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Abstract

Background: The role of natural background radiation (NBR) in childhood acute leukemia (AL) remains unclear. Several large record based studies have recently reported heterogeneous results. Differences in exposure assessment timing may explain this heterogeneity.

Objectives: In a previous ecological study we did not observe any association between childhood AL incidence in France and NBR exposure at the time of diagnosis. With the same methodology, the present study focused on NBR exposure at the time of birth. Based on data from the French national registry of childhood cancer, we analyzed all AL together, and lymphoblastic and myeloid AL, separately.

Methods: We included 6,059 childhood AL cases born and diagnosed in mainland France between 1990 and 2009. NBR levels in municipalities of residence at birth were estimated by cokriging models, using NBR measurements and precise geological data. The incidence rate ratio (IRR) per unit variation of exposure was estimated with Poisson regression models, with adjustment for socio-demographic indicators and ultraviolet radiation levels. NBR exposures were considered at the time of birth, and cumulatively from birth to diagnosis. We also estimated a total NBR dose to red-bone marrow (RBM).

Results: There was no evidence for an association between NBR exposure at birth and childhood AL incidence, neither overall (gamma radiation: IRR = 0.99 (0.94,1.05) per 50 nSv/h; radon: IRR = 0.97 (0.91,1.03) per 100 Bq/m^3) nor for the main AL types. The conclusions were similar with the cumulative exposures, and the total RBM dose.

Conclusions: The study was based on high quality incidence data, large numbers of AL cases, and validated models of NBR exposure assessment. In all, the results further support the hypothesis that NBR are not associated to childhood AL in France.

Keywords: childhood cancer; leukemia; natural background radiation; radon; gamma radiation

1. Introduction

Acute leukemia (AL) is the most common cancer in 0-14-year-old children, with an average of 465 cases per year in France (Goujon et al. 2018). In children, there are two main types of AL: acute lymphoblastic leukemia (ALL, 82% of AL), which stems from hematopoietic precursors of the lymphoid lineage (B-lineage or T-lineage), and acute myeloid leukemia (AML, 16% of AL), which originates in myeloid precursor cells. In 80 % of ALL, B lymphoblasts invade RBM at the early stage of their development, and the ALL is qualified as precursor B-Cell ALL (BCP-ALL). Most BCP-ALL are diagnosed between 2 and 6 years old, and constitute the incidence peak of childhood AL.

In the last decade, several studies have addressed the risk factors for childhood leukemia (Belson et al. 2007; Eden 2010) but the etiology of childhood AL remains poorly elucidated. Radon and gamma radiation were classified as carcinogenic to humans by the International Agency for Research on Cancer in 1988 and 2000, respectively (IARC, 2000, 1988), with a reevaluation in 2012 (IARC, 2012). A causal relationship between moderate-to-high dose IR exposure and AL has been established, with a size effect depending on gender, exposure duration, age at time of exposure and time since exposure (Belson et al. 2007). Numerous studies have reported higher IR radiosusceptibility in children than in adults for some cancers, particularly leukemia and thyroid, skin, breast and brain cancer (UNSCEAR 2013).

Medical procedures may give rise to fractionated but moderate-to-high lifetime IR exposures in situations of repeated examinations. A higher risk of childhood AL after therapeutic radiation has been confirmed (Wakeford 2013), and, to a lesser extent, a higher risk after diagnostic radiation has been discussed (Abalo et al., 2021; Nikkilä et al., 2018). A pooled analysis of nine studies showed that the risks of ALL and AML were higher after (medical or non-medical) exposure to low IR doses (less than 100 mSv), with a statistically significant trend over the radiation dose range. The association was also observed when the analyses were restricted to children exposed to doses lower than 50 mSv (Little et al. 2018). A similar conclusion was reported in a recent review, which evaluated cancer risks after low-dose exposures, taking into account potential study biases (Hauptmann et al., 2020).

The carcinogenicity of natural background radiation (NBR) has long been discussed with regard to childhood AL and other cancer types, but is difficult to assess. NBR consists of gamma radiation, with a cosmic and a terrestrial component, plus radon gas and its decay products. The disintegration of U-238, K-40 and Th-232 contained in rocks results in terrestrial gamma radiation, radon gas and radioactive progeny. The level of radon gas in the atmosphere depends on soil geology and the ability of the gas to reach the surface. The cosmic gamma radiation component is produced when cosmic rays enter the Earth's atmosphere.

Gamma radiation penetrates the whole body (external exposure), including RBM, while radon gas enters the respiratory tract and may then diffuse into RBM (internal exposure) (Harley and Robbins, 2009; Kendall and Smith, 2005). People may also be internally exposed by food and water consumption.

Risk assessment calculations have suggested that an association between RBM doses due to NBR and childhood leukemia incidence is possible, and that up to 20% of childhood AL cases might be due to NBR exposure (Laurent et al. 2013; Little et al. 2009).

The first generation of epidemiological studies on NBR and childhood cancer suffered from marked limitations: the ecological studies considered NBR exposures averaged over large geographic areas (Henshaw et al. 1990) or radon concentrations in drinking water as a proxy for radiation exposure (Collman et al. 1991), while the case-control studies based on NBR measurements were limited by low participation rates. In addition, the small differences between case and control exposure levels, and the small expected effect of the exposure on childhood AL made the studies statistically underpowered (Kaletsch et al., 1999; Kendall et al., 2021; UKCCS, 2002a, 2002b).

More recently, record-linkage studies conducted on a national scale further investigated the association between NBR and childhood cancers in 7 European countries (Denmark, Switzerland, Great Britain, Norway, Finland, Germany and France). Five studies addressed the association with radon exposure (Del Risco Kollerud et al. 2014; Demoury et al. 2017; Hauri et al. 2013; Kendall et al. 2013; Raaschou-Nielsen et al. 2008). Only the Danish study reported a positive association between ALL and cumulative radon exposure from birth to diagnosis (Raaschou-Nielsen et al. 2008).

The results for gamma radiation were more heterogeneous. In Great Britain, a study that included 9,058 AL cases found positive associations between cumulative gamma radiation exposure and AL, and the main types, ALL and AML (Kendall et al. 2013). In that study, Kendall et al. also estimated a total RBM radiation dose in order to consider jointly the effect of gamma radiation and indoor radon concentration exposures taking into account the biological effects of each type of radiation. They concluded that there was a positive association between the total RBM dose and the incidence of AL, particularly for ALL. In a Swiss study, a positive association between cumulative gamma radiation exposure was observed for AL and suggested for ALL (Spycher et al. 2015). In Finland, gamma radiation was found to be positively associated with AL incidence, specifically for children between 2 and 7 years old, when the gamma dose-rate or cumulative RBM gamma radiation dose was considered (Nikkila et al. 2016). In contrast, no association between gamma radiation exposure and AL was observed in two large studies, one conducted in Germany using gamma dose-rate (13,374 cases (Spix et al. 2017)) and

66 the other in France using gamma dose-rate and cumulative gamma radiation exposure (9,056 cases
67 (Demoury et al. 2017)).

68 By definition, childhood cancers occur relatively soon after birth and, in ALL the initiation process has
69 been shown to begin at early stages of development, during the perinatal period (Greaves 2018). NBR
70 might thus be involved in the initiation or development of the AL process if children were exposed
71 before conception, *in-utero*, or soon after birth (Belson et al. 2007).

72 The record-based studies did not consider NBR exposures during the same periods relative to AL
73 development, which may partly explain the inconsistent results. NBR exposure was estimated by place
74 of residence at birth (Kendall et al. 2013), at diagnosis (Demoury et al. 2017), at intermediate dates or
75 during intermediate periods (Del Risco Kollerud et al. 2014; Hauri et al. 2013; Raaschou-Nielsen et al.
76 2008). Five studies investigated NBR exposure cumulatively from birth to diagnosis (Demoury et al.
77 2017; Kendall et al. 2013; Nikkila et al. 2016; Raaschou-Nielsen et al. 2008; Spycher et al. 2015).

78 In our previous ecological study, we included 9,056 AL cases registered in the French national registry
79 of childhood cancer (RNCE) during the period 1990-2009 (Demoury et al. 2017). We did not show any
80 association between AL incidence and estimated NBR exposure in the municipality of residence at the
81 time of diagnosis. AL cases diagnosed in 2002-2007 were also included in a case-control study with
82 geocoded data and information on several potential individual confounders. The same conclusions
83 were reported (Demoury et al. 2017).

84 Using a similar methodology, the study reported herein aimed to investigate further the ecological
85 association between childhood AL and NBR in France by considering NBR exposure at the time of birth.
86 We considered birth cohorts from 1990 to 2009. The cases diagnosed during that period were
87 identified by the RNCE. Despite the low incidence rate of leukemia in children, the large time period
88 enabled us to include numerous cases and investigate the specific role of NBR in childhood ALL, AML,
89 and BCP-ALL, separately.

90 **2. Methods**

91 Municipalities are the smallest administrative units in France. In this study, some municipalities were
92 grouped to take into account the changes in their perimeters during the study period. In addition, 52
93 municipalities had no births between 1990 and 2009. The analyses were therefore based on 35,800
94 units (referred to as municipalities hereafter).

95 *2.1 Population and incidence data*

All children born in mainland France between 1990 and 2009 were included in the study. We considered they were at risk of AL until their fifteenth birthday or December 31, 2009. The annual numbers of births in French municipalities were provided by the French National Institute for Statistics and Economic Studies (INSEE). Between 1990 and 2009, mortality rates in infants (less than 1-year-old children) decreased from 6/1000 live births in 1990 to 3.2/1000 live births in 2009 (INED 2020). For older children (1-14 years old), the mortality rate was less than 1/1000 over the whole study period. We calculated the at-risk population by age (a=0 to 14) for each municipality i based on the annual numbers of birth $N_{y,i}$ (y=1990 to 2009) and assuming that mortality and emigration rates had little impact on those estimates ($PY_{y,i,a}=N_{y,i}$ if a<2009-y, $PY_{y,i,a}=N_{y,i}/2$ if a=2009-y, and 0 otherwise). Neoplasms are coded in the RNCE using the International Classification of Diseases for Oncology, third edition (ICD-O-3), and then aggregated as per the International Classification of Childhood Cancers, third edition (ICCC-3). We included all the AL cases from the first ICCC-3 group (i.e. 1.a, 1.b, and 1.e) aged less than 15 years at diagnosis.

The municipality of birth, i.e. municipality where the maternity hospital is located, is systematically recorded for each case in the RNCE. The precise address of residence at birth for all cancer cases diagnosed before 2010 was collected from birth certificates (available in the municipality of birth) after obtaining the agreement of the regional administrative authorities (GEOCAP Past project).

Age-specific national incidence rates were derived from the RNCE and calculated for the whole study period, insofar as there was no heterogeneity in childhood AL incidence rates between years of birth. The numbers of childhood AL cases expected in each municipality of residence at birth were obtained by multiplying the age-specific national incidence rates by the at-risk population.

2.2 NBR exposure assessment

NBR exposure data were provided by the French Institute for Radiological Protection and Nuclear Safety (IRSN). Assessment methods have been reported elsewhere (IRSN 2012; Warnery et al. 2015). Briefly, we used 10,843 measurements of indoor radon concentration resulting from national surveys conducted in French households (1982-2003) and 97,595 indoor measurements of gamma dose rates conducted in 17,404 veterinary clinics and dental surgeries throughout France (2011-2012). NBR exposures were estimated by cokriging models derived from those measurements and French maps of geogenic radon potential and uranium potential (Ielsch et al., 2010; Warnery et al., 2015).

Radon concentration and gamma radiation were estimated on a 5x5 km^2 grid and a 1x1 km^2 grid, respectively. The gamma radiation and radon exposures were estimated for each French municipality as the average of exposures in the squares whose centers lay within the perimeter of the municipality (Demoury et al. 2017).

2.3 Confounder data

We adjusted for several suspected AL risk factors that had been identified in previous studies. We considered a French Deprivation index (FDep), estimated for the year 1999 on the municipality scale. FDep was developed as the first axis of a principal component analysis of four census variables: median household income per consumption unit; percentage of high school graduates; percentage of blue-collar workers, and unemployment rate (Rey et al. 2009). In a previous study, childhood ALL was negatively associated with deprivation, both with the FDep index and with a French version of the European Deprivation Indicator (EDI), with a 20% decrease in ALL risk in the most deprived quintile (Odds Ratio $(OR)_{EDI \geq Q5 \text{ vs. } <Q5}$ = 0.80 95%CI (0.73, 0.88)). The study was conducted on the IRIS (Merged Islet for Statistical Information) scale (about 50,000 IRIS in mainland France), but similar results were observed on the municipality scale (Marquant et al. 2016). In the following analyses, we distinguished the municipalities of the most deprived quintile of FDep from the others.

We also considered urbanization as a potential confounding factor. In France, each municipality is included in an Urban Unit (UU), defined by the INSEE as a group of adjacent municipalities with a continuous built-up area. UU are classified by population. The rural municipalities (population less than 2,000) constitute the first UU category. The largest UU is the Paris area UU (population about 11 million). Considering five UU categories (rural municipalities, UU with population: 2,000-9,999, UU with population: 10,000-99,999, UU with population: 100,000-2,000,000, Paris UU), Marquant et al. concluded that living in the Paris UU at the time of diagnosis was associated with a lower risk of childhood ALL than living in rural municipalities, irrespective of the FDep level (OR = 0.78 95%CI (0.70;0.87)), while no difference in childhood ALL risk between rural municipalities and other UU categories was observed (Marquant et al. 2016). Therefore, in the present study, we considered a binary indicator separating the Paris UU from the others.

We also took a solar ultraviolet (UV) radiation index into account. In recent French studies, a higher incidence rate of ALL, in particular BCP-ALL, was reported in the French municipalities exposed to the highest UV radiation levels (Coste et al. 2015; Coste et al. 2017). In light of those results, we split the municipalities into two groups with 105.5 J/cm^2 (70th percentile) as the cutoff.

As shown in table S1, NBR levels are lower in the municipalities of the Paris urban unit than in other municipalities and they are slightly higher in the municipalities exposed to the highest UV radiation levels. NBR levels are quite similar in both deprivation categories.

2.4 Statistical analysis

The data were analyzed using SAS V9.4 software (SAS Institute Inc. Cary, North Carolina, USA).

In an initial approach, the municipalities were divided into ten groups of increasing radon concentration and gamma radiation level with a similar population size for each. Standardized incidence ratios (SIR) between observed (O_i) and expected (E_i) numbers of cases were estimated for each exposure decile (i) and we tested for overall heterogeneity of categories using a chi-squared test. We applied Poisson regression models on the municipality scale to investigate the log-linear relationship between SIRs and NBR levels when appropriate.

We tested for departure from the log-linearity hypothesis using a log-likelihood ratio test to compare the following qualitative [1] and semi-quantitative [2] models:

$$\ln(E(O_i)) = \ln(E_i) + \sum_{k=1}^{10} \beta_k \, Z_k\,(i) \quad [1]$$

in which $\ln(E_i)$ is the offset, $Z_k(i)$ the dummy variable equal to 1 if i = k, 0 otherwise (i = 1 to 10), and β_k the parameter associated with the kth exposure decile, and

$$\ln(E(O_i)) = \ln(E_i) + \alpha + \beta X_{d(i)} \quad [2]$$

in which $X_{d(i)}$ is the population-weighted median of radiation exposure in the decile d(i) to which the municipality i belongs, α the intercept and β the slope parameter.

When the log-linearity was not rejected, we implemented a model with a continuous exposure variable:

$$\ln(E(O_i)) = \ln(E_i) + \alpha + \beta X_i \quad [3]$$

in which X_i is the radiation exposure level estimated in municipality i.

The model fit was evaluated with the chi-squared test on Pearson's residuals. In some situations, model [1] did not fit the data well and the log-linearity hypothesis was rejected (mainly for AL and the ALL group). Accounting for potential confounders (deprivation, urbanization and UV radiation levels) improved the fit of the models, which were therefore included in all the Poisson regression models.

Gamma radiation and indoor radon concentration exposures were considered separately and jointly.

The cumulative NBR exposures of children were estimated for each year of age on the basis of exposure levels in the municipality of residence at birth, assuming that they remained constant over time.

We also estimated the total NBR dose delivered to RBM, using conversion factors to weight radon concentration and gamma radiation exposure levels by physical characteristics, and biological effects (Kendall and Smith 2005; Petoussi et al. 1991). Those factors were derived from hypotheses on the

penetrance of gamma radiation and diffusion of radon gas and its decay products into blood and organs.

ALL (and particularly BCP-ALL, ICD-O-3 code 9836/3) and AML were analyzed separately.

Several sensitivity analyses were carried out: as the youngest children were likely to be more sensitive to radiation exposure, we considered the 0-6-year-old children separately from the oldest children. We conducted analyses with cumulative NBR exposure estimated from conception to diagnosis by adding nine months to the period of exposure to account for the pregnancy period. We adjusted for urbanization, deprivation and UV radiation levels each in turn rather than all together.

3. Results

3.1 Population and AL cases

Annually from 1990 to 2009, approximately 800,000 children were born to mothers living in mainland France. Of those children, 6,081 AL cases were diagnosed before the age of fifteen and before December 31, 2009. The municipality of residence at birth was unknown for 32 cases (0.5%), so that the analyses included 6,059 AL (4,984 ALL, 4,158 BCP-ALL, and 957 AML).

3.2 NBR exposure in the municipalities

Natural radiation exposure levels were estimated on the municipality scale. The population-weighted mean of gamma radiation exposure in the municipalities was estimated to be 91 nSv/h, with an interquartile range (IQR) of 34 nSv/h (71-105 nSv/h, table 1). The mean radon concentration was 65 Bq/m^3 with an IQR of 40 Bq/m^3 (39-79 Bq/m^3).

3.3 NBR exposure at birth and childhood AL

With SIRs varying from 0.91 to 1.09, heterogeneity between the gamma dose-rate deciles was detected for AL as a whole (p = 0.02, table 2). This heterogeneity may be partially explained by the lower SIR values in the first and second deciles (SIR = 0.91 (0.84;0.99) for both). The log-linear model did not fit the data well ($p_{log\text{-}linearity}$ = 0.05) but adjustment for deprivation, urbanization and UV radiation indexes improved the model's adequacy ($p_{log\text{-}linearity}$ = 0.31). No association between gamma radiation and childhood AL incidence was evidenced (IRR = 0.99 (0.94;1.05) per 50 nSv/h, table 2, figure S1). Similarly, we did not observe any association between gamma radiation and ALL or BCP-ALL (fully-adjusted model: IRR = 0.98 (0.92;1.04) and IRR = 0.99 (0.93;1.06) per 50 nSv/h, respectively, table 2, figure S1).

With regard to AML, we did not evidence any SIR heterogeneity between the categories of gamma radiation exposure, and no evidence of a log-linear association was found (IRR = 1.06 (0.94;1.20) per

50 nSv/h). Adjustment for UU size and FDep index did not significantly change the parameter estimates (IRR = 1.04 (0.90;1.20), table 2).

There was a statistically significant SIR heterogeneity between radon concentration deciles for AL, ALL and BCP-ALL (table 3). Adjustments improved the model's adequacy, even though the log-linearity hypothesis was still questionable for ALL ($p_{log\text{-}linearity}$ = 0.07). In all, no statistically significant log-linear association was observed for all AL taken together or ALL (IRR = 0.97 (0.91;1.03) and IRR = 0.96 (0.89;1.02) per 100 Bq/m^3, respectively). Furthermore, the variation of SIRs by radon concentration category did not show any particular trend, but suggested that the overall heterogeneity for ALL was driven by a lower SIR in the second decile (crude SIRs are given in table 3, SIRs adjusted for UU size, FDep index and UV radiation exposure are shown on figure S1). The same findings were made for BCP-ALL (IRR = 0.97 (0.90;1.04) per 100 Bq/m^3, table 3 and figure S1).

For AML, there was no heterogeneity between SIRs in the radon decile categories (p = 0.35, table 3), and no log-linear association (IRR = 1.03 (0.90;1.18) per 100 Bq/m^3). Adjustment for FDep and urbanization indexes did not change the results.

The results were unchanged when gamma radiation and radon concentration were considered jointly in a multivariate model (table 4).

3.4 Cumulative NBR exposure and childhood AL

The cumulative exposure to NBR was estimated for each year of age. On average, the cumulative exposure to gamma radiation was estimated to be 4.7 mSv with a maximum of 32.4 mSv (table 1). The average cumulative exposure to radon was about 390 Bq/m^3×y, with a maximum of 11,988 Bq /m^3×y.

We did not observe any association between cumulative gamma radiation exposure and AL, considered together or by diagnostic group (table 5).

The results suggested a slight negative association between cumulative radon exposure and childhood AL, particularly for AML (IRR = 0.78 (0.59;1.04) per KBq/m^3×y, table 5), which was not expected given our current knowledge of radiation oncogenicity.

The mean cumulative RBM dose was estimated to be about 6.5 mSv and the highest RBM dose was close to 65 mSv (table 1). With this cumulative exposure indicator, our models fitted the data well and we did not evidence any association with childhood AL (IRR = 0.94 (0.88;1.01) per 5 mSv, table 6) or AL types.

3.5 Sensitivity analyses

For the sensitivity analyses, we considered 0-6- and 7-14-year-old children separately. Overall, no association with gamma radiation levels was observed irrespective of age group (table S2). We noted a negative association between radon concentration levels and AL for the 7-14-year-old children, in particular for AML (IRR = 0.66 (0.45;0.98) per 100 Bq/m^3, table S2). However, the results were based on small numbers of cases (e.g. only 16 AML cases aged 7-14 years were diagnosed in children born between 1990 and 2009 in the 4,767 municipalities of the 10th radon concentration decile). The results with cumulative NBR exposure (table S3) and total RBM dose (not shown) were similar for the 0-6 and 7-14 age groups.

In an additional analysis, we added nine months of NBR exposure to the cumulative exposure estimates to account for the pregnancy period; the results were unchanged (table S4).

Lastly, we adjusted for the urbanization index, deprivation index and UV radiation level, each in turn rather than all together. These analyses showed that the inclusion of the urbanization index contributed the most to improving the model's adequacy for AL and ALL (not shown). Overall, the results were unchanged when the analyses were only adjusted for the urbanization index (table S5).

4. Discussion

In this study, we investigated the role of NBR exposure at birth (gamma dose-rate and indoor radon concentration) in childhood AL. The study addressed mainland France and a 20-year period (1990-2009) during which more than 6,000 AL cases were born and diagnosed. No association between NBR exposure estimated in the municipality of residence at birth and childhood AL or the main broad subgroups, ALL (particularly BCP-ALL) and AML (taken as a whole), was found. Nor was there evidence for an association between cumulative NBR exposures based on estimates of gamma dose-rate and radon concentration of the municipality of birth and childhood AL.

For ALL and BCP-ALL, the shape of the association with radon concentration levels in the municipalities of residence at birth was not clear and the log-linear assumption was questionable, even after adjustment for potential confounders. Further examination of the distribution of SIRs between radon decile categories suggested that it was due to a pointwise difference between observed and expected numbers of cases in intermediate exposure categories and no trend was obvious (figure S1). A decrease in the incidence rate of AL, particularly AML, with increasing levels of radon exposure (for 7-14-year-old children) and cumulative radon exposure was also suggested. These unexpected results may not be reliable because of the small number of AML cases, in particular in the highest radon categories. A decrease in childhood AL risk (both for ALL and AML) with increased level of radon concentration was also reported in the large UKCCS case-control study (UKCCS, 2002a). The interpretation of this result is however limited by the large proportion of missing radon data (42% for cases and 51% for controls).

Those results may also reflect the role of a factor, not considered in this study, which may be associated with AML and inversely correlated with radon exposure on the municipality scale.

Given the higher solubility of radon in fat a significant proportion of inhaled or ingested radon may reach children's RBM, and potentially induce malignant transformation of cells, because of radon's marked biological effect on the organs impacted (Kendall and Smith 2005). Irradiation of circulating lymphocytes in the tracheobronchial epithelium may also lead to acute leukemia (Harley and Robbins, 2009). The role of radon exposure in childhood AL is thus an important issue and has been investigated in several studies. Overall, we did not find any evidence of a positive association between childhood AL and radon concentration in the municipality of residence at birth, which is in line with the results of our previous work based on radon concentration exposure at the time of diagnosis (Demoury et al. 2017) (Table S6). These results were also concordant with those reported in three other recent studies conducted in Norway (Del Risco Kollerud et al., 2014), Switzerland (Hauri et al., 2013) and Great Britain (Kendall et al., 2013). Only a Danish study showed a positive association with cumulative radon exposure, for ALL, with a relative risk (RR) of 1.56 (1.05;2.30) per $kBq/m^3 \times y$ (Raaschou-Nielsen et al. 2008).

Gamma rays have less biological effect than radon on the cells impacted, but they are particularly penetrative, and reach RBM in the same way as for other organs without being significantly attenuated. In our study, ~~there was no~~ we did not evidence any significant association between gamma radiation exposure in the municipality of residence at birth and childhood AL. Similarly, our previous study, which particularly focused on gamma radiation exposure at diagnosis and included 9,056 cases, did not show any association with childhood AL for external or cumulative gamma radiation exposure (Demoury et al. 2017) (Table S6). A large German study, which included 13,374 AL cases diagnosed from 1987 to 2011, came to the same conclusion that there was no evidence for an association between external gamma radiation exposure level in municipalities at diagnosis and childhood AL (Spix et al. 2017). In contrast, three studies conducted in Great Britain (Kendall et al. 2013), Switzerland (Spycher et al. 2015) and Finland (Nikkila et al. 2016) identified a positive association between childhood AL and gamma radiation (for children aged 2-7 years in the Finnish study).

The hypothesis that a childhood AL risk factor not considered in the present study masked a true association with radon concentration or gamma radiation cannot be ruled out. However, to date we do not have any candidate for such a confounding factor that should be strongly associated both with childhood AL and NBR levels on the municipality scale.

The above findings were addressed at an international scientific workshop in 2018 and presented in a recent review with a focus on methodology, main study limitations, and possible sources of bias

316 (Mazzei-Abba et al. 2020). They were also discussed in a recent review by Kendall et al. (Kendall et al.
317 2021).

318 NBR exposure levels in the European countries vary (from 21 Bq/m^3 in Great Britain to 86 Bq/m^3 in
319 Switzerland, on average, for radon concentration; from 51 nSv/h in Finland to 109 nSv/h in Switzerland,
320 on average, for gamma radiation), but it would appear that the differences are not in themselves
321 sufficient to explain the heterogeneity of the results of European studies (Mazzei-Abba et al. 2020).

322 Most childhood AL cases are diagnosed during the first years of life, with an incidence peak between
323 2 and 6 years of age for ALL, and a higher incidence rate before one year of age for AML. Intrauterine
324 exposure may be of paramount importance in the induction of the first stage of the leukemogenic
325 process, while exposure around diagnosis may play a role in disease promotion. This issue is of
326 particular interest in the context of the British and French studies (Demoury et al., 2017; Kendall et al.,
327 2013). Despite the fact that both studies included a large number of cases and reported quite similar
328 variability in gamma radiation exposure, their conclusions were different. In the British study, which
329 reported a positive association between childhood AL and cumulative gamma radiation (RR = 1.54
330 (1.10;2.19) per 5 mSv, and RR = 1.40 (1.05;1.84) per 5 mSv of total RBM dose), the cumulative exposure
331 was estimated on the basis of the levels of exposure in the county district of the mother's residence
332 at birth. A positive association with gamma dose-rate (RR = 1.18 (0.99;1.41) per 50 nSv/h, result
333 derived from table S18 in (Kendall and Smith 2005)) was also suggested. Using the place of residence
334 at diagnosis to estimate gamma dose-rate and cumulative dose since birth, Demoury et al. did not
335 evidence any association with childhood AL incidence (Demoury et al. 2017) (Table S6). The timing of
336 exposure assessment is thought to be a possible explanation for the discordant results (Mazzei-Abba
337 et al. 2020). However, in the present study, we considered the child's birth as the reference time point
338 for NBR exposure estimates, as in the British study, but we did not find any evidence of an association
339 with childhood AL. Our results were very similar to those reported in Demoury's study (Table S6), with
340 smaller confidence intervals than those reported in other studies, a surprising result Kendall et al.
341 pointed out (Kendall et al., 2021, 2018). The smaller number of cases was likely to explain, at least in
342 part, why the confidence intervals were larger in the Swiss and Finnish studies. The difference with the
343 British study was actually more surprising since both studies included the same number of cases and
344 the gamma exposure distributions were not so different in Great Britain and France. However, in the
345 British study, the matching of cases and controls on the place of birth registration resulted in a high
346 proportion of case-control pairs with the same estimated gamma exposure, which might have
347 increased the relative risk estimate uncertainty. Interestingly, the RR estimates and the confidence
348 intervals reported in the large German study (Spix et al., 2017) and in Demoury et al. (Demoury et al.,
349 2017) for gamma radiation exposure were very similar (RR=1.04 (0.91;1.20) when comparing 1.5 mSv/y

to 0.5 mSv/y with a non-linear model, i.e. RR approximately equal to 1.00 (0.99;1.02) for a 10 nSv/h increase, and RR=1.01 (1.00;1.02) per 10 nSv/h respectively).

Irrespective of the exposure window considered, our studies do not support the hypothesis of an association between NBR exposure and childhood AL in France.

Our study has some limitations, with the main concern being NBR exposure modeling, in particular for radon concentration, a limitation our study shares with others (Kendall et al., 2021). Radon concentrations vary markedly even between neighboring houses, depending, in particular, on building materials and domestic habits, such as the frequency of ventilation (Demoury et al. 2013). In the published studies, the coefficient of determination, R^2, of the model varied from 0.20 to 0.45 (Mazzei-Abba et al. 2020), with a maximum in the Danish study (Raaschou-Nielsen et al. 2008). In France, the coefficient of determination was estimated to be 0.32 (Demoury et al. 2017), which means that a substantial proportion of measurement variance was not explained by the model. Regarding gamma radiation measurements, we used data from the routine monitoring of veterinary clinics and dental surgeries, throughout France. An average exposure level of 76 nSv/h was estimated based on those measurements (Warnery et al., 2015) which was higher than the level of indoor gamma radiation reported by Billon et al. from measurement surveys conducted in French households (mean=55 nSv/h (Billon et al., 2005)). This difference is still unexplained to date (Marquant et al., 2018). However, most of Billon's data were based on surveys that were conducted in arbitrary selected sites with no standardized measurement protocol. Therefore, we assumed that gamma measurements made in veterinary clinics and dental surgeries were more representative of the French population exposure levels over the whole territory. Besides, we considered that the cokriging estimates derived from those measurements were able to capture correctly radiation exposure contrasts between municipalities (Marquant et al., 2018).

Furthermore, we used NBR levels estimated in the municipality where the child lived at birth, with no information on the precise residential address, which may be a limitation. However, based on the geocoded addresses of 30,000 population controls included in the GEOCAP program, we have previously shown that there is a high correlation between NBR levels estimated at the townhall of the municipality and NBR levels estimated at the precise residential addresses (r = 0.99 (Demoury et al. 2017)).

IR exposure around birth is of particular interest because fetuses and young children may be more sensitive to radiation owing to immature biological response (Olshan et al. 2000; UNSCEAR 2013). Since we did not have information on the mothers' residences during pregnancy, we considered NBR exposure in the municipality of residence at the time of the child's birth. We assumed that the mother's

residences during pregnancy and at the time of the child's birth were the same for the majority of children, and that when mothers moved house they did not move far away, so that NBR exposures during pregnancy and at birth were highly correlated.

In our studies, as was the case in the British study, residential histories were not collected and cumulative NBR exposures were estimated by multiplying the background radiation level by the child's age, assuming that exposure levels at birth (or diagnosis) were good estimate of lifelong average exposure. In a previous national case-control study, we showed that 66% of children had been living in the same municipality between birth and diagnosis for the cases or inclusion for the controls. There was a high correlation between radon concentration and gamma radiation exposure for those time periods ($r = 0.86$ and $r = 0.89$, respectively (Demoury et al. 2017)). However, house moving and residential history during childhood would constitute additional data that might help improve the precision of cumulative exposure estimates (Nikkila et al. 2018a, Kendall et al., 2021).

Lastly, we did not consider exposure by ingestion of radionuclides in contaminated food or water, which is likely to represent approximately 10% of the total dose for children (IRSN 2015), and may vary depending on individual consumption habits. In addition, we did not have any information on medical gamma radiation exposure due to diagnostic examinations, such as conventional radiology or CT scans. A radiological examination may deliver an IR dose of approximately 0.5 mGy, while for CT-scans the dose delivered to the target organ may be several tens of mGy. In a recent meta-analysis, while prenatal medical diagnostic radiation exposure was not associated with childhood leukemia, an increased risk was reported for postnatal CT scan and X-ray examinations (Abalo et al. 2020). However, medical exposures and exposures by ingestion are unlikely to be correlated with NBR levels on the municipality scale.

This ecological study, based on high quality data, has major strengths. First, the completeness of the French national registry of childhood cancer, for which the data are collected by trained and qualified investigators. Each case is confirmed by three independent sources of information, on average, and the diagnoses are characterized using the international classification. In the RNCE, the country of birth was known for all the cases born and diagnosed during the period 1990-2009, so that cases born out of France could be excluded. The precise address of residence at birth could be collected for almost all the remaining cases (99.5%). In addition, the long study period enabled inclusion of almost 6,000 AL cases and thus guaranteed high statistical power. The use of validated cokriging models, which used data from national measurement campaigns and precise geological information (IRSN 2012, Warnery et al. 2015, Marquant et al. 2018) to estimate NBR exposure, constitutes a major strength of our studies. In particular, we considered gamma radiation levels estimated from a geostatistical model,

416 which combined information from 97,595 measurements made at 17,404 sites throughout France and
417 a map of the uranium potential of the French geological formations. The model explained a significant
418 proportion of the variance of indoor gamma radiation measurements (r^2 = 0.65 (Warnery et al. 2015)).

419 In conclusion, using high quality data, we did not find any association between radon or gamma
420 radiation exposures in the municipality of residence at birth (gamma dose rate and radon
421 concentration, cumulative exposures and total RBM dose) and childhood AL. No association was
422 observed either for the main AL types, ALL and AML. These results are consistent with those reported
423 in our previous study on NBR exposure at the time of diagnosis, and thus suggest that the timing of
424 exposure assessment may not have a strong impact on the study results and may not explain the
425 discrepancy between the British and French study results. A clearer understanding of the
426 heterogeneity of the study gamma radiation results remains a challenge (Kendall et al., 2021).
427 Moreover, although several NBR studies did not suggest any association with radon concentration,
428 further research is needed in order to improve exposure assessment and enhance cumulative exposure
429 estimates based on residential histories. These issues will be considered carefully in the ongoing
430 RadoNorm project (Euratom research and training programme 2019-2020 under grant agreement No
431 900009), a large European project on radon and naturally occurring radiation material (NORM).

Table 1: Distribution of ambient and cumulative exposures to natural background radiation (radon and gamma radiation) and estimated total red-bone marrow (RBM) dose in the 35,852 French municipalities

Type of exposure	Mean	Min	p5%	p25%	p50%	p75%	p95%	Max	IQR
Gamma radiation									
Ambient exposure (nSv/h)	100.1	54.4	68.9	80.4	94.9	114.2	150.0	254.8	33.8
Population-weighted exposure (nSv/h)	90.8	54.4	61.3	70.7	83.6	104.5	142.7	254.8	33.8
Cumulative population-weighted exposure[a] (mSv)	4.7	0.2	0.4	1.9	4.0	6.9	11.6	32.4	5.0
Radon concentration									
Ambient exposure (Bq/m^3)	91.8	12.5	38.3	54.2	72.7	107.5	203.8	827.5	53.4
Population-weighted exposure (Bq/m^3)	65.3	12.5	20.1	39.1	53.2	78.5	143.7	827.5	39.4
Cumulative population-weighted distribution of exposure[a] (Bq /m^3×y)	389.7	6.2	25.8	120.2	271.6	516.7	1,141.7	11,988.2	396.5
Total RBM dose									
Cumulative population-weighted exposure[b] (mSv)	6.5	0.3	0.5	2.5	5.5	9.4	16.3	63.6	6.9

Note: radon concentration and gamma radiation were estimated at the town hall of each municipality.
Mean: arithmetic mean, Min: minimum, p: percentile, Max: maximum, IQR: interquartile range
[a] The cumulative exposure was estimated over the period 1990-2009 as follows: $X_{ia}^{cum} = X_i \times (a + 0.5)$ in which X_{ia}^{cum} is the cumulative exposure level (gamma radiation or radon concentration) estimated for a child aged 'a' who was born in municipality 'i', and X_i the exposure level in municipality 'i' (ambient exposure)
[b] The total RBM dose was estimated using conversion coefficients estimated with gas diffusion models from air to different organs in a child body for radon (Kendall and Smith 2005, Petoussi 1991).

Table 2: Association between childhood acute leukemia (AL) and the main AL groups, and gamma dose-rate in the municipality of residence at birth (mainland France, children born and diagnosed between 1990 and 2009)

	All AL (N = 6,059)			ALL (N = 4,984)			BCP ALL (N = 4,158)			AML (N=957)		
Gamma dose-rate (nSv/h)	O	E	SIR 95%CI	O	E	SIR 95%CI	O	E	SIR 95%CI	O	E	SIR 95%CI
[54.4,64.9]	551	602.5	0.91 (0.84;0.99)	442	495.7	0.89 (0.81;0.98)	365	413.5	0.88 (0.80;0.98)	101	95.1	1.06 (0.87;1.29)
]64.9,69.0]	552	605.5	0.91 (0.84;0.99)	459	498.1	0.92 (0.84;1.01)	394	415.5	0.95 (0.86;1.05)	85	95.6	0.89 (0.72;1.10)
]69.0,73.0]	620	609.4	1.02 (0.94;1.10)	527	501.3	1.05 (0.97;1.15)	442	418.1	1.06 (0.96;1.16)	81	96.3	0.84 (0.68;1.05)
]73.0,78.6]	560	580.7	0.96 (0.89;1.05)	472	477.7	0.99 (0.90;1.08)	386	398.5	0.97 (0.88;1.07)	77	91.7	0.84 (0.67;1.05)
]78.6,83.6]	630	628.9	1.00 (0.93;1.08)	504	517.3	0.97 (0.89;1.06)	418	431.7	0.97 (0.88;1.07)	115	99.4	1.16 (0.96;1.39)
]83.6,90.4]	615	607.4	1.01 (0.94;1.10)	499	499.6	1.00 (0.91;1.09)	409	416.8	0.98 (0.89;1.08)	97	95.9	1.01 (0.83;1.23)
]90.4,99.5]	652	609.0	1.07 (0.99;1.16)	537	501.0	1.07 (0.98;1.17)	447	418.0	1.07 (0.97;1.17)	101	96.1	1.05 (0.86;1.28)
]99.5,111.1]	662	605.1	1.09 (1.01;1.18)	551	497.7	1.11 (1.02;1.20)	460	415.3	1.11 (1.01;1.21)	99	95.6	1.04 (0.85;1.26)
]111.1,127.7]	622	603.8	1.03 (0.95;1.11)	496	496.6	1.00 (0.91;1.09)	416	414.5	1.00 (0.91;1.10)	110	95.5	1.15 (0.96;1.39)
]127.7,254.8]	595	606.6	0.98 (0.91;1.06)	497	499	1.00 (0.91;1.09)	421	416.3	1.01 (0.92;1.11)	91	95.8	0.95 (0.77;1.17)
$p_{heterog.}$ [a]		0.02			0.03			0.07			0.23	
$p_{log\text{-}linearity}$ [b]		0.05			0.04			0.12			0.21	
IRR by 50 nSv/h and p [c]									1.04 (0.98;1.11) 0.08			1.06 (0.94;1.20) 0.18
Adjusted model [d]												
$p_{heterog.}$ [a]		0.40			0.20			0.19			0.30	
$p_{log\text{-}linearity}$ [b]		0.31			0.14			0.14			0.23	
IRR by 50 nSv/h and p [d]			0.99 (0.94;1.05) 0.64			0.98 (0.92;1.04) 0.73			0.99 (0.93;1.06) 0.61			1.04 (0.90;1.20) 0.29

Note: AL: acute leukemia, ALL: Acute Lymphoblastic Leukemia; BCP-ALL: Precursor B Cell Acute Lymphoblastic Leukemia; AML: Acute Myeloid Leukemia; N: total number of cases; O: number of observed cases in each exposure category; E: number of cases expected in each exposure category under the hypothesis of homogeneous age-specific incidence rates throughout France; IRR: incidence rate ratio per unit of exposure; SIR: standardized incidence ratio defined as O/E; 95% CI: 95% confidence interval.

[a] p-value of the Chi-square test for heterogeneity in SIRs between gamma radiation exposure categories.

[b] p-value of the test of departure from log-linearity.

[c] Estimated slope parameter from a Poisson regression model under the hypothesis of a log-linear association between childhood AL and gamma radiation exposure. Parameters were not estimated if the log-linearity hypothesis was rejected. p: one-sided p-value for the slope parameter estimate.

[d] Results from a Poisson regression model under the hypothesis of a log-linear association between childhood AL and gamma radiation exposure, adjusted for the size of urban unit, a deprivation index (FDep), and UV-radiation (for AL, ALL and BCP-ALL). p: one-sided p-value for the slope parameter estimate.

Table 3: Association between childhood acute leukemia (AL) and the main AL groups, and radon concentration in the municipality of residence at birth (mainland France, children born and diagnosed between 1990 and 2009)

	All AL (N = 6,059)			ALL (N = 4,984)			BCP ALL (N = 4,158)			AML (N=957)		
Radon concentration (Bq/m^3)	O	E	SIR 95%CI	O	E	SIR 95%CI	O	E	SIR 95%CI	O	E	SIR 95%CI
[12.5,27.0]	553	606.5	0.91 (0.84;0.99)	461	498.9	0.92 (0.84;1.01)	379	416.3	0.91 (0.82;1.01)	85	95.7	0.89 (0.72;1.10)
]27.0,35.1]	537	610.6	0.88 (0.81;0.96)	419	502.2	0.83 (0.76;0.92)	350	418.9	0.84 (0.75;0.93)	107	96.4	1.11 (0.92;1.34)
]35,1,41.9]	603	600.6	1.00 (0.93;1.09)	508	494.0	1.03 (0.94;1.12)	432	412.0	1.05 (0.95;1.15)	84	94.8	0.89 (0.72;1.10)
]41.9,47.1]	630	606.3	1.04 (0.96;1.12)	503	498.8	1.01 (0.92;1.10)	414	416.0	1.00 (0.90;1.10)	117	95.8	1.22 (1.02;1.46)
]47.1,53.2]	614	605.3	1.01 (0.94;1.10)	514	497.9	1.03 (0.95;1.13)	439	415.4	1.06 (0.96;1.16)	91	95.6	0.95 (0.78;1.17)
]53.2,60.1]	627	611.4	1.03 (0.95;1.11)	524	502.9	1.04 (0.96;1.14)	425	419.4	1.01 (0.92;1.11)	90	96.6	0.93 (0.76;1.15)
]60.1,71.8]	623	599.4	1.04 (0.96;1.12)	519	493.0	1.05 (0.97;1.15)	431	411.4	1.05 (0.95;1.15)	89	94.7	0.94 (0.76;1.16)
]71.8,86.5]	647	606.8	1.07 (0.99;1.15)	543	499.2	1.09 (1.00;1.18)	454	416.5	1.09 (0.99;1.19)	92	95.9	0.96 (0.78;1.18)
]86.5,117.5]	622	606.7	1.03 (0.95;1.11)	509	499.0	1.02 (0.94;1.11)	425	416.6	1.02 (0.93;1.12)	98	95.9	1.02 (0.84;1.25)
]117.5,827.5]	603	605.5	1.00 (0.92;1.08)	484	498.1	0.97 (0.89;1.06)	409	415.5	0.98 (0.89;1.08)	104	95.6	1.09 (0.90;1.32)
$p_{heterog}$ [a]		0.02			<0.01			0.01			0.35	
$p_{log\text{-}linearity}$ [b]		0.04			<0.01			0.01			0.30	
Trend: IRR by 100 Bq/m^3 and p [c]												1.03 (0.90;1.18) 0.31
Adjusted model [d]												
$p_{heterog}$ [a]		0.57			0.11			0.13			0.39	
$p_{log\text{-}linearity}$ [b]		0.47			0.07			0.08			0.30	
Trend: IRR by 100 Bq/m^3 and p [d]			0.97 (0.91;1.03) 0.84			0.96 (0.89;1.02) 0.90			0.97 (0.90;1.05) 0.76			1.01 (0.87;1.17) 0.44

Note: AL: acute leukemia, ALL: Acute Lymphoblastic Leukemia; BCP-ALL: Precursor B Cell Acute Lymphoblastic Leukemia; AML: Acute Myeloid Leukemia; N: total number of cases; O: number of observed cases in each exposure category; E: number of cases expected in each exposure category under the hypothesis of homogeneous age-specific incidence rates throughout France; IRR: incidence rate ratio per unit of exposure; SIR: standardized incidence ratio defined as O/E; 95% CI: 95% confidence interval.

[a] p-value of the Chi-square test for heterogeneity in SIRs between radon exposure categories.

[b] p-value of the test of departure from log-linearity.

[c] Estimated slope parameter from a Poisson regression model under the hypothesis of a log-linear association between childhood AL and radon exposure. Parameters were not estimated if the log-linearity hypothesis was rejected. p: one-sided p-value for the slope parameter estimate

[d] Results from a Poisson regression model under the hypothesis of a log-linear association between childhood AL and radon exposure, adjusted for the size of urban unit, a deprivation index (FDep), and UV-radiation (for AL, ALL and BCP-ALL). p: one-sided p-value for the slope parameter estimate.

Table 4: Association between childhood acute leukemia (AL), and the main AL groups, and NBR, considering jointly gamma radiation and radon concentration, with adjustment for urbanization, deprivation and UV radiation levels in the municipalities

	All AL (6,057 cases [a])			ALL (4,982 cases [a])			BCP-ALL (4,156 cases [a])			AML (957 cases)		
	IRR	95%CI	p	IRR	95%CI	p	IRR	95%CI	p	IRR	95%CI	p
Gamma radiation (per 50 nSv/h)	**1.01**	**(0.94;1.09)**	**0.36**	**1.01**	**(0.93;1.10)**	**0.39**	**1.01**	**(0.93;1.10)**	**0.41**	**1.06**	**(0.88;1.27)**	**0.27**
Radon concentration (per 100 Bq/m^3)	**0.96**	**(0.89;1.04)**	**0.84**	**0.95**	**(0.87;1.04)**	**0.88**	**0.97**	**(0.88;1.06)**	**0.76**	**0.98**	**(0.80;1.18)**	**0.60**
Size of UU (Paris urban unit *vs.* other UU)	0.87	(0.81;0.94)	<0.01	0.87	(0.8;0.95)	<0.01	0.89	(0.81;0.98)	0.01	0.94	(0.78;1.14)	0.55
FDep (most deprived quintile *vs.* Q1-Q4)	0.94	(0.88;1.01)	0.07	0.94	(0.88;1.01)	0.10	0.91	(0.84;0.99)	0.03	0.95	(0.80;1.11)	0.50
UV (>105.5 J/cm^2 *vs.* ≤105.5 J/cm²)	1.02	(0.96;1.08)	0.58	1.05	(0.98;1.12)	0.18	1.07	(1.00;1.15)	0.06			

Note: AL: acute leukemia, ALL: Acute Lymphoblastic Leukemia, BCP-ALL: Precursor B-Cell Acute Lymphoblastic Leukemia, AML: Acute Myeloid Leukemia, IRR = Incidence rate ratio, 95%CI: 95% confidence interval. p: p-value (one-sided test for gamma radiation and radon concentration parameters). UU: urban unit. FDep: French deprivation Index. UV: UV radiation level in the municipality

[a] 298 municipalities (two BCP-ALL cases) were excluded from the analyses because of missing values for FDep

Table 5: Association between childhood acute leukemia (AL) and the main AL groups, and cumulative NBR exposures, with adjustment for urbanization, deprivation and UV radiation levels in the municipalities

	All AL (6,057 cases [a])			ALL (4,982 cases [a])			BCP-ALL (4,156 cases [a])			AML (957 cases)		
	IRR	95%CI	p	IRR	95%CI	p	IRR	95%CI	p	IRR	95%CI	p
Cumulative gamma exposure (per 5 mSv)	**0.96**	**(0.87;1.07)**	**0.77**	**0.98**	**(0.87;1.09)**	**0.66**	**1.01**	**(0.89;1.16)**	**0.43**	**0.94**	**(0.73;1.21)**	**0.69**
Size of UU (Paris urban unit vs. other UUs)	0.87	(0.81;0.94)	<0.01	0.88	(0.81;0.96)	<0.01	0.90	(0.82;0.98)	0.02	0.91	(0.76;1.08)	0.28
FDep (Most deprived quintile vs. Q1-Q4)	0.94	(0.88;1.01)	0.07	0.94	(0.88;1.01)	0.10	0.91	(0.84;0.99)	0.03	0.94	(0.80;1.11)	0.48
UV (>105.5 J/cm^2 vs. ≤105.5 J/cm^2)	1.02	(0.96;1.08)	0.56	1.05	(0.98;1.12)	0.18	1.07	(1.00;1.15)	0.06			
Cumulative radon exposure (per 1,000 Bq/m3×y)	**0.89**	**(0.80;0.99)**	**0.99**	**0.91**	**(0.81;1.02)**	**0.95**	**0.93**	**(0.81;1.06)**	**0.86**	**0.78**	**(0.59;1.04)**	**0.95**
Size of UU (Paris urban unit vs. other UUs)	0.86	(0.80;0.93)	<0.01	0.87	(0.8;0.94)	<0.01	0.88	(0.81;0.97)	0.01	0.88	(0.74;1.05)	0.15
FDep (Most deprived quintile vs. Q1-Q4)	0.94	(0.88;1.00)	0.07	0.94	(0.88;1.01)	0.10	0.91	(0.84;0.99)	0.03	0.94	(0.80;1.11)	0.46
UV (>105.5 J/cm^2 vs. ≤105.5 J/cm^2)	1.02	(0.96;1.08)	0.55	1.05	(0.98;1.12)	0.17	1.07	(1.00;1.15)	0.06			

Note: AL: acute leukemia, ALL: Acute Lymphoblastic Leukemia, BCP-ALL: Precursor B-Cell Acute Lymphoblastic Leukemia, AML: Acute Myeloid Leukemia, IRR = Incidence rate ratio, 95%CI: 95% confidence interval. UU: urban unit. FDep: French deprivation Index. UV: UV radiation level in the municipality
p: p-value (one-sided for gamma radiation and radon concentration slope parameters).
[a] 298 municipalities (two PCB-ALL cases) were excluded from the analyses because of missing values for Fdep

Table 6: Association between total red-bone marrow (RBM) dose and childhood acute leukemia (AL), and the main AL groups, with adjustment for urbanization, deprivation and UV-radiation level in the municipalities

	All AL (6,057 cases [a])			ALL (4,982 cases [a])			BCP-ALL (4,156 cases [a])			AML (957 cases)		
	IRR	95%CI	p	IRR	95%CI	p	IRR	95%CI	p	IRR	95%CI	p
RBM dose (for an increase of 5 mSv)	**0.95**	**(0.89;1.02)**	**0.92**	**0.97**	**(0.9;1.04)**	**0.83**	**0.99**	**(0.91;1.07)**	**0.62**	**0.92**	**(0.78;1.08)**	**0.85**
Size of UU (Paris urban unit vs. others)	0.87	(0.80;0.93)	<0.01	0.87	(0.80;0.95)	<0.01	0.89	(0.82;0.98)	0.01	0.89	(0.75;1.06)	0.20
FDep (Most deprived quintile vs. Q1-Q4)	0.94	(0.88;1.01)	0.07	0.94	(0.88;1.01)	0.10	0.91	(0.84;0.99)	0.03	0.94	(0.80;1.11)	0.47
UV (>105.5 J/cm^2 vs. ≤105.5 J/cm^2)	1.02	(0.96;1.08)	0.55	1.05	(0.98;1.12)	0.17	1.07	(1.00;1.15)	0.06			
Departure from log-linearity [b]			0.12			0.16			0.05			0.57

Note: AL: acute leukemia, ALL: Acute Lymphoblastic Leukemia, BCP-ALL: Precursor B-Cell Acute Lymphoblastic Leukemia, AML: Acute Myeloid Leukemia, IRR = Incidence rate ratio, 95%CI: 95% confidence interval. UU: urban unit. FDep: French deprivation Index. UV: UV radiation level in the municipality
p: p-value (one-sided test for RBM dose slope parameters).
[a] 298 municipalities (two PCB-ALL cases) were excluded from the analyses because of missing values for FDep
[b] p-value of the test of departure from the log-linearity hypothesis for the association between RBM dose and childhood leukemia.

Acknowledgments
The authors are grateful to Didier Gay, Christophe Debayle, Olivier Laurent and Jérôme Guillevic of the IRSN for providing the data and discussing the methodology on natural background radiation exposure assessment. The authors are also grateful to the staff of the French national registry of childhood cancer, who contributed to the active search for information in clinical departments. The authors thank ADISP (Archives de Données Issues de la Statistique Publique) for providing birth data from the INSEE (application form N°19728).

Funding sources
The study was supported by the 'Institut National du Cancer'; 'Santé Publique France'; 'The French National Research Program for Environmental and Occupational Health of Anses with the support of the Cancer TMOI of the French National Alliance for Life and Health Sciences
(AVIESAN) (EST-2016/1/161) (ANSES)'; 'Electricité de France' (EDF, EP 2016-05); and 'Paris Descartes University'.
The sponsor(s) did not participate in the study design; in the collection, analysis and interpretation of data; in the writing of the report; nor in the decision to submit the article for publication.

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