9	[0.8-1.1]		272	278.6	1.0	[0.9-1.1]	
≥ 20 km	2654	28940	1.0																	
Age < 5 years^c																				
0-4.99 km	6	27	1.6	[0.7-4.1]		8	3.6	2.2	[1.0-4.4]	*	6	6.6	0.9	[0.3-2.0]		14	10.2	1.4	[0.8-2.3]	
5-9.99 km	7	55	1.0	[0.5-2.3]		10	10.2	1.0	[0.5-1.8]		21	19.3	1.1	[0.7-1.7]		31	29.5	1.1	[0.7-1.5]	
10-14.99 km	11	103	0.8	[0.4-1.4]		11	12.6	0.9	[0.4-1.6]		18	23.5	0.8	[0.5-1.2]		29	36.1	0.8	[0.5-1.2]	
15-19.99 km	17	136	1.0	[0.6-1.7]		18	20.8	0.9	[0.5-1.4]		39	39.7	1.0	[0.7-1.3]		57	60.6	0.9	[0.7-1.2]	
≥ 20 km	1248	9396	1.0																	
Total <20 km	41	321	1.0	[0.7-1.4]		47	47.3	1.0	[0.7-1.3]		84	89.1	0.9	[0.8-1.2]		131	136.4	1.0	[0.8-1.1]	
≥ 20 km	1248	9396	1.0																	

^a Odds ratios (OR) and 95% confidence intervals (95%CI) estimated by logistic regression adjusted for age at the end of the year (5-year age groups for the 5-14-year-old children, 1-year age groups for the 0-4-year-old children) and *Département* of residence; ^b Standardized incidence ratio (SIR) calculated as the ratio of the observed (O) to the expected (E) number of cases with Byar's approximation of the 95% confidence interval (95%CI); ^c Age at the end of the year in the Geocap study; exact age in the incidence studies

* One-sided <0.5

Table 3: Description of the registered cases within 20 km of the nuclear power plants (NPP) over the period, 2002-2007.

	Distance: residence - nearest NPP											
	0-4.99 km		5-9.99 km		10-14.99 km		15-19.99 km		< 20 km		≥ 20 km	
	n	%	n	%	n	%	n	%	n	%	n	%
Gender	14		17		27		41		99		2654	
Female	7	50.0%	8	47.1%	13	48.1%	20	48.8%	48	48.5%	1202	45.3%
Male	7	50.0%	9	52.9%	14	51.9%	21	51.2%	51	51.5%	1452	54.7%
Age												
< 5 years	6	42.9%	7	41.2%	11	40.7%	17	41.5%	41	41.4%	1248	47.0%
5-9 years	5	35.7%	6	33.3%	11	40.7%	14	34.1%	36	36.4%	829	31.2%
10-14 years	3	21.4%	4	23.5%	5	18.6%	10	24.4%	22	22.2%	577	21.7%
Down's syndrome	0	0%	0	0%	0	0%	1	2.4%	1	1.0%	41	1.5%
Acute leukemia type												
ALL	14	100.0%	13	76.5%	23	85.2%	30	73.2%	80	80.8%	2179	82.1%
B-cell precursor ALL	11	78.6%	10	58.8%	19	70.4%	26	63.4%	66	66.7%	1810	67.2%
T-cell ALL	2	14.3%	3	17.6%	3	11.1%	4	9.8%	12	12.1%	249	9.4%
AML	0	0.0%	4	23.5%	3	11.1%	10	24.0%	17	17.2%	407	15.3%
Other AL	0	0.0%	0	0.0%	1	3.7%	1	2.0%	2	2.0%	68	2.6%

AL: acute leukemia; ALL: acute lymphoblastic leukemia; AML: acute myeloblastic leukemia

Table 4: Distance to the nearest French nuclear power plant (NPP) and childhood acute leukemia –Geocap and incidence studies, 2002-2007, different stratified analyses.

	Geocap case-control study ^a (residence address)						Incidence study, 2002-2007 ^b (town hall address)														
	< 5 km vs. ≥ 20 km			< 20 km vs. ≥ 20 km			< 5 km			< 20 km											
	Cases	Controls	OR	95%CI	p	Cases	Controls	OR	95%CI	p	O	E	SIR	95%CI	p	O	E	SIR	95%CI	p	
Electrical power																					
5200-5400 MW	3	22	1.4	[0.4-4.9]		28	303	0.9	[0.6-1.4]		3	1.8	1.7	[0.3-4.8]		27	26.2	1.0	[0.7-1.5]		
3600 MW	4	22	2.1	[0.7-6.3]	*	28	325	1.0	[0.6-1.4]		3	1.9	1.6	[0.3-4.5]		27	31.6	0.9	[0.6-1.2]		
2600-2800 MW	6	29	2.1	[0.8-5.1]	#	33	345	1.1	[0.7-1.5]		7	3.0	2.3	[0.9-4.8]	*	34	30.8	1.1	[0.8-1.5]		
1800 MW	1	7	1.4	[0.2-11.6]		10	87	1.3	[0.6-2.6]		1	0.6	1.7	[0.0-9.3]		11	7.1	1.5	[0.8-2.8]		
Year																					
2002	0	12	0.0			15	180	0.8	[0.5-1.5]		1	1.2	0.8	[0.0-4.5]		15	16.2	0.9	[0.5-1.5]		
2003	3	15	2.1	[0.6-7.5]		18	182	1.2	[0.7-2.0]		3	1.2	2.4	[0.5-7.1]		17	16.2	1.1	[0.6-1.7]		
2004	1	13	0.8	[0.1-6.4]		19	168	1.2	[0.7-2.0]		1	1.3	0.8	[0.0-4.4]		18	16.3	1.1	[0.7-1.7]		
2005	1	13	0.8	[0.1-6.6]		14	161	1.1	[0.6-1.9]		0	1.2	0.0	[0.0-3.1]		17	15.5	1.1	[0.6-1.8]		
2006	5	13	4.9	[1.6-14.8]	*	18	175	1.1	[0.6-1.9]		5	1.2	4.1	[1.3-9.6]	*	17	15.7	1.1	[0.6-1.7]		
2007	4	14	3.9	[1.2-12.9]	*	15	195	0.8	[0.4-1.4]		4	1.2	3.3	[0.9-8.4]	*	15	15.7	1.0	[0.5-1.6]		
Coastal location																					
Yes	3	18	1.7	[0.5-6.0]		26	258	1.1	[0.7-1.3]		3	1.5	2.0	[0.4-5.9]		29	24.7	1.2	[0.8-1.7]		
No	11	62	1.9	[1.0-3.6]	*	73	802	1.0	[0.8-1.3]		11	5.9	1.9	[0.9-3.4]	*	70	71.1	1.0	[0.8-1.2]		
Border location																					
Yes	4	19	1.9	[0.6-5.9]		17	187	0.9	[0.5-1.5]		4	1.3	3.0	[0.8-7.6]	*	19	16.4	1.2	[0.7-1.8]		
No	10	61	1.8	[0.9-3.6]		82	873	1.1	[0.8-1.3]		10	6.0	1.7	[0.8-3.1]	#	80	79.3	1.0	[0.8-1.3]		
Status of the Commune																					
Rural	9	49	2.2	[1.0-4.7]	*	49	445	1.2	[0.8-1.6]		9	3.9	2.3	[1.1-4.4]	*	51	41.8	1.2	[0.9-1.6]	#	
Semi-urban	3	16	2.2	[0.6-7.9]		26	388	0.8	[0.5-1.3]		3	2.5	1.2	[0.2-3.5]		26	34.6	0.8	[0.5-1.1]		
Urban	2	15	1.5	[0.3-6.6]		24	227	1.3	[0.8-2.1]		2	0.9	2.1	[0.2-7.7]		22	19.4	1.1	[0.7-1.7]		
Median income of the Commune																					
< median	11	51	2.3	[1.2-4.4]	*	63	703	1.0	[0.8-1.3]		11	4.6	2.4	[1.2-4.3]	*	63	64.7	1.0	[0.8-1.3]		
≥ median	3	27	1.1	[0.3-3.6]		35	352	1.1	[0.7-1.6]		3	2.8	1.1	[0.2-3.2]		36	31.0	1.2	[0.8-1.6]		
Proportion of blue-collar workers in the Commune																					
< median	2	15	1.6	[0.4-7.3]		18	175	1.2	[0.7-2.1]		2	1.4	1.5	[0.2-5.2]		18	15.8	1.1	[0.7-1.8]		
≥ median	12	65	1.9	[1.0-3.5]	*	81	885	1.0	[0.7-1.2]		12	6.0	2.0	[1.0-3.5]	*	81	79.9	1.0	[0.8-1.3]		
Proportion of baccalaureate holders in the Commune																					
< median	13	70	1.9	[1.0-3.6]	*	79	819	1.0	[0.8-1.3]		13	6.0	2.2	[1.2-3.7]	*	78	71.5	1.0	[0.9-1.4]		
≥ median	1	10	1.4	[0.2-11.6]		20	241	1.0	[0.6-1.6]		1	1.4	0.7	[0.0-4.1]		21	21.3	0.9	[0.5-1.3]		

^aOdds ratios (OR) and 95% confidence intervals (95%CI) estimated by logistic regression adjusted for age at the end of the year (5-year age groups for the 0-14-year-old children, 1-year age groups for the 0-4-year-old children) and *Département* of residence; ^bStandardized incidence ratio (SIR) calculated as the ratio of the observed (O) to the expected (E) number of cases with Byar's approximation of the 95% confidence interval (95%CI) * p_{One-sided} <0.05; # p_{One-sided} <0.10

Table 5: Cross-classification of the 30,000 controls (2002-2007) by the distance to the nearest French NPP and by the Dose Based Geographic Zoning (DBGZ).

Distance to the nearest NPP	Dose Based Geographic Zoning ^a					Total
	Reference	≤ 0.093 μSv	0.094-0.20 μSv	0.21-0.72 μSv	> 0.72 μSv	
0-4.99 km	0	5	5	38	39	87
5-9.99 km	0	33	50	93	43	219
10-14.99 km	0	119	104	62	11	296
15-19.99 km	1	260	158	20	4	443
≥ 20 km	28,955	0	0	0	0	28,955
Total	28,956	417	317	213	97	30,000

^a The "Dose Based Geographic Zoning" is based on the estimated bone marrow radiation dose related to NPP gaseous discharge at the location of the *Commune* town hall and expressed in μSv. By definition, the "Reference" geographic zone of the DBGZ is the same as that which is used for the distance based zoning, that is the *Communes* which town hall is located 20 km or farther away from any NPP.

Accepted Preprint

Table 6: Association between Dose Based Geographic Zoning (DBGZ^a) around the French NPPS and childhood acute leukemia - Geocap case-control study and incidence studies.

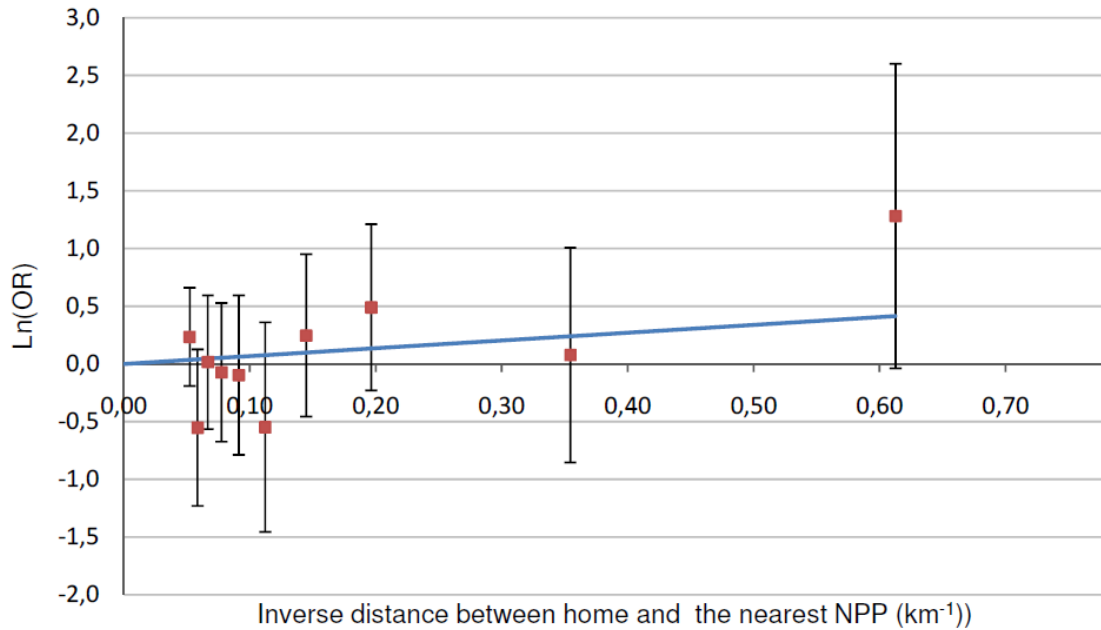
	Case-control study, 2002-2007 ^b (distance: municipality-nearest NPP)				Incidence study, 2002-2007 ^c (distance: municipality-nearest NPP)				Incidence study, 1990-2001 ^c (distance: municipality-nearest NPP)				Incidence study 1990-2007 ^c (distance: municipality-nearest NPP)			
	Cases	Controls	OR	95% CI	O	E	SIR	95% CI	O	E	SIR	95% CI	O	E	SIR	95% CI
Age < 15 years^d																
> 0.72 μSv ^a	8	97	1.0	[0.5-2.1]	8	8.3	1.0	[0.4-1.9]	13	16.4	0.8	[0.4-1.4]	21	24.7	0.9	[0.5-1.3]
0.21-0.71 μSv	19	213	1.0	[0.6-1.6]	20	18.5	1.1	[0.7-1.7]	42	36.7	1.1	[0.8-1.6]	62	55.2	1.1	[0.9-1.4]
0.094-0.20 μSv	29	317	1.0	[0.7-1.5]	31	30.0	1.0	[0.7-1.5]	54	56.8	1.0	[0.7-1.2]	85	86.7	1.0	[0.8-1.2]
≤ 0.093 μSv	40	417	1.0	[0.7-1.4]	40	39.0	1.0	[0.7-1.4]	64	73.1	0.9	[0.7-1.1]	104	112.0	0.9	[0.8-1.1]
≥ 20 km	2657	28956	1.0													
<20 km	96	1044	1.0	[0.8-1.3]	99	95.7	1.0	[0.8-1.3]	173	182.9	1.0	[0.8-1.1]	272	278.6	1.0	[0.9-1.1]
≥ 20 km	2657	28956	1.0													
Age < 5 years^d																
> 0.72 μSv ^a	4	28	1.1	[0.4-3.2]	5	4.0	1.2	[0.4-2.9]	7	8.0	0.9	[0.4-1.8]	12	12.0	1.0	[0.5-1.8]
0.21-0.71 μSv	6	59	0.9	[0.4-2.0]	8	9.2	0.9	[0.4-1.7]	23	17.9	1.3	[0.8-1.9]	31	27.1	1.1	[0.8-1.6]
0.094-0.20 μSv	15	88	1.3	[0.7-2.3]	16	14.9	1.1	[0.6-1.7]	29	27.9	1.0	[0.7-1.5]	45	42.8	1.1	[0.8-1.4]
≤ 0.093 μSv	16	137	0.9	[0.5-1.5]	18	19.1	0.9	[0.6-1.5]	25	35.3	0.7	[0.5-1.1]	43	54.5	0.8	[0.6-1.1]
≥ 20 km	1248	9396	1.0													
< 20 km	41	312	1.0	[0.7-1.4]	47	47.3	1.0	[0.7-1.3]	84	89.1	1.0	[0.8-1.1]	131	136.4	1.0	[0.8-1.1]
≥ 20 km	1248	9405	1.0													

^aThe "Dose Based Geographic Zoning" is based on the estimated bone marrow radiation dose related to NPP gaseous discharge at the location of the *Commune* town hall and expressed in μSv. By definition, the "Reference" geographic zone of the DBGZ is the same as that which is used for the distance based zoning, that is the *Communes* which town hall is located 20 km or farther away from any NPP.

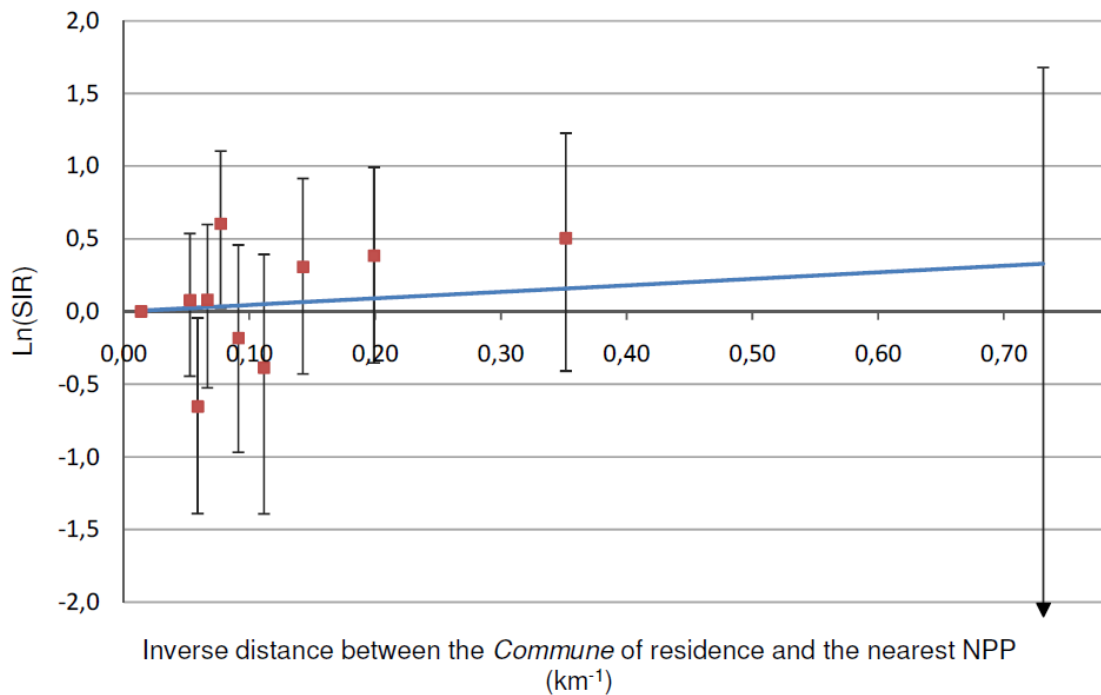
^bOdds ratios (OR) and 95% confidence intervals (95%CI) estimated by logistic regression adjusted for age at the end of the year (5-year age groups for the 0-14-year-old children, 1-year age groups for the 0-4-year-old children) and *Département* of residence; ^cStandardized incidence ratio (SIR) calculated as the ratio of the observed (O) to the expected (E) number of cases with Byar's approximation of the 95% confidence interval (95%CI); ^dAge at the end of the year in the Geocap study; exact age in the incidence studies

Additional figure 1: Association between childhood acute leukemia and inverse distance between the place of residence and nearest nuclear power plant (NPP) – GEOCAP case-control study (1.a) and incidence study (1.b) over 2002-2007. In the 1.b figure, the arrow indicates that the value of Ln(SIR) is $-\infty$ (SIR=0) in the closest ring of distance to NPP

(1.a) GEOCAP case-control study 2002-2007



(1.b) Incidence study 2002-2007



Additional table 1: Characteristics of the 19 French nuclear power plants.

	Commissioning date	Power (Megawatt)	Coastal location	Border location
Belleville	1987	2600		
Bugey	1971	3600		
Cattenom	1986	5200		<i>Luxembourg</i>
Chinon	1963	3600		
Chooz	1996	2800		<i>Belgium</i>
Civaux	1997	2800		
Cruas	1983	3600		
Dampierre	1980	3600		
Fessenheim	1977	1800		<i>Germany</i>
Flamanville	1985	2600	<i>Channel</i>	
Golfech	1990	2600		
Gravelines	1980	5400	<i>North Sea</i>	
Le Blayais	1981	3600		
Nogent	1987	2600		
Paluel	1984	5200	<i>Channel</i>	
Penly	1990	2600	<i>Channel</i>	
Saint-Alban	1985	2600		
Saint-Laurent	1969	1800		
Tricastin	1980	3600		

Additional table 2: Association between acute leukemia and 2 indicators of exposure: distance from the nearest nuclear power plant (NPP) or the Dose Based Geographic Zoning (DBGZ^a) in the Geocap case-control study (2002-2007), by type of leukemia.

	Acute lymphoblastic leukemia				Acute myeloblastic leukemia			
	Cases	Controls	OR ^b	95%CI	Cases	Controls	OR ^b	95%CI
Age < 15 years^c								
Distance								
0-4.99 km	14	80	2.4	[1.3-4.2]	0	80	0.0	-
5-9.99 km	13	213	0.9	[0.5-1.5]	4	213	1.4	[0.5-3.8]
10-14.99 km	23	320	1.0	[0.6-1.5]	3	320	0.6	[0.2-1.9]
15-19.99 km	30	447	0.9	[0.6-1.4]	10	447	1.4	[0.7-2.8]
Total < 20 km	80	1060	1.0	[0.8-1.3]	17	1060	1.0	[0.6-1.8]
≥ 20 km	2173	28940	1.0	[Ref.]	405	28940	1.0	[Ref.]
DBGZ^a								
≥ 0.72 μSV ^a	8	97	1.3	[0.6-2.8]	0	97	0.0	-
0.21-0.71 μSV	16	213	1.0	[0.6-1.7]	3	213	0.9	[0.3-2.8]
0.094-0.20 μSV	24	317	1.1	[0.7-1.6]	5	317	0.9	[0.4-2.3]
≤ 0.093 μSV	33	417	1.1	[0.7-1.5]	6	417	0.9	[0.3-2.2]
Total < 20 km	81	1044	1.1	[0.8-1.4]	14	1044	0.8	[0.5-1.5]
≥ 20 km	2172	28956	1.0	[Ref.]	408	28956	1.0	[Ref.]
Age < 5 years^c								
Distance								
0-4.99 km	6	27	2.1	[0.8-5.4]	0	27	0.0	-
5-9.99 km	6	55	1.1	[0.5-2.7]	1	55	0.7	[0.1-5.5]
10-14.99 km	9	103	0.8	[0.4-1.6]	1	103	0.4	[0.1-2.8]
15-19.99 km	10	136	0.8	[0.4-1.5]	6	136	1.7	[0.7-4.1]
Total < 20 km	31	321	0.9	[0.6-1.4]	8	321	0.9	[0.4-2.1]
≥ 20 km	1024	9396	1.0	[Ref.]	194	9396	1.0	[Ref.]
DBGZ¹								
≥ 0.72 μSV ¹	4	28	1.5	[0.5-4.6]	0	28	0.0	-
0.21-0.71 μSV	6	59	1.2	[0.5-2.8]	0	59	0.0	-
0.094-0.20 μSV	12	88	1.3	[0.7-2.6]	3	88	1.1	[0.3-3.3]
≤ 0.093 μSV	11	137	0.8	[0.4-1.4]	4	137	1.2	[0.4-3.3]
Total < 20 km	33	312	1.0	[0.7-1.4]	7	312	0.8	[0.4-1.9]
≥ 20 km	1022	9405	1.0	[Ref.]	195	9405	1.0	[Ref.]

^a The "Dose Based Geographic Zoning" is based on the estimated bone marrow radiation dose related to NPP gaseous discharge at the location of the *Commune* town hall and expressed in μSv. By definition, the "Reference" geographic zone of the DBGZ is the same as that which is used for the distance based zoning, that is the *Communes* which town hall is located 20 km or farther away from any NPP. ^b Odds ratios (OR) and 95% confidence intervals (95%CI) estimated by logistic regression adjusted for age at the end of the year (5-year age groups for the 0-14-year-old children, 1-year age groups for the 0-4-year-old children) and *Département* of residence. ^c Age at the end of the year

Additional table 3: Acute leukemia and residence less than 5 km from a nuclear power plant, 2002-2007 – stability of the estimates after exclusion of each plant, in turn.

	Case-control study ^a		Incidence study ^b	
	OR	95% CI	SIR	95% CI
without Belleville	1.9	[1.0-3.3]	2.0	[1.1-3.3]
without Bugey	1.9	[1.1-3.4]	1.9	[1.1-3.3]
without Cattenom	2.1	[1.2-3.7]	2.1	[1.2-3.6]
without Chinon	1.8	[1.0-3.4]	1.9	[1.0-3.2]
without Chooz	1.7	[0.9-3.2]	1.6	[0.8-2.8]
without Civaux	1.8	[1.0-3.2]	1.8	[1.0-3.1]
without Cruas	1.7	[0.9-3.1]	1.7	[0.9-3.0]
without Dampierre	1.9	[1.1-3.4]	2.0	[1.1-3.3]
without Fessenheim	1.8	[1.0-3.3]	1.8	[1.0-3.1]
without Flamanville	1.9	[1.1-3.4]	1.9	[1.1-3.3]
without Golfech	2.0	[1.1-3.5]	2.0	[1.1-3.4]
without Gravelines	1.9	[1.0-3.6]	1.9	[1.0-3.3]
without Le Blayais	1.9	[1.0-3.3]	1.9	[1.0-3.2]
without Nogent	1.9	[1.0-3.3]	1.9	[1.0-3.2]
without Paluel	1.7	[1.0-3.2]	1.8	[1.0-3.1]
without Penly	1.9	[1.1-3.4]	2.0	[1.1-3.3]
without Saint-Alban	1.8	[1.0-3.4]	2.0	[1.0-3.4]
without Saint-Laurent	2.0	[1.1-3.5]	2.0	[1.1-3.3]
without Tricastin	1.9	[1.1-3.5]	2.1	[1.1-3.5]

^a Odds Ratios (OR) were estimated by unconditional logistic regression with adjustment for *Département* and age, with living more than 20 km away as a reference. ^b Standardized Incidence Ratios (SIR) were calculated as the ratio of the observed to the expected number of cases with Byar's approximation of the 95% confidence interval (CI)