



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

| | |
|-------------------------------|--|
| Journal: | <i>International Journal of Cancer</i> |
| Manuscript ID: | IJC-11-1995 |
| Wiley - Manuscript type: | Epidemiology |
| Date Submitted by the Author: | 24-Aug-2011 |
| Complete List of Authors: | Sermage-Faure, Claire; INSERM, CESP Environmental epidemiology of cancer, U1018, eq6 Laurier, Dominique; Institut de Radioprotection et de Sûreté Nucléaire, DPRH/SRBE/LEPID Goujon-Bellec, Stéphanie; INSERM, CESP U1018, Environmental epidemiology of cancer, Eq6 Chartier, Michel; Institut de Radioprotection et de Sûreté Nucléaire, DPRH/SER Guyot-Goubin, Aurélie; INSERM, CESP U1018, Environmental epidemiology of cancer, Eq6 Rudant, Jérémie; INSERM, CESP U1018, Environmental epidemiology of cancer, Eq6 Hémon, Denis; INSERM, CESP U1018, Environmental epidemiology of cancer, Eq6 Clavel, Jacqueline; INSERM, CESP U1018, Environmental epidemiology of cancer, Eq6 |
| Key Words: | childhood leukemia, epidemiology, incidence, case-control, nuclear reactors |
| | |

SCHOLARONE™
Manuscripts

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

Sermage-Faure Claire^{1,2}, Laurier Dominique⁴, Goujon-Bellec Stéphanie^{1,2,3}, Chartier Michel⁴, Guyot-Goubin Aurélie^{1,2,3}, Rudant Jérémie^{1,2}, Hémon Denis^{1,2}, Clavel Jacqueline^{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

1
2
3
4
5
6 Keywords: Childhood leukemia; epidemiology; incidence; case-control; nuclear reactors
7
8
9

10 Financial disclosure: The authors declare that there is no potential conflict of interest.
11
12
13

14
15 Abbreviations and definitions:
16

17 AL: childhood acute leukemia

18
19 ALL: childhood acute lymphoblastic leukemia

20
21 AML: childhood acute myeloblastic leukemia

22
23 DGBZ: Dose Based Geographic Zoning

24
25 IGN: National Geographic Institute

26
27 IRSN: National Institute of Radiological Protection and Nuclear Safety

28
29 NPP: Nuclear Power Plant

30
31 NRCH: French National Registry of Childhood Hematopoietic Malignancies

32
33 O (resp. E): Observed (resp. expected) number of cases

34
35 OR: Odds Ratio

36
37 SIR: Standardized Incidence Ratio

38
39
40
41
42
43
44
45 Submission for a research article
46

47
48 The very good representativeness of our sample relative to the source population, the careful
49 and precise geocoding, and the use of dose-based geographic zoning are the major assets of
50 the study.
51
52
53
54
55
56
57
58
59
60

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 DGBZ 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 further refining the DBGZ, 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 sites ^{1, 2} and, more specifically, nuclear power plants ³⁻⁷. Persistent localized excesses of childhood acute leukemia (AL) have been reported around the Sellafield ⁸⁻¹⁰ and Dounreay ^{11, 12} nuclear fuel reprocessing plants in the United Kingdom, and around the Krummel nuclear power plant ^{5, 13, 14} in Germany. Given the low radiation levels measured near the sites, the hypothesis that local population mixing might induce the spread of a leukemogenic agent was raised ¹⁵⁻¹⁷ and appeared consistent with some further observations ¹⁸. In general, no excess risk had been evidenced by the multisite studies ² before the publication of the German KiKK population-based case-control study that showed an association between leukemia in children less than 5 years old and living less than 5 km from a nuclear power plant (NPP) ^{19, 20}. Following this publication, several studies demonstrated no excess risk in that specific population ^{3, 6, 21}. In France, a national geographic study of the period 1990-1998 was carried out ^{6, 22} 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 sites ²³.

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)²⁴.

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.

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

The incidence studies addressed the same period, 2002-2007, as the case-control study, the preceding period, 1990-2001, and 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

1
2
3 periods. The annual national incidence rates of AL estimated by the NRCH were taken as
4
5 reference rates.
6

7
8 The estimates of *Commune* (the smallest French administrative unit) populations by year of
9
10 age were directly provided by the INSEE for the census years: 1990, 1999, 2006 and 2007.
11
12 For the other years, the estimates were interpolated from the census data and the yearly
13
14 estimates provided by the INSEE for the 96 French mainland *Départements*. Person-years and
15
16 expected numbers of AL cases were then computed for each year of the 1990-2007 period by
17
18 *Commune* and five-year age group.
19
20
21

22 23 24 ***Geocoding of addresses, 2002-2007*** 25

26
27 The addresses of the cases and controls were geocoded by the GEOCIBLE company using the
28
29 geographic information system MAPINFO, the NAVTEQ street databases and detailed
30
31 vectorized maps from the National Geographic Institute (IGN). The process resulted in the
32
33 location of 96% of the addresses with an uncertainty of at most 100 meters, and of 80% with
34
35 an uncertainty of 15 meters. Less than 2% of the children were only located by their
36
37 *Commune* of residence, and were thus allocated the coordinates of the town hall of their
38
39 *Commune*. The uncertainties were similar for the cases and controls.
40
41
42
43
44
45

46 47 ***NPP characteristics*** 48

49
50 There are 19 NPPs in France (additional table 1), all but two (*Chooz and Civaux*) having been
51
52 commissioned before 1990. The majority of the NPPs are located near a river, but 4 of them
53
54 are coastal. The NPPs *Cattenom*, *Chooz* and *Fessenheim*, are located less than 20 km from the
55
56 border with Luxembourg, Belgium and Germany, respectively. The nuclear electrical power
57
58 generated ranges from 1,800 to 5,400 MW.
59
60

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 analysis²⁵. 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

1
2
3 All the statistical analyses were performed using the SAS software package (version 9; SAS
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
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 approximation ²⁶.

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.

Stratified analyses were conducted by NPP characteristic, i.e. electrical power, coastal
location and border location. 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. Additional
analyses were also adjusted for the deprivation index computed by Rey et al.²⁷. The data were
also analyzed after exclusion of the cases and controls who lived less than 200 meters from a

1
2
3 high-voltage power line, since an association between the proximity of power lines and the
4 risk of AL has been suggested^{28, 29}. Sensitivity analyses were performed by excluding, in
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

high-voltage power line, since an association between the proximity of power lines and the risk of AL has been suggested^{28, 29}. Sensitivity analyses were performed by excluding, in turn, each year or each NPP, or by using a 6-year moving 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

For the Geocap study, using a one-sided test at the 5% level, the power to detect an OR of two was equal to 40% 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 Day²⁶, the power to detect a SIR of two 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 odds ratios 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 in the continuous 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 3).

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

1
2
3 slightly with the inverse distance from the nearest NPP (additional figure 1), but this trend
4
5 was not statistically significant in the continuous model ($p_{\text{one-sided}} = 0.25$).
6
7
8
9

10 For the 1,060 controls who lived within 20 km of the nearest NPP, the distances from NPP
11
12 based on the coordinates of the *Commune* town hall used in the incidence study, and on the
13
14 individual coordinates used in the case-control study, were closely correlated ($r = +0.98$). This
15
16 finding is connected to the fact that most French NPPs are located in rural areas in which
17
18 most of the dwellings are located close to the town hall.
19
20
21
22
23

24 *Incidence study, 1990-2001*

25
26 In the preceding period, 1990-2001, already covered by a previous analysis²³, 5,356 AL cases
27
28 less than 15 years old were registered in the NRCH. Among the cases, 173 lived less than 20
29
30 km from a NPP (table 2). The SIR did not differ from one for any of the four 5-km rings
31
32 around the NPPs.
33
34
35
36
37
38

39 *Incidence study 1990-2007*

40
41 Over the whole period, 1990-2007, 272 of the 8,187 cases registered by the NRCH lived less
42
43 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],
44
45 respectively (table 2). The SIR for the closest area was slightly but not significantly higher for
46
47 the 0-4 year age group (1.4 [0.8-2.3]; $p_{\text{one-sided}} = 0.15$).
48
49
50
51
52

53 *Subgroup analyses, control of confounders and sensitivity analyses*

54
55 The stratified analyses showed that the association between AL and living within 5 km of a
56
57 NPP did not vary substantially with the power of the NPP, with location on a coast or border,
58
59 or with the urban/rural status of the *Commune* (table 4). The increased risk with living less
60

1
2
3 than 5 km from a NPP appeared more marked, although not significantly so, in *Communes*
4
5 with the lowest median income or lowest proportion of baccalaureate holders than in other
6
7
8 *Communes*.
9

10 Adjustments for the contextual variables and for the deprivation index did not change the
11
12 estimates. Excluding the cases who lived within 200 meters of a high-voltage power line did
13
14 not substantially modify the estimates. Using the distance between the municipality and NPP
15
16 rather than individual distances led to very similar OR and SIR.
17
18

19
20
21
22 The small numbers hampered the detailed analyses by NPP or year. No specific association
23
24 with living less than 5 km from a given NPP was evidenced. When each NPP was excluded,
25
26 in turn, from the case-control and incidence analyses, the OR/SIR estimated on the 18
27
28 remaining NPPs was very similar to that for the 19 NPPs (additional table 2). There was no
29
30 heterogeneity of the SIRs estimated by NPP ($p = 0.13$) and the test of the hypothesis that they
31
32 were all equal to one was on the borderline of statistical significance ($p = 0.07$).
33
34

35
36 Over the period, 2002-2007, AL cases living less than 5 km from a NPP were mostly
37
38 diagnosed in 2003, 2006 and 2007 (table 4). However, the results remained similar when each
39
40 year of observation was excluded, in turn, from the case-control and incidence analyses. For
41
42 the whole period, 1990-2007, no significant heterogeneity of the annual SIRs was evidenced
43
44 ($p = 0.12$), but the test of the hypothesis that the SIRs were all equal to one was on the
45
46 borderline of significance ($p = 0.06$). When the incidence analyses were restricted to
47
48 successive 6-year periods over the whole 1990-2007 period, 2002-2007 was the only period
49
50 for which an association with living less than 5 km from a NPP was observed. The use of
51
52 simulations resulted in similar values of the statistics and the same conclusions.
53
54
55
56
57
58
59

60 ***Childhood AL and DBGZ***

1
2
3 The estimated bone marrow doses related to radioactive gaseous discharge did not result in
4 the same categorization of the cases and controls (table 5): 40% of the controls in the highest
5 exposure category ($> 0.72 \mu\text{Sv}$) were in the 0-4.99 km ring, 44% in the 5-9.99 km ring, 11%
6 in the 10-14.99 km ring and 4% in the 15-19.99 km ring.
7
8
9
10
11
12

13
14
15 No association between AL and DBGZ was observed in the case-control study or in the 2002-
16 2007 incidence study (table 6). The SIRs and ORs were close to one for all the DBGZ
17 categories. The results were the same when the DBGZ categories were based on the quartiles
18 of the control exposure distribution (not shown). Exclusion of the NPPs close to other nuclear
19 sites did not change the results. There was no association between AL and DBGZ for the
20 whole period, 1990-2007 (table 6).
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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 with a high degree of exhaustiveness since 1990³⁰. 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 approaches, case-control and incidence, may have resulted in different potential biases, but the fact that both approaches resulted in almost identical findings is a strong argument in favor 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

1
2
3 or other socioeconomic or demographic variables, which were taken into account. Also, the
4
5 Geocap study allowed adjustment on the proximity of high-voltage power lines. Population
6
7 mixing could not be evaluated in this study.
8
9

10 Like most studies of childhood leukemia in the neighborhood of NPPs, the Geocap study did
11
12 not have access to complete residential histories, which is an important limitation for the
13
14 evaluation of the true exposure to radiation or any factor related to the proximity of NPPs.
15
16 Restricting the analyses to children aged less than 5 years, who are less likely to have moved
17
18 house since birth than older children, resulted in similar ORs and SIRs. Three NPPs are
19
20 located close to a French border, but only the French part of the 20-km radius was considered.
21
22 However, excluding the three NPPs did not markedly change the results. None of the NPPs in
23
24 neighboring countries was less than 20 km from the French border.
25
26
27
28
29
30
31

32 The method used to estimate the dose of radiation delivered to bone marrow by the NPPs was
33
34 based on the average annual gaseous discharge levels, discharge composition and local
35
36 meteorological parameters. Due to the lack of data on real discharge rates, the discharge rates
37
38 for carbon 14 were based on the regulatory limits. The contribution of carbon 14 to the
39
40 radiation dose may therefore have been overestimated. However, the method was the same for
41
42 all the NPPs. In consequence, the *Communes* are likely to have been correctly ranked within a
43
44 given NPP area in terms of exposure despite the potential errors in dose estimates. Contrary to
45
46 a classic assumption³⁰, table 5 clearly illustrates that the distribution of the population in
47
48 terms of the dispersion of radionuclides released into the atmosphere cannot be represented by
49
50 a simple function of the distance from the NPP. The use of the innovative DBGZ appears to
51
52 be one step toward overcoming the limitations of studies using conventional circular zoning
53
54³¹. The model did not take into account liquid discharges, although their contribution to the
55
56 total radiation exposure related to NPP activity may have been of the same order of
57
58
59
60

1
2
3 magnitude as that of the gaseous discharges. The radiation doses due to liquid discharges are
4
5 mainly determined by individual behaviors (food consumption and water use) and are
6
7 therefore not expected to comply with geographic zoning around NPPs. Furthermore, in many
8
9 situations the doses are not expected to decrease smoothly with distance from the NPP. In
10
11 addition, although the NPPs located on a coast or river may be expected to differ with regard
12
13 to doses from liquid discharges, in the stratified analyses the associations with AL were
14
15 similar. Overall, the estimated doses due to NPPs were very low compared to the doses due to
16
17 natural radiation sources. Such doses are not expected to result in an observable excess risk on
18
19 the basis of the available evidence ³².
20
21
22
23
24
25
26

27 In the authors' previous multisite incidence studies^{22, 23} no association between proximity to
28
29 NPPs and AL was observed. This was in line with most multisite studies^{1-3, 6, 21}, and is also in
30
31 line with the results of the authors' incidence analysis over the whole period, 1990-2007. In
32
33 Germany, the KiKK case-control study of children aged less than 5 years evidenced an
34
35 association between AL and NPP proximity¹⁹. However, there are several important
36
37 differences between those results and the results of the present study. The German incidence
38
39 study showed that incidence rates were higher specifically in the 0-4 year age group³³, which
40
41 was not the case in this study. Also, in the German study, the risk estimates obtained in the
42
43 incidence analysis³⁴ appeared to be lower than those obtained with the case-control approach
44
45 ¹⁹, while in this study, the estimates obtained with the two approaches were very similar. In
46
47 the German study, the estimated risk in the 5 km ring was highly sensitive to whether or not
48
49 the Krummel NPP was included³, while no noteworthy difference between the NPPs was
50
51 observed in this study. A reassessment of the KiKK results showed the marked impact of the
52
53 urban/rural status of the residence area on the estimated risk³⁵, while no noteworthy
54
55 difference was observed in the present study. In the KiKK study, an increasing trend with the
56
57
58
59
60

1
2
3 inverse distance from the sites, considered as a continuous variable, was reported; the trend
4
5 was not detected when the distance was categorical¹⁹. In the Geocap study, a slight but non-
6
7 significant increasing trend of the OR and SIR with inverse distance was observed.
8
9

10
11
12 Overall, the results suggest a possible excess risk of AL in the close vicinity of French NPPs
13
14 in 2002-2007. The increased incidence observed at less than 5 km from the NPPs in the
15
16 Geocap study only partially supports the recent German findings since the increase was
17
18 limited to recent years and was not specific to the youngest children. The absence of any
19
20 association with DBGZ may indicate that the association observed with distance <5 km over
21
22 2002-2007 is not explained by NPP gaseous discharges. Overall, the results suggest a
23
24 potential excess risk over 2002-2007 that may be due to unknown factors related to the
25
26 proximity of NPPs. Among the potential factors are population mixing and exposures to
27
28 physical agents, including natural or man-made exposures to radiation not modeled by the
29
30 DBGZ. Overall, the findings call for further refining the DBGZ, investigation for potential
31
32 risk factors related to the vicinity of NPP, and collaborative analysis of all the evidence
33
34 available from multisite studies conducted in various countries.
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6 **Acknowledgments:**
7

8 This work was supported by the *Institut de Veille Sanitaire (InVS)*, *Agence Nationale de*
9 *Sécurité Sanitaire de l'Alimentation, de l'Environnement et du Travail (ANSES)*, *Association*
10 *pour la Recherche sur le Cancer (ARC)*, *Fondation Pfizer*, *Institut National du Cancer*
11 *(INCa)* and *Agence Nationale de la Recherche (ANR)*.
12
13
14
15
16

17 The authors are particularly grateful to Olivier LAMY and Mathieu CARRÈRE
18 (GEOCIBLE), who carefully ensured all the geocoding, and IGN, which made precise maps
19 available for the whole country. The authors are also grateful to Magda TOMASINI and
20 Laurent AUZET (INSEE), who conducted the control sampling, Aline MORIN (IRSN), who
21 conducted the dose-based geographic zoning, all the NRCH research assistants who collected
22 the cases' addresses and the pediatric oncology teams for their help in data collection.
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

References

1. Bithell JF, Keegan TJ, Kroll ME, Murphy MF, Vincent TJ. Childhood leukaemia near British nuclear installations: methodological issues and recent results. *Radiat Prot Dosimetry* 2008;132:191-7.
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;132:182-90.
3. Committee On Medical Aspects of Radiation in the Environment (COMARE), Fourteenth Report. Further consideration of the incidence of childhood leukaemia around nuclear plants in Great Britain. Health Protection Agency, 2011.
4. Heinavaara S, Toikkanen S, Pasanen K, Verkasalo PK, Kurttio P, Auvinen A. Cancer incidence in the vicinity of Finnish nuclear power plants: an emphasis on childhood leukemia. *Cancer Causes Control* 2010;21:587-95.
5. Kaatsch P, Kaletsch U, Meinert R, Michaelis J. An extended study on childhood malignancies in the vicinity of German nuclear power plants. *Cancer Causes Control* 1998;9:529-33.
6. Laurier D, Hemon D, Clavel J. Childhood leukaemia incidence below the age of 5 years near French nuclear power plants. *J Radiol Prot* 2008;28:401-3.
7. 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.
8. 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;309:501-5.
9. 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; discussion 43-55.
10. 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;53:823-31.
11. Heasman MA, Kemp IW, Urquhart JD, Black R. Childhood leukaemia in northern Scotland. *Lancet* 1986;1:266.
12. 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;48:232-6.
13. Hoffmann W, Dieckmann H, Schmitz-Feuerhake I. A cluster of childhood leukemia near a nuclear reactor in northern Germany. *Arch Environ Health* 1997;52:275-80.
14. Hoffmann W, Terschueren C, Richardson DB. Childhood leukemia in the vicinity of the Geesthacht nuclear establishments near Hamburg, Germany. *Environ Health Perspect* 2007;115:947-52.
15. Kinlen L. Childhood leukaemia, nuclear sites, and population mixing. *Br J Cancer* 2011;104:12-8.
16. Kinlen LJ. Epidemiological evidence for an infective basis in childhood leukaemia. *Br J Cancer* 1995;71:1-5.
17. 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;310:763-8.
18. Dickinson HO, Parker L. Quantifying the effect of population mixing on childhood leukaemia risk: the Seascale cluster. *Br J Cancer* 1999;81:144-51.

19. Kaatsch P, Spix C, Schulze-Rath R, Schmiedel S, Blettner M. Leukaemia in young children living in the vicinity of German nuclear power plants. *Int J Cancer* 2008;122:721-6.
20. 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;44:275-84.
21. Spycher BD, Feller M, Zwahlen M, Roosli 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.
22. White-Koning ML, Hemon D, Laurier D, Tirmarche M, Jouglà E, Goubin A, Clavel J. Incidence of childhood leukaemia in the vicinity of nuclear sites in France, 1990-1998. *Br J Cancer* 2004;91:916-22.
23. Evrard AS, Hemon D, Morin A, Laurier D, Tirmarche M, Backe JC, Chartier M, Clavel J. Childhood leukaemia incidence around French nuclear installations using geographic zoning based on gaseous discharge dose estimates. *Br J Cancer* 2006;94:1342-7.
24. Lacour B, Guyot-Goubin A, Guissou S, Bellec S, Desandes E, Clavel J. Incidence of childhood cancer in France: National Children Cancer Registries, 2000-2004. *Eur J Cancer Prev* 2010;19:173-81.
25. Morin A, Backe JC, Programme Environnement et Santé 1999. Une estimation de l'exposition du public due aux rejets radioactifs des centrales nucléaires. Institut de Radioprotection et de Sureté Nucléaire, 2002.
26. Breslow NE, Day NE. Statistical methods in cancer research. Volume II - The design and analysis of cohort studies., vol. 82. Lyon: IARC Sci Publ, 1987.
27. Rey G, Jouglà E, Fouillet A, Hemon D. Ecological association between a deprivation index and mortality in France over the period 1997 - 2001: variations with spatial scale, degree of urbanicity, age, gender and cause of death. *BMC Public Health* 2009;9:33.
28. 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;83:692-8.
29. 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;11:624-34.
30. 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.
31. Wing S, Richardson DB, Hoffmann W. Cancer risks near nuclear facilities: the importance of research design and explicit study hypotheses. *Environ Health Perspect* 2011;119:417-21.
32. United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), Exposure from natural radiation sources., 2000.
33. Grosche B. The 'Kinderkrebs in der Umgebung von Kernkraftwerken' study: results put into perspective. *Radiat Prot Dosimetry* 2008;132:198-201.
34. Kaatsch P, Spix C, Jung I, Blettner M. Childhood leukemia in the vicinity of nuclear power plants in Germany. *Dtsch Arztebl Int* 2008;105:725-32.
35. Strahlenschutzkommission (SSK). Bewertung der epidemiologischen Studie zu Kinderkrebs in der Umgebung von Kernkraftwerken (KiKK-Studie). Bundesministerium für Umwelt, Naturschutz und Reaktorsicherheit, Heft 58 2009.

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

| | Source population % | Geocap sample % |
|--|------------------------|--------------------|
| Individual characteristics | | |
| Age at the end of the year | | |
| 0 | 6.2% | 6.1% |
| 1 | 6.6% | 6.3% |
| 2 | 6.7% | 6.9% |
| 3 | 6.7% | 6.7% |
| 4 | 6.7% | 6.4% |
| 5 | 6.7% | 6.9% |
| 6 | 6.7% | 6.7% |
| 7 | 6.7% | 6.8% |
| 8 | 6.6% | 6.5% |
| 9 | 6.6% | 6.9% |
| 10 | 6.6% | 6.6% |
| 11 | 6.7% | 6.7% |
| 12 | 6.7% | 6.8% |
| 13 | 6.8% | 6.9% |
| 14 | 6.9% | 7.0% |
| Number of children in the household | | |
| 1 | 29.7% | 29.4% |
| 2 | 42.9% | 43.1% |
| 3 | 19.8% | 20.0% |
| ≥ 4 | 7.7% | 7.5% |
| Contextual variables | | |
| Size of the urban unit^a of the <i>Commune</i> of residence | | |
| Rural unit | 26.1% | 25.8% |
| < 5,000 inhabitants | 6.3% | 6.3% |
| 5,000-9,999 inhabitants | 5.5% | 5.5% |
| 10,000-19,999 inhabitants | 5.0% | 5.0% |
| 20,000-49,999 inhabitants | 6.0% | 6.0% |
| 50,000-99,999 inhabitants | 6.6% | 6.5% |
| 100,000-199,999 inhabitants | 5.0% | 5.1% |
| 200,000-1,999,999 inhabitants | 21.7% | 21.9% |
| Paris urban unit | 17.9% | 17.9% |
| Median annual income of the <i>Commune</i> (€) | | |
| <12,850 | 25.0% | 24.5% |
| 12,850 – 14,329 | 25.0% | 25.5% |
| 14,330 - 16,448 | 25.0% | 24.5% |
| >16,448 | 25.0% | 25.5% |
| Proportion of blue-collar workers in the <i>Commune</i> | | |
| < 20% | 25.0% | 26.3% |
| 20-26.5% | 25.0% | 24.6% |
| 26.6-34.2% | 25.0% | 24.0% |
| >34.2% | 25.0% | 25.1% |
| Proportion of baccalaureate holders in the <i>Commune</i> | | |
| < 19.2% | 25.0% | 24.6% |
| 19.2-24.4% | 25.0% | 24.9% |
| 24.5-30.7% | 25.0% | 25.3% |
| >30.7% | 25.0% | 25.1% |
| Proportion of homeowners in the <i>Commune</i> | | |
| <42.5% | 25.0% | 25.1% |
| 42.5-59.4% | 25.0% | 24.8% |
| 59.5-75.5% | 25.0% | 25.1% |
| >75.5% | 25.0% | 25.1% |

^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 | | | | | | | | | | | | | | | | | |

^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 5-14-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); ^c Age at the end of the year in the Geocap study; exact age in the incidence studies

* Pone-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 DGBZ 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.

Table 6: Association between Dose Based Geographic Zoning (DGBZ^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] |
| $\leq 0.093 \mu\text{Sv}$ | 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] |
| $\geq 20 \text{ km}$ | 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] |
| $\geq 20 \text{ km}$ | 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] |
| $\leq 0.093 \mu\text{Sv}$ | 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] |
| $\geq 20 \text{ km}$ | 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] |
| $\geq 20 \text{ km}$ | 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 DGBZ 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