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## ► To cite this version:

Astrid Coste, Stéphanie Goujon, Laure Faure, Denis Hémon, Jacqueline Clavel. Agricultural crop density in the municipalities of France and incidence of childhood leukemia: An ecological study. *Environmental Research*, 2020, 187, pp.109517 -. 10.1016/j.envres.2020.109517 . hal-03490496

**HAL Id: hal-03490496**

**<https://hal.science/hal-03490496>**

Submitted on 20 May 2022

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1 **Agricultural crop density in the municipalities of France and incidence of**  
2 **childhood leukemia: an ecological study**

3

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22 **Conflict of interest:** The authors declare that they have no conflict of interest.

**Abbreviations**

AL: Acute leukemia; ALL: Acute lymphoblastic leukemia; AML: Acute myeloid leukemia; CASD: Centre d'Accès Sécurisé aux Données (Secure Data Access Center); UAA: Utilized Agricultural Area; RNHE: French National Registry of Childhood Hematological Malignancies; UV: Ultraviolet; Fdep: French deprivation index at the municipality level; SES: socio-economic status; SIR: Standardized Incidence Ratio; SIRR: Relative Standardized Incidence Ratio; JEM: Job exposure matrix; CLIC: Childhood Leukemia International Consortium; IARC: International Agency for Research on Cancer

23 **Abstract:**

24

25 **Background:** Pesticide exposure is suspected to play a role in the etiology of childhood leukemia (AL).  
26 Various sources of exposure have been explored, but few studies have investigated the risk of  
27 childhood AL in relation to residential exposure to agricultural pesticides. Since around 50% of France  
28 is agricultural land, with marked pesticide use, France is a suitable location to investigate for an  
29 association. We aimed to analyze the association between the agricultural crop density in the  
30 municipalities of France and the incidence of childhood AL between 1990 and 2014.

31 **Methods:** 11,487 cases of AL diagnosed in children aged 0-14 years were registered by the French  
32 National Registry of Childhood Hematological Malignancies over 1990-2014. National agricultural  
33 census data for 1990, 2000 and 2010 were used to estimate the densities of the most common crops  
34 in France. The incidence of AL was estimated in the 35,512 municipalities, by age and gender, and 3  
35 observation periods, and expressed as the standardized incidence ratio (SIR).

36 **Results:** We observed a moderate log-linear association between viticulture density and the  
37 incidence of AL, with a 3% increase in SIR for a 10% increase in viticulture density (SIRR = 1.03; 95%CI  
38 [1.00-1.06]). The association remained for lymphoblastic AL but not for myeloid AL. The association  
39 was stable after stratification by geographic area, age and period, and after adjustment on UV  
40 radiation and a French deprivation index. No consistent association was observed for other crop  
41 types.

42 **Discussion:** This nationwide study shows a moderate increase in incidence of childhood AL in  
43 municipalities where viticulture is common. Future individual studies are needed to know whether  
44 this observation is confirmed and related to particular use of pesticides.

45

46 **Keywords:** Childhood leukemia, pesticides, agriculture, ecological study, record-based study

**47 Ethics approval**

48 The research undertaken with the RNHE data is covered by agreements on the ethical use of data  
49 and the protection of personal data and have been approved by French national authorities (French  
50 data protection authority CNIL N° n°998198). This study was part of a wider project called “GEOCAP-  
51 AGRI” and the use of the agricultural census data for this project have been approved by the French  
52 Committee of the Statistical Confidentiality and the CNIL was notified of data processing (N° 2077682  
53 v0).

**54 Funding sources**

55 The study was supported by the ‘Institut National du Cancer’, ‘Santé Publique France’, ‘Agence  
56 Nationale de Sécurité Sanitaire de l’Alimentation, de l’Environnement et du travail’ (ANSES), ‘Agence  
57 Nationale de la Recherche, Investment for the future’ (ANR-10-COHO-0009 grant for HOPE-EPI).  
58 Astrid Coste also received funding from the Fondation pour la Recherche Médicale  
59 (FDT20160435122) for her PhD. This work is also supported by a public grant overseen by the French  
60 National Research Agency (ANR) as part of the « Investissements d’avenir » program (reference:  
61 ANR-10-EQPX-17 – Centre d’accès sécurisé aux données – CASD).

**62 Introduction:**

63 The causes of childhood acute leukemia (AL) have not been fully elucidated. AL is the most common  
64 type of childhood cancer in industrialized countries, with an incidence rate of about 5 cases per  
65 100,000 person-years per annum in children aged 0-14 years in France (Lacour et al., 2010). Among  
66 children, acute lymphoblastic leukemia (ALL) is more frequent (80% of cases) than acute myeloid  
67 leukemia (AML) (15% of cases). Several rare genetic diseases such as Down syndrome, some genetic  
68 polymorphisms (Orsi et al., 2012), and high dose ionizing radiation exposure are known risk factors  
69 (Hsu et al., 2013; Pearce et al., 2012; Preston et al., 1994). A range of environmental factors are  
70 suspected to play a role in the etiology of childhood leukemia, including exposure to pesticides  
71 (Bailey et al., 2015).

72 Pesticides include all the chemicals designed to control insects, weeds, fungi and other pests.  
73 Carcinogenic effects of some pesticides have been observed in animal studies but also in  
74 epidemiological studies. Most of the latter have focused on occupational exposure and strong  
75 associations have been found for adult hematological malignancies (Miligi et al., 2006; Van Maele-  
76 Fabry et al., 2007). The general population is also exposed to those compounds, although at lower  
77 doses than in the context of occupational exposure. Children constitute a particularly vulnerable  
78 population in that they consume more food per kilogram of body weight than adults, have a higher  
79 inhalation rate and have a higher body surface area to body weight ratio. They also have less ability  
80 to metabolize and eliminate chemicals (Roberts et al., 2012). In addition, early life is a critical time  
81 window of heightened susceptibility to environmental aggressions due to the high rate of cell  
82 proliferation and the immaturity of organs (Bassil et al., 2007; Ostrea et al., 2009; WHO, 2006).  
83 Before birth, embryo and fetus could be exposed through parental occupational and domestic  
84 exposures. The main exposure route for children is dietary intake of contaminated food/water and  
85 air inhalation. The main sources of airborne particles derived from pesticide application are domestic  
86 use and agricultural application on fields near children's homes. Children living close to treated land  
87 may be exposed through several pathways: direct pesticide drift, dust tracked into the home after  
88 pesticide volatilization, and contact with the clothing and shoes of occupationally exposed family  
89 members (Deziel et al., 2017; Gunier et al., 2011).

90 Several studies have investigated for the potential effects of pesticide exposure on leukemia risk in  
91 children. Meta-analyses of home pesticide exposures have shown a consistent positive association  
92 between the risk of leukemia and pesticide exposure (Bailey et al., 2015; Van Maele-Fabry et al.,  
93 2019). The meta-analysis of the Childhood Leukemia International Consortium (CLIC) (Bailey et al.,  
94 2015) included a large pooled analysis of individual data from 12 case-control studies and found  
95 evidence of an association between ALL/AML and prenatal exposure to pesticides, and between  
96 childhood exposure and ALL. Systematic reviews and meta-analyses investigating parental  
97 occupational exposure found evidence of an association with the risk of AL (Van Maele-Fabry et al.,  
98 2010; Wigle et al., 2009). More recently, the CLIC conducted a large pooled analysis of 13 case-  
99 control studies (Bailey et al., 2014). A positive association between maternal occupational exposure  
100 to pesticides during pregnancy and the risk of AML was found. A slight increase in the risk of ALL was  
101 observed with paternal exposure around conception. A study from the International Childhood  
102 Cancer Cohort Consortium (I4C) pooling five birth cohorts also suggested an increased risk of AML,  
103 but not ALL, in children whose father was occupationally exposed to pesticides. Those results were  
104 based however on small numbers (Patel et al., 2019). Few studies have investigated the risk of  
105 childhood AL in relation to residential exposure to agricultural pesticides. A Spanish record-based  
106 case-control study (Gómez-Barroso et al., 2016) showed weak associations between proximity to  
107 crops/specific crops and AL. A small Italian case-control study found no association between

108 residential proximity to all or specific crops and AL (Malagoli et al., 2016). Two Texan ecological  
109 studies (Carozza et al., 2009; Walker et al., 2007) did not evidence any associations between AL and  
110 crop density/proximity to crops. Two large ecological studies based on numerous US states used  
111 county-level agricultural census data to estimate crop density (Booth et al., 2015; Carozza et al.,  
112 2008) and found associations between specific crops and the incidence of AL. With regard to specific  
113 pesticides, propargite, metam sodium, dicofol, azoles and possibly organophosphates were  
114 associated with a higher risk of childhood AL in two Californian studies (Reynolds et al., 2002, 2005b),  
115 but in two other similar studies, no clear patterns were found (Reynolds et al., 2005a; Rull et al.,  
116 2009).

117 There were around 27 million hectares of Utilized Agricultural Areas (UAA) in the most recent (2010)  
118 French agricultural census (“Ministère de l’agriculture et de l’alimentation - agreste - La statistique,  
119 l’évaluation et la prospective agricole - Recensement agricole 2010,” n.d.). The area constitutes  
120 about 50% of mainland France. The use of agricultural pesticides is thus considerable, and it has been  
121 estimated that about 65,000 to 70,000 metric tons of agricultural pesticides, most of them  
122 fungicides, are sold each year (INSERM, 2013). Therefore, France is a pertinent location to study the  
123 effects of residential exposure to agricultural pesticides on the risk of childhood leukemia. In this  
124 study, we investigated the ecological association between the agricultural crop densities in the  
125 municipalities of France and the incidence of childhood AL between 1990 and 2014.

## 126 **Material and Methods**

### 127 *Geographic units*

128 The municipalities are the smallest administrative subdivisions in France. During the study period,  
129 1990-2014, boundaries changed: some municipalities were merged and others divided. To harmonize  
130 the dataset, we regrouped the municipalities where appropriate and obtained 35,512 harmonized  
131 units (referred to as “municipalities” hereafter).

### 132 *Crop densities in the municipalities*

133 Nationwide agricultural censuses are conducted in France by the French Ministry of Agriculture every  
134 ten years and collect data based on questionnaires applied to every farm in France. The information  
135 relating to a farm is linked to the municipality of the main building on the farm. These data were  
136 used to assess the crop densities in the municipalities because of their exhaustiveness, high quality  
137 and the detailed list of crops they included. We were able to access the detailed data via a secure  
138 platform of the secure data access center (CASD). We extracted UAA by type of crop at the  
139 municipality level from the 1988, 2000 and 2010 national agricultural censuses. We calculated the  
140 crop densities for a given municipality as the ratio of the crop specific UAA to the total area of the  
141 municipality.

142 We considered the total UAA (sum of permanent crops, arable land and pastures) and the UAA of the  
143 most common crops grown in France. Our main analysis focused on two permanent crops:  
144 “viticulture” and “arboriculture”, the locations of which are relatively stable over time, and 7 groups  
145 of non-permanent crops: “corn”, “straw cereals”, “oilseeds”, “potatoes”, “fresh vegetables,  
146 strawberries, melons”, “legumes: beans, peas, protein crops”, “industrial crops”, which may be  
147 rotated annually. In an additional analysis, we addressed 6 other specific non-permanent crops that  
148 were aggregated in the main analysis: “durum wheat”, “common wheat”, “barley”, “rapeseed”,  
149 “sunflower”, “beets”.

### 150 *Incidence data*

151 We included all the children registered in the French National Registry of Childhood Hematological  
152 Malignancies (RNHE) (Lacour et al., 2010) between 1990 and 2014, who were less than 15 years old,  
153 diagnosed with AL, and residing in mainland France at the time of diagnosis. There were 11,487 cases  
154 of AL. For each case, the registry provided the date of birth, date of diagnosis and address where the  
155 child was living at the time of diagnosis. Since we used three different agricultural censuses (1988,  
156 2000, 2010) to estimate crop densities over time, we subdivided the study period into three sub-  
157 periods, in order to obtain incidence data associated with the closest agricultural census: 1990-1994,  
158 1995-2004, 2005-2014.

#### 159 *Population data*

160 The annual estimates of the municipality populations, by year of age and gender, were provided by  
161 the French National Institute for Statistics and Economic Studies (INSEE) for the census years: 1990,  
162 1999, 2006-2014. For the inter-census years (1991-1998 and 2000-2005), the municipality  
163 populations were estimated using the annual estimates provided by INSEE for the 96 French  
164 mainland *départements*, and a linear interpolation of the proportion of children in the municipalities  
165 related to their *département* population between 1990 and 1999, and between 1999 and 2006. The  
166 national incidence rates of childhood AL, by year of age, gender and period, were used as reference  
167 rates to estimate the number of AL cases expected in each municipality under the hypothesis of  
168 homogeneous incidence rate over the whole country.

#### 169 *Potential confounder data*

170 In previous studies of the French data (Coste et al., 2017, 2015; Marquant et al., 2016), we evidenced  
171 an ecological association between the incidence of childhood ALL and 1) the residential UV radiation  
172 exposures of the municipalities, 2) the socio-economic statuses (SES) of the municipalities expressed  
173 as a deprivation index based on the 1999 census data. We considered these factors as potential  
174 confounders for the associations between ALL incidence and crop density index. Residential UV  
175 radiation exposure was defined as a dichotomous variable, with lower exposure for the  
176 municipalities with an annual average daily exposure less than or equal to 105.5 J/cm<sup>2</sup>. The median  
177 income of the households, proportion of blue-collar workers, proportion of unemployed and  
178 proportion of baccalaureate (high school diploma) holders were integrated in a principal component  
179 analysis. The first component, which explained 68% of the total variation, was used to define the  
180 French deprivation index "FDep99" (Rey et al., 2009).

#### 181 *Statistical analysis*

182 All analyses were implemented with SAS v9.4 software. Spearman coefficients were estimated to  
183 assess the correlations between the specific crops we selected for the study. The standardized  
184 incidence ratio (SIR) was used to characterize the spatial variations of incidence over the study  
185 period. Poisson regression models were fitted for all the analyses using the municipalities of  
186 residence at diagnosis for each sub-period as the basic statistical units (i.e. 106,536 "municipalities x  
187 period"). The corresponding expected numbers of cases were incorporated in the models as the  
188 offsets.

189 For each of the crop types (total UAA, 9 groups of crops, 6 subgroups of crops nested within some of  
190 the groups), two models were used to make statistical inferences about the association between  
191 municipality crop density and childhood AL incidence. In the first model, the crop density was  
192 qualitative and categorized by the following procedure: for the main analysis of total UAA density,  
193 the municipalities with a total UAA density less than 5% were grouped into the first category. Above  
194 that threshold, four quartiles with equal pediatric populations were defined based on the

195 distribution of total UAA in the municipalities. For the main analyses of a specific crop, the first  
 196 category was unchanged (total UAA density <5%). The second category consisted of the  
 197 municipalities with total UAA density greater than or equal to 5% but a density less than 5% for the  
 198 specific crop “c”. Above that threshold four quartile categories of equal pediatric population were  
 199 considered. After obtaining the crop density-based on geographic zoning, which consisted of 5 (total  
 200 UAA) or 6 (specific crop UAA) groups of municipalities, we fitted the first model:

$$201 \quad \ln(E(O_{kp})) = \ln(E_{kp}) + \sum_{h=1}^5 \beta_h \times X_h$$

202 In which  $E(O_{kp})$  is the expected value of the observed number of cases ( $O_{kp}$ ) in  $k^{\text{th}}$  group of  
 203 municipalities for period  $p$  (1990-1994, 1995-2004, 2005-2014);  $E_{kp}$  is the corresponding expected  
 204 number of cases;  $X_h$  is a dummy variable with a value of one if  $h=k$ , 0 otherwise; and  $\beta_h$  is the  
 205 corresponding regression coefficient. To test for heterogeneity between categories of agricultural  
 206 density, we conducted a likelihood ratio test comparing an empty model with the first model.

207 For the second model, a semi-quantitative discrete crop density variable was built:

$$208 \quad \ln(E(O_{kp})) = \ln(E_{kp}) + \alpha_0 + \beta \times Z_{kp}$$

209 in which  $Z_{kp}$  is the pediatric population-weighted average value of the crop density (total UAA or  
 210 crop-specific) in the  $k^{\text{th}}$  category for period  $p$ . In this model,  $e^{\beta}$  estimated the SIR variation for an  
 211 increase of 1 unit in  $Z_{kp}$  (referred to as SIRR, for standardized incidence rate ratio). In this study,  $Z_{kp}$   
 212 was calibrated to correspond to a 10% increase in the total area of the municipality. We used a  
 213 likelihood ratio test comparing both models to test for a departure from the log-linearity hypothesis.

214 While the null hypothesis to be tested was the absence of any association between AL incidence rate  
 215 and crop density, the alternative hypothesis of interest was that the association was positive.  
 216 Therefore, we calculated one-sided  $p$ -values for the second model. The Pearson chi-square test  
 217 based on model residuals was used to check that the models fitted the data well and to detect the  
 218 existence of any extra-Poisson variability in the observed numbers of cases. The main analyses were  
 219 conducted for all leukemia, the ALL and AML subgroups, and two age groups (0-6, 7-14 years old).

220 In a secondary analysis, we systematically adjusted our models with the ALL subtype for the  
 221 residential UV radiation level and the deprivation level of the municipalities. The temporal and  
 222 spatial stability of the main analysis results was assessed by examining their consistency across three  
 223 time periods (1990–1994, 1995–2004, 2005–2014), by excluding the Paris urban unit, where a lower  
 224 AL incidence rate had been observed in a previous study (Marquant et al., 2016), and then by  
 225 splitting the rest of the country into 4 large regions (North-West, South-West, North-East, South-  
 226 East). An additional qualitative model was fitted by splitting the crop density categories into two so  
 227 as to obtain “semi-quartiles”, in order to better describe the shape of the association observed in the  
 228 main analysis.

229 It was difficult to formulate precise credible alternative hypotheses for statistical power calculations  
 230 because of the lack of *a priori* information on the expected effect size of the associations, and the  
 231 heterogeneity of the selected crops in terms of frequency, range of spatial variation of their  
 232 densities, and agricultural practices. However, we calculated minimum detectable SIR ensuring a  
 233 power of 80 % for the one-sided test at the 5% level under the null hypothesis of no association  
 234 between crop density and AL. Those calculations were based on the expected number of cases in  
 235 each leukemia diagnosis group and calculated for the quartile of municipalities with the highest crop  
 236 density (S1). For AL and ALL, we were able to detect SIR varying from about 1.07, for total agriculture

237 area and cereals area, to about 1.30 for potatoes, arboriculture and fresh vegetables areas. The  
238 statistical power was more limited for AML, with minimum detectable SIRs varying from about 1.15  
239 for total agriculture area and cereals area to 1.94 for potatoes and arboriculture areas.

240

## 241 **Results**

242 Between 1990 and 2014, the French National Registry of Childhood Hematological Malignancies  
243 registered 11,487 cases of childhood AL diagnosed in France, 82,5% of which were ALL cases  
244 (n=9,488) and 15.6% AML (n=1,803). ALL was more frequent between 1 and 6 years old, whereas  
245 AML had a higher incidence rate among the youngest (less than 1 years old) (Fig 1).

246 Half of the French pediatric population lived in a municipality with 23.8% or more of its area used for  
247 agriculture (S2, Fig 2, S3). Some municipalities had a crop density above 100% because the UAA  
248 reported by the farmers was greater than the area of the municipalities where the farms were  
249 located. In the agricultural censuses, the UAA reported by a farmer was allocated to the municipality  
250 of the main building on the farm, which was not always the municipality where all the agricultural  
251 land was situated. There are few non-agricultural municipalities (UAA/area < 5%) in France. They  
252 consisted in the most urban areas (Paris region), the Landes forest in the South-West, and the  
253 mountainous regions (Vosges, Pyrénées, Alpes, Massif Central, Jura) (Fig 2, S3).

254 The distributions of the specific crop densities were different from each other. The median of the  
255 population-weighted crop density distribution was 3.6% for straw cereals, and 0.1% or less for the  
256 others (S2). The highest values of the 99th percentile of the population-weighted distribution were  
257 observed for straw cereals (57.9%) and viticulture (35.2%), reflecting a right-skewed distribution. This  
258 was the results of the organization of French agriculture, with specialized regions for most of the  
259 crops under study, even the most prevalent ones. Straw cereals and corn, for example, are common  
260 crops in the North and North-West, respectively (Fig 3, S4), but less common in other regions. Straw  
261 cereals density was highly correlated with oilseeds, legumes and industrial crops (Spearman  
262 coefficients  $r > 0.60$ ); potatoes density with fresh vegetables and industrial crops ( $r \geq 0.60$ ); and  
263 legumes density with industrial cultures ( $r = 0.57$ ) (S5). Viticulture was not associated with any of the  
264 other crops, except moderately with arboriculture ( $r = 0.22$ ) (S5). Overall, municipal densities of the  
265 different types of crops were highly correlated between censuses. However, the reported cultivation  
266 of potatoes, legumes and fresh vegetables were less stable over time (S6).

267 Poisson regression showed no evidence of an association between total agricultural density and the  
268 incidence of childhood AL (SIRR = 1.00; 95%CI [0.99-1.01], for a 10% increase in density) or its  
269 subgroups (Table 1).

270 For permanent crops, we observed a positive association between viticulture density and incidence  
271 of AL (Table 2). This association was slightly stronger for ALL (SIRR = 1.04; 95%CI [1.01-1.07] for a 10%  
272 increase in viticulture density), with increased SIRs in the two categories with the highest viticulture  
273 densities (SIR = 1.12; 95%CI [0.97-1.29] and SIR = 1.17; 95%CI [1.01-1.35], respectively, Table 2). No  
274 log-linear trend was observed for AML (SIRR = 0.99 (95%CI [0.92-1.07])). For arboriculture, no trend  
275 and no pattern were observed for any type of childhood leukemia, but the numbers of cases were  
276 more limited, in particular for the AML subgroup (Table 2).

277 For the cereals group, heterogeneity between the SIRs of the different categories of corn density was  
278 detected for all AL and ALL, and the log-linearity of the association was rejected (S7), but the results  
279 did not suggest an increase in incidence rate with increasing corn density (Table 3, S7). No

280 association was observed for AML (Table 3, S7). The log-linear regression models showed SIRR  
281 between straw cereals density and AL, ALL and AML that were almost equal to 1 (Table 3, S7).  
282 Additional analyses on specific straw cereals (common wheat, durum wheat and barley) did not show  
283 any evidence of an association with the AL incidence rate (S8).

284 A positive log-linear association was suggested for oilseeds density and ALL (SIRR = 1.04; 95%CI [0.99-  
285 1.09], Table 4), but the categorical model did not show a clear pattern (S7), and there was no  
286 evidence of an increased SIR in the category with the highest oilseed densities. Heterogeneity of the  
287 SIRs in the categorical model was observed for AML (S7), with a lower SIR in the intermediate oilseed  
288 density category, but no evidence of a positive trend (Table 3, S7). Additional analyses of specific  
289 oilseeds (rapeseed, sunflower), did not show any association with the AL incidence rate (S8).

290 For vegetables, no evidence of a log-linear association between potatoes/fresh vegetables,  
291 strawberries or melons and any group of AL was found, with no pattern observed in the categorical  
292 models (Table 3, S7). For legumes (beans, peas, protein crops), a positive log-linear association was  
293 observed for all AL (SIRR = 1.09; 95%CI [0.98-1.22]) for a 10% increase in legume density (Table  
294 3). However the categorical models showed no clear pattern (S7). Analysis of AML showed a positive  
295 trend, but with very wide confidence intervals, and based on a limited number of cases (Table 3, S7).

296 Analysis of industrial crops showed no evidence of an association with any subtype of AL (Table 3,  
297 S7). An additional analysis of industrial beets did not detect any heterogeneity of the SIRs or any  
298 clear log-linear trend (S8).

299 The distribution of the French deprivation index in the pediatric population by crop density category  
300 showed a moderate positive trend with all the specific crop densities of the municipalities except for  
301 viticulture, oilseeds, fresh vegetables and legumes (S9). Indeed, for most crop types, the proportion  
302 of children living in the most deprived municipalities was higher (about 25-30%) in the highest crop  
303 density categories than in the other categories. Additionally, the residential exposure to UV radiation  
304 in the pediatric population was not homogeneous by crop density category. Strong positive trends  
305 between residential exposure to UV radiation  $> 105.5 \text{ J/cm}^2$  and viticulture and arboriculture  
306 densities were observed. Strong negative trends for potatoes, legumes and industrial crops  
307 densities were observed (S9). Additional analyses of the association between crop densities and ALL  
308 incidence with systematic adjustment for both residential UV radiation and the French deprivation  
309 index were possible for all cultures except potatoes, legumes and industrial crops. For the latter  
310 three crops, which were rarely grown in the municipalities with higher UV radiation levels, we  
311 considered only municipalities with UV radiation  $\leq 105.5 \text{ J/cm}^2$  and adjustment on the deprivation  
312 index was conducted (Table 4). After adjustment, we found no change in the associations observed in  
313 the main analysis except for viticulture, for which there was a slight decrease in the log-linear slope  
314 (SIRR = 1.02; 95%CI [0.99-1.06] for a 10% increase in density); and legumes, for which there was a  
315 slight increase in the slope (SIRR = 1.12; 95%CI [0.99-1.27] for a 10% increase in density).  
316 Nevertheless, for legumes, the SIRs in the qualitative model adjusted for the French deprivation  
317 index did not differ from those in the main analysis (data not shown). Residential exposure to UV  
318 radiation was strongly correlated with viticulture density ( $r = 0.44$ ), and a supplementary analysis  
319 with stratification on the two categories of UV radiation (UV  $> 105.5 \text{ J/cm}^2$  versus UV  $\leq 105.5 \text{ J/cm}^2$ )  
320 showed a weaker association with ALL in the highest category of UV radiation exposure (SIRR = 1.02;  
321 95%CI [0.98-1.06] for a 10% increase in density) compared to the results of the main analysis. The  
322 slope in the lowest category of exposure was similar to that of the main analysis (SIRR=1.04; 95%CI  
323 [0.97-1.10] for a 10% increase in density) (S10). However, no significant interaction was detected ( $p =$   
324 0.60).

325 The associations between the incidences of AL and ALL and viticulture density were unchanged when  
326 the Paris region was excluded from the analysis (Table 5). When the country was subdivided into four  
327 large regions excluding Paris (Table 5), the log-linear model showed somewhat positive trends for AL  
328 and ALL by viticulture density in the North-East, North-West and South-East. There was no trend for  
329 the South-West, and no significant interaction was observed ( $p = 0.44$  for AL and  $p = 0.61$  for ALL).  
330 Stratification by two age groups (Table 5) did not modify the associations between viticulture density  
331 and AL and ALL; the log-linear trend was slightly stronger for ALL for children aged 7 to 14 years,  
332 compared to the younger children (Table 5). The association remained stable for both the AL and ALL  
333 groups when stratified by three periods (Table 5). Given that viticulture was not strongly correlated  
334 with any other specific crop, we did not adjust on other crop densities. We subdivided the viticulture  
335 density quartiles into semi-quartiles, and observed no change in the log-linear trend, but a stronger  
336 SIR in the highest exposure category (municipalities with a viticulture density greater than 38%) for  
337 AL (SIR = 1.24; 95%CI [1.03-1.48]) and ALL (SIR = 1.25; 95%CI [1.02-1.52]) (S11).

### 338 Discussion

339 We found a moderate positive log-linear trend for the viticulture densities of the French  
340 municipalities and the incidence rate of childhood AL over the period 1990-2014, with a 3% increase  
341 in SIR for a 10% increase in viticulture density (SIRR = 1.03; 95%CI [1.00-1.06]). In the categorical  
342 model, the highest category of exposure had an SIR of 1.16; 95%CI [1.02-1.32]. In that category, the  
343 number of cases observed over 25 consecutive years ( $O = 226$ ) was greater, by 31.5, than the  
344 corresponding expected number of cases ( $E = 194.5$ ) based on national age-gender specific incidence  
345 rates. However, no evidence of any other positive associations between AL incidence and total  
346 agricultural density or any of the specific crop densities considered was observed. When considering  
347 the main subgroups of AL and two age groups, the association with viticulture remained for ALL, but  
348 not for AML, and was stable for the two age groups. A secondary analysis of ALL subgroups with  
349 adjustment on two potential confounders, residential UV radiation and SES of the municipality,  
350 showed a small decrease in the association of ALL with viticulture density, because of a strong  
351 positive correlation between UV radiation and viticulture density, and an increase in the association  
352 with legumes. Stratification on periods and geographic regions of the association between viticulture  
353 density and incidence of AL and ALL showed no heterogeneity of the log-linear slope between the  
354 strata. Analysis of the semi-quartiles showed a stronger association in the highest category of  
355 viticulture density.

356 This is the first study of the association between municipal agricultural densities and the incidence of  
357 childhood leukemia in France. Few studies have investigated the role of environmental exposure to  
358 agricultural pesticides and the risk of childhood leukemia, because of the difficulty of combining  
359 precise exposures and a large sample size in order to detect small effects. The previous studies were  
360 mainly conducted in the United States (Booth et al., 2015; Carozza et al., 2008; Reynolds et al.,  
361 2005b, 2005a, 2002; Rull et al., 2009; Thompson et al., 2008; Walker et al., 2007) and based on  
362 different designs and exposure assessment methods. Most of the studies analyzed the association  
363 between AL and either total agricultural land density (or proximity) or specific crop densities (or  
364 proximities). The results with total agriculture land density (or proximity) are inconsistent (Booth et  
365 al., 2015; Carozza et al., 2008; Gómez-Barroso et al., 2016; Walker et al., 2007). We did not find any  
366 evidence of an association between total UAA density and the incidence of AL. The area considered  
367 consisted in arable land, permanent cropland and permanent pastures. The quantities and types of  
368 pesticides spread on those land categories are very heterogeneous and, in addition, permanent  
369 pastures may be a proxy for contact with farm animals, an exposure that was inversely associated  
370 with childhood leukemia in some recent studies (Orsi et al., 2018). Moreover, total agricultural land

371 density may not be a pertinent indicator for the assessment of exposure to agricultural pesticides  
372 because of the wide range of agricultural practices covered.

373 The analyses of specific crops showed a moderate log-linear association between AL incidence rate  
374 and viticulture density. Two large US ecological studies of numerous states, based on agricultural  
375 census data at county level, found positive associations between AL and specific crops such as oats  
376 (Booth et al., 2015; Carozza et al., 2008), corn (Carozza et al., 2008), soybean (Carozza et al., 2008),  
377 sugar beets (Booth et al., 2015), and dry beans (Booth et al., 2015). Viticulture was not considered in  
378 either of the studies. A Spanish population-based case-control study based on land use maps showed  
379 a moderate positive trend for leukemia and proximity of irrigated and heterogeneous cropland, but  
380 no association with vineyards or olive groves (Gómez-Barroso et al., 2016). However, the study was  
381 based on a smaller number of subjects than in our study, and the controls and cases had different  
382 exposure time windows (time of diagnosis for the cases, time of birth for the controls). An Italian  
383 case-control study conducted in two agricultural regions and based on land use maps and a very  
384 limited number of exposed subjects found a positive but non-significant association with arable land  
385 (Malagoli et al., 2016). California is the only state for which comprehensive data on pesticides spread  
386 on croplands since the 1990s are available. Epidemiological studies based on the Californian  
387 Pesticides Use Reporting database and investigating the role of environmental exposure to  
388 agricultural pesticides in the risk of childhood leukemia found moderate associations with some  
389 specific compounds such as metam sodium, propargite and dicofol but there were no clear patterns  
390 (Reynolds et al., 2005b, 2005a, 2002; Rull et al., 2009). Although now prohibited, those three  
391 compounds were used in France during our study period, but their use was not restricted to  
392 viticulture only. However, it is very difficult to compare our results with those of the Californian or  
393 US-based studies because the crops grown, their proportions, and agricultural practices are different  
394 from those in France (S12). In addition, the majority of the pesticides used in France are fungicides  
395 (INSERM, 2013), and they are mainly used for vineyards, while the majority used in the USA are  
396 herbicides (US EPA, 2015).

397 One of the challenges of epidemiological studies of the health effects related to exposure to  
398 agricultural pesticides is to accurately assess the exposure. Because there is no database for the use  
399 of pesticides on cropland in France, we used the agricultural crop density as a proxy for agricultural  
400 pesticide use. Agricultural census data are advantageous in that they are exhaustive for the entire  
401 country, available for the various study time points and provide a detailed list of crops on the  
402 municipal scale. This enabled our results to be broadly linked with national data on agricultural  
403 practices. In 2000, viticulture accounted for less than 4% of the total UAA and 20% of the pesticides,  
404 mainly fungicides, sold (INRA, 2011). However, even though the agricultural census affords data on  
405 the types of crop grown in the census year, crop rotations are not taken into account. Annual  
406 rotations on the same land may be a reason why several crop density indicators were correlated. In  
407 consequence, we probably had less power to detect an association with rotated crops than with  
408 permanent crops. In addition, even if the three censuses allowed us to consider temporal variations,  
409 local changes occurring between the censuses could not be accounted for.

410 Another limitation of the proxy is that farmers report their UAA for the municipality where the farm  
411 is located and not for the municipalities where the crops are located. This may introduce non-  
412 differential misclassification of the crop density in the municipalities. The misclassification may either  
413 over- or underestimate the observed effects (Jurek et al., 2005). Nevertheless, when the farmland is  
414 not situated in the municipality of the farm, it is likely to be located in a neighboring municipality as  
415 there is a clear regional structure to the type of crops grown. The agricultural crop density of the

416 municipality is therefore likely to be an accurate reflection of the crop density in the area where the  
417 children lived.

418 This is one of the largest studies on this issue, with 25 years of observations and 11,847 AL cases,  
419 based on a national registry of childhood cancers with a high degree of completeness, and exhaustive  
420 agricultural census data for the various time points. However, the analysis addresses a rare disease  
421 and exposure. The analyses of leukemia subgroups were limited by the number of subjects for AML.

422 We conducted several statistical tests in this study, but we did not take them into formal account.  
423 Given the descriptive nature of this investigation, we focused not only on statistical significance but  
424 also on the quantitative values of the SIR and SIRR observed to describe our results. From this point  
425 of view, the associations observed between viticulture and AL and ALL were consistent in the log-  
426 linear and categorical models, and the results were quite stable after several sensitivity analyses.

427 We did not incorporate an autocorrelated structure in our models, although the crop densities of the  
428 municipalities were highly autocorrelated, because our outcome was not spatially autocorrelated in  
429 all of the studies conducted in France (Goujon et al., 2018).

430 Previous French studies have found associations between ALL and residential UV radiation exposure  
431 (Coste et al., 2017, 2015) and SES of the residence area (Marquant et al., 2016). We therefore took  
432 those two factors into account in a secondary analysis. Adjusting on SES did not materially modify the  
433 association of ALL with viticulture or lack of association of ALL with any of the other crops, except for  
434 legumes. As expected, ambient UV radiation was spatially positively or negatively strongly associated  
435 with specific crops throughout France. There was a strong association between ambient UV radiation  
436 and vineyard density; the adjusted log-linear association between ALL and vineyards density was  
437 slightly less than in the main analysis. After stratification, we still found a positive association of the  
438 same magnitude as in the crude analysis in the stratum with the lowest exposure to UV radiation,  
439 even though the confidence interval was somewhat wider. However, adjusting on ambient UV  
440 radiation exposure did not modify the observed lack of association between ALL and the other crops.

441 We were unable to adjust on other potential environmental confounders such as traffic-related air  
442 pollution, which has been found to be associated with the risk of childhood leukemia in numerous  
443 studies and may be inversely associated with crop density. In addition, other sources of pesticide  
444 exposure, such as domestic or parental exposure, were not considered and may modify the  
445 association. We cannot either exclude that the association observed could reflect at least in part an  
446 association between AL and parental occupational exposure, as our ecological exposure metric do  
447 not allow to disentangle environmental, parental and parent mediated exposures.

#### 448 **Conclusion**

449 This is the first French study to analyze the association between the incidence of childhood leukemia  
450 and crop density, a proxy of environmental exposure to agricultural pesticides. The study was based  
451 on the high-quality data of the French National Registry of Childhood Hematological Malignancies  
452 and the exhaustive agricultural census data at three time points on the municipality scale. We did not  
453 find any clear association with specific crops, except a moderate positive association between  
454 viticulture density and AL incidence rate. In France, vineyards undergo intense pesticide treatments,  
455 mainly with fungicides. However, fungicides or intense treatments are used in other agricultural  
456 sectors such as arboriculture. In addition, the results may reflect an effect of factors other than  
457 pesticide treatment that may have a spatial distribution similar to that of vineyards. This study was  
458 part of a wider project that will include a complementary study based on a record-based case-control  
459 study with precise geocoding of children's addresses and a combination of different land use data.

460 The study will have an observation period somewhat shorter than that of the present study but with  
461 much more precise localization of the croplands. It will also be possible to adjust for other  
462 environmental risk factors. Further studies at the individual level and with better exposure  
463 assessment are needed to clarify the role of agricultural pesticides in the etiology of childhood  
464 leukemia. Improving exposure assessment implies deploying an effective surveillance system for the  
465 pesticides spread on fields in order to identify the specific compounds utilized.

**466 Authors contributions**

467 AC, SG, DH, JC designed the study. AC extracted and prepared the agricultural census data from the  
468 CASD platform and performed the statistical analyses. SG extracted and prepared the RNHE and  
469 INSEE data and contributed to the statistical analysis. LF was involved in data extraction of the RNHE.  
470 SG, DH, JC supervised the analyses. AC, SG, JC, DH interpreted the results. AC drafted the initial  
471 report. All coauthors revised the report and approved the final version. AC, SG, DH, JC are  
472 responsible for the overall content as the guarantors of this paper.

473

**474 Acknowledgments:**

475 The study was supported by the 'Institut National du Cancer', 'Santé Publique France', 'Agence  
476 Nationale de Sécurité Sanitaire de l'Alimentation, de l'Environnement et du travail' (ANSES), 'Agence  
477 Nationale de la Recherche, Investment for the future' (ANR-10-COHO-0009 grant for HOPE-EPI).  
478 Astrid Coste also received funding from the Fondation pour la Recherche Médicale  
479 (FDT20160435122) for her PhD. This work is also supported by a public grant overseen by the French  
480 National Research Agency (ANR) as part of the « Investissements d'avenir » program (reference:  
481 ANR-10-EQPX-17 – Centre d'accès sécurisé aux données – CASD). The authors are particularly  
482 grateful to all the RNHE research assistants who collected the case data and the pediatric oncology  
483 teams for their help in data collection. We would also like to thank the Environment and Health  
484 Directorate of Santé Publique France, and particularly Joëlle Le Moal and Perrine De Crouy-Chanel,  
485 who helped us understand and collect the agricultural census data.

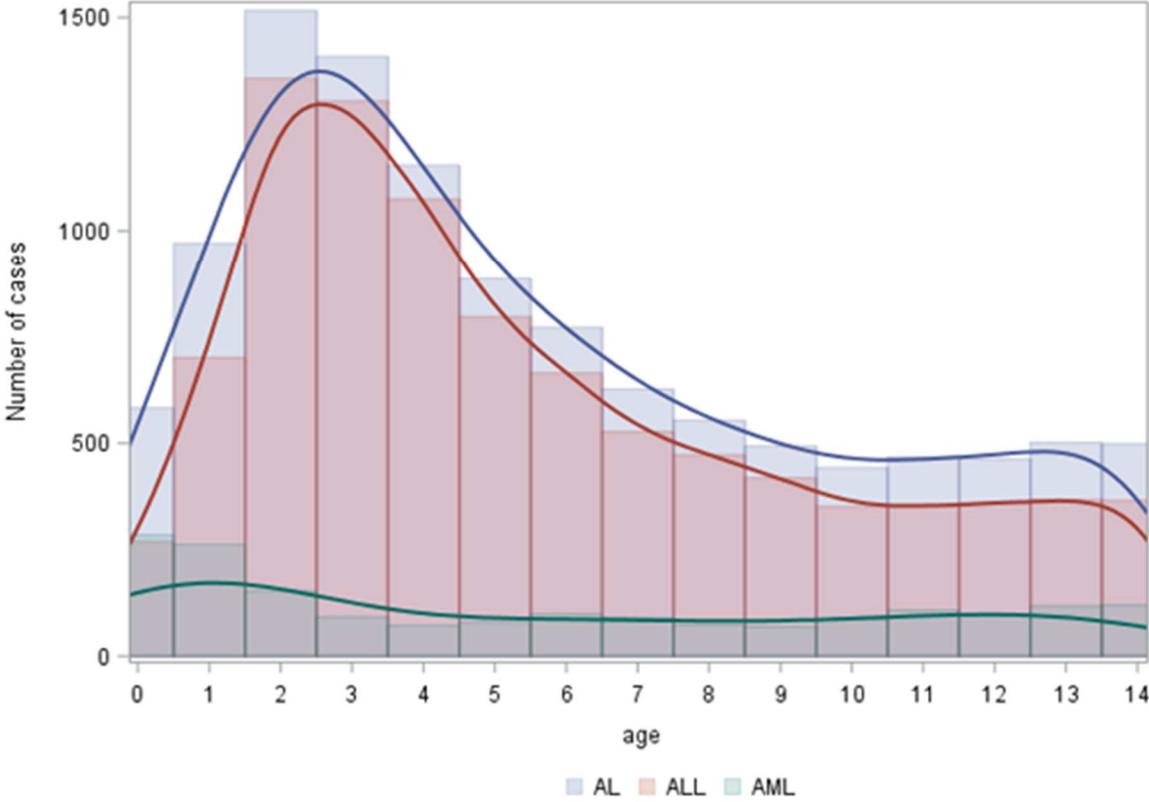
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Figure 1 Distribution of childhood acute leukemia (AL) cases by age and main types, mainland France, 1990-2014



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

Figure 2 Density of agriculture in the municipalities of France – Agricultural census 2000

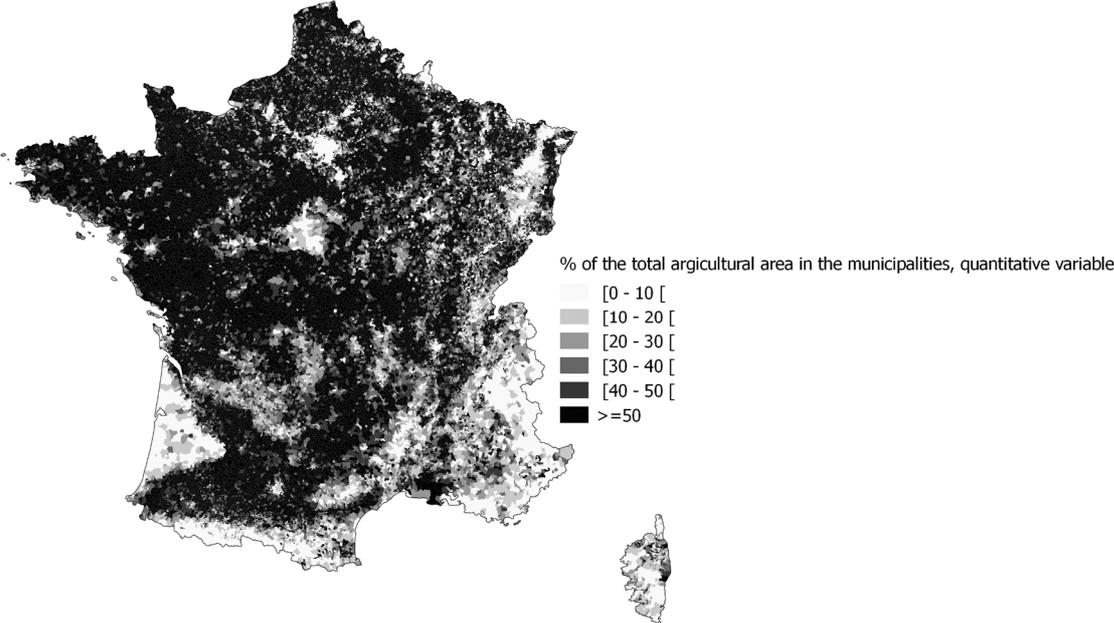


Figure 3 Density of the specific crops studied in the municipalities of France – Agricultural census 2000

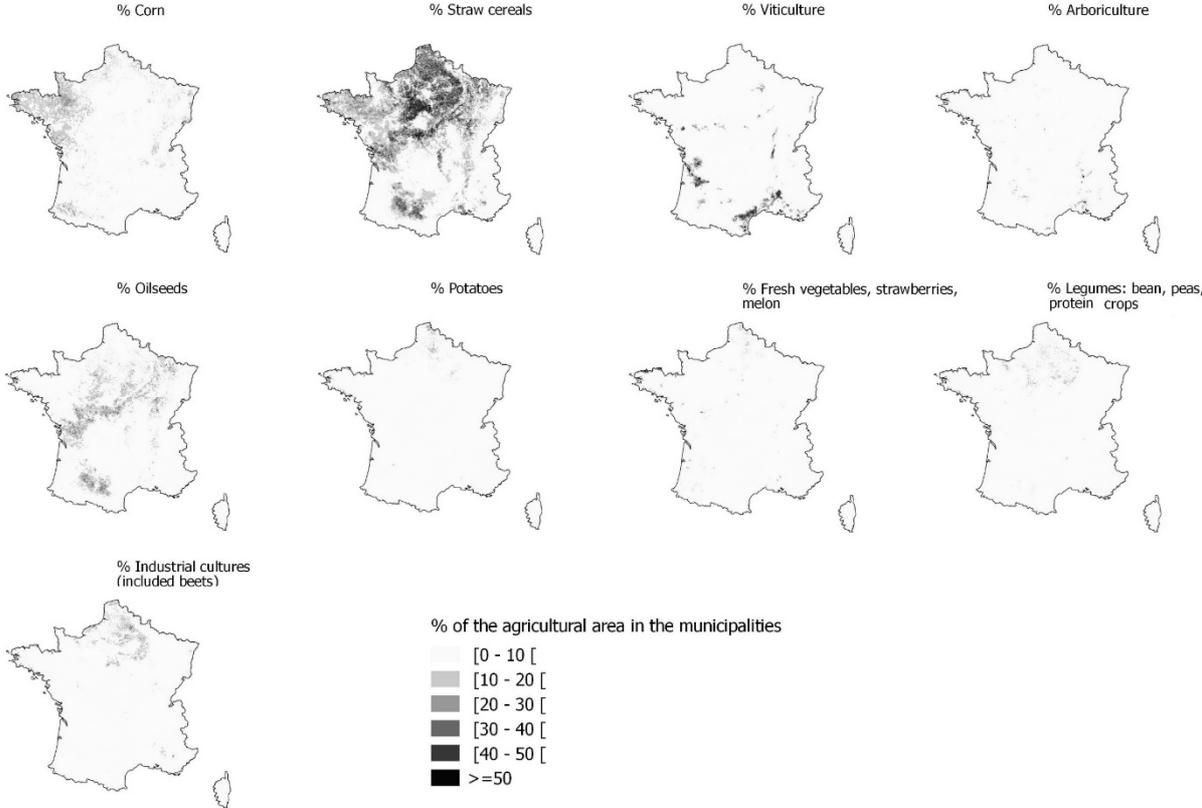




Table 2 Association between the incidence rate of childhood leukemia and permanent crop density<sup>1</sup> in the French municipalities, 1990-2014

	Average density <sup>2</sup>	Number of units <sup>3</sup>	PY/year	Acute leukemia					Acute lymphoblastic leukemia					Acute myeloid leukemia					
				O	E	SIR	CI	P <sup>4</sup>	O	E	SIR	CI	P <sup>4</sup>	O	E	SIR	CI	P <sup>4</sup>	
<b>Viticulture</b>																			
% UAA [0-5[	0.1	6,081	3,241,048	3,315	3,336.2	0.99	0.96-1.03												
% UAA≥5 & % vit. <5	0.2	92,487	7,333,552	7,365	7,373.6	1.00	0.98-1.02												
[5-9.9[	7.2	2,087	193,902	198	193.5	1.02	0.89-1.18												
[9.9-15.9[	12.5	1,565	193,855	179	195.1	0.92	0.79-1.06												
[15.9-25[	19.7	1,577	193,241	204	194.0	1.05	0.92-1.21												
>=25	43.1	2,739	194,142	226	194.5	1.16	1.02-1.32												
Total		106,536	11,349,740	11,487	11,487.0														
Test of heterogeneity																			0.42
Test of departure from log-linearity																			0.30
SIRR for Δx=10% <sup>5</sup>						1.03	1.00-1.06	0.02			1.04	1.01-1.07	0.01			0.99	0.92-1.07	0.59	
<b>Arboriculture</b>																			
% UAA [0-5[	0.1	6,081	3,241,048	3,315	3,336.2	0.99	0.96-1.03												
% UAA≥5 & % arb. <5	0.3	98,337	7,827,851	7,906	7,869.1	1.00	0.98-1.03												
[5-6.4[	5.7	586	71,194	66	71.2	0.93	0.73-1.18												
[6.4-9.3[	7.6	619	69,322	60	69.8	0.86	0.67-1.11												
[9.3-13.2[	11.2	397	70,126	70	70.4	0.99	0.79-1.26												
>=13.2	23.4	516	70,199	70	70.3	1.00	0.79-1.26												
Total		106,536	11,349,740	11,487	11,487.0														
Test of heterogeneity																			0.49
Test of departure from log-linearity																			0.52
SIRR for Δx=10% <sup>5</sup>						0.98	0.90-1.07	0.68			1.01	0.92-1.11	0.43			0.88	0.69-1.12	0.85	

O: Observed number of cases; E: expected number of cases under the hypothesis of a homogeneous incidence rate by period, for each age x sex category throughout mainland France; SIR: Standardized Incidence Ratio = O/E; CI: 95% Confidence Interval; UAA: total utilized agricultural area

<sup>1</sup> The crop density in a municipality is defined as the ratio of the area used for the crop over the total area of this municipality (based on national agricultural census data);

<sup>2</sup> Average crop density weighted by the pediatric population at risk living in the municipalities of the category;

<sup>3</sup> Number of statistical units, defined as "municipalities x period" in each category;

<sup>4</sup> p-value of the tests (chi-square test of heterogeneity between categories of agricultural density, departure from log-linearity test, one-sided test of the regression coefficient in the semi-

quantitative model (H<sub>0</sub>: slope = 0 vs H<sub>1</sub>: slope >0);

<sup>5</sup> SIRR (for Δx=10%) = Relative Standardized Incidence Ratio with 95% confidence limits: Multiplicative variation of the SIR for a 10% increase in the crop density derived from a log-linear

Poisson regression model adjusted to the observations (the outcome is the observed number of cases by municipality x period; the offset is the expected number of cases; and the

independent covariate is the crop density).

Table 3 Association between the incidence rate of childhood leukemia and non-permanent crop density<sup>1</sup> in the French municipalities, 1990-2014

Crop density	Average density <sup>2</sup>	% population in a municipality with crop density $\geq$ Q3 <sup>3</sup>	Acute leukemia (n=11,487)			Acute lymphoblastic leukemia (n=9,488)			Acute myeloid leukemia (n=1,803)		
			SIRR <sup>4</sup>	CI	p <sup>5</sup>	SIRR <sup>4</sup>	CI	p <sup>5</sup>	SIRR <sup>4</sup>	CI	p <sup>5</sup>
<b>Corn</b>	12.3	4.6		-			-		0.98	0.90-1.08	0.65
<b>Straw cereals</b>	19.3	11.3	1.00	0.98-1.01	0.47	1.00	0.98-1.02	0.48	1.00	0.96-1.03	0.43
<b>Oilseeds</b>	11.2	3.5	1.03	0.98-1.07	0.13	1.04	0.99-1.09	0.07		-	
<b>Potatoes</b>	10.3	0.5	0.98	0.87-1.10	0.65	0.94	0.83-1.07	0.82	1.12	0.86-1.47	0.20
<b>Fresh vegetables</b>	10.5	0.7	1.01	0.92-1.11	0.43	0.99	0.88-1.10	0.60	1.06	0.84-1.34	0.30
<b>Legumes</b>	8.5	0.8	1.09	0.98-1.22	0.06	1.07	0.95-1.21	0.13	1.17	0.90-1.53	0.12
<b>Industrial crops</b>	11.2	1.6	1.00	0.94-1.06	0.49	1.00	0.93-1.07	0.48	1.01	0.87-1.18	0.44

CI: 95% Confidence Interval

<sup>1</sup> The crop density in a municipality is defined as the ratio of the area used for the crop over the total area of this municipality (based on national agricultural census data);

<sup>2</sup> Average of the specific crop densities in the municipalities of France with a density  $\geq$  5%, weighted by the pediatric population at risk living in the municipalities.

<sup>3</sup> % pediatric population living in a municipality with a specific crop density greater than or equal to the limit value of the third quartile of the crop density distribution in the qualitative model

<sup>4</sup> SIRR = Relative Standardized Incidence Ratio with 95% confidence limits: multiplicative variation of the SIR for a 10% increase in the crop density derived from a log-linear Poisson regression model where the outcome is the observed number of cases by municipality x period; the offset is the expected number of cases; and the independent covariate is the crop density. The SIRR is shown when log-linearity is not rejected by the test of departure from log-linearity.

<sup>5</sup> p-value of the one-sided test of the regression coefficient in the semi-quantitative model ( $H_0$ : slope = 0 vs  $H_1$ : slope >0).

Table 4 Association between crop densities and childhood acute lymphoblastic leukemia incidence rate in the French municipalities, jointly adjusted for UV radiation and deprivation index (FDep99), 1990-2014 (9,422 cases of ALL, because of some missing values for Fdep99)

Semi-quantitative log-linear model adjusted on potential confounders <sup>1</sup>	SIRR <sup>2</sup>	CI	p <sup>3</sup>
Total agricultural density ( $\Delta x = 10\%$ increase in total UAA density)	1.00	0.997-1.01	0.16
UV >105.5 J/cm <sup>2</sup> versus UV ≤105.5 J/cm <sup>2</sup>	1.08	1.04-1.13	0.0003
FDep99 most deprived quintile versus Less deprived	0.92	0.88-0.97	0.003
Viticulture density ( $\Delta x = 10\%$ increase in viticulture density)	1.02	0.99-1.06	0.07
UV radiation >105.5 J/cm <sup>2</sup> versus UV radiation ≤105.5 J/cm <sup>2</sup>	1.07	1.03-1.12	0.002
FDep99 most deprived quintile versus Less deprived	0.93	0.88-0.97	0.003
Arboriculture density ( $\Delta x = 10\%$ increase in arboriculture density)	0.98	0.89-1.08	0.66
UV radiation >105.5 J/cm <sup>2</sup> versus UV radiation ≤105.5 J/cm <sup>2</sup>	1.09	1.04-1.14	0.0003
FDep99 most deprived quintile versus Less deprived	0.93	0.88-0.98	0.004
Straw cereals density ( $\Delta x = 10\%$ increase in cereal density)	1.01	0.99-1.03	0.10
UV radiation >105.5 J/cm <sup>2</sup> versus UV radiation ≤105.5 J/cm <sup>2</sup>	1.09	1.04-1.14	0.0002
FDep99 most deprived quintile versus Less deprived	0.92	0.88-0.97	0.003
Oilseeds density ( $\Delta x = 10\%$ increase in oilseed density)	1.04	0.99-1.09	0.05
UV radiation >105.5 J/cm <sup>2</sup> versus UV radiation ≤105.5 J/cm <sup>2</sup>	1.08	1.04-1.13	0.0003
FDep99 most deprived quintile versus Less deprived	0.92	0.88-0.97	0.003
Potatoes density <sup>4</sup> ( $\Delta x = 10\%$ increase in potatoes density)	0.96	0.84-1.10	0.73
FDep99 most deprived quintile versus Less deprived	0.93	0.88-0.99	0.02
Fresh vegetables density ( $\Delta x = 10\%$ increase in fresh vegetables density)	0.99	0.89-1.10	0.58
UV radiation >105.5 J/cm <sup>2</sup> versus UV radiation ≤105.5 J/cm <sup>2</sup>	1.08	1.04-1.13	0.0003
FDep99 most deprived quintile versus Less deprived	0.93	0.88-0.98	0.004
Legumes density <sup>4</sup> ( $\Delta x = 10\%$ increase in legumes density)	1.12	0.99-1.27	0.04
FDep99 most deprived quintile versus Less deprived	0.93	0.87-0.98	0.01
Industrial crops density <sup>4</sup> ( $\Delta x = 10\%$ increase in industrial crops density)	1.04	0.97-1.11	0.16
FDep99 most deprived quintile versus Less deprived	0.92	0.88-0.97	0.003

CI: 95% Confidence Interval

<sup>1</sup>Results for corn not shown because log-linearity was rejected in the main analysis in table 4

<sup>2</sup>SIRR = Relative Standardized Incidence Ratio with 95% confidence limits

<sup>3</sup> p-value of the tests: for crop density, one-sided test of the adjusted regression coefficient in the semi-quantitative model, with H<sub>0</sub>: slope = 0 vs H<sub>1</sub> slope >0; two-sided test for the adjusted regression coefficients for UV radiation and the deprivation index, included as binary covariates in the model

<sup>4</sup> Restriction of the sample to the municipalities where UV radiation ≤ 105.5 J/cm<sup>2</sup>, because the crops were rarely grown in the municipalities where UV radiation > 105.5 J/cm<sup>2</sup>

Table 5 Sensitivity analyses on the association between viticulture density and acute leukemia

Variable	Strata	Average density <sup>1</sup>	% population in a municipality $\geq$ 25% viticulture Density <sup>2</sup>	Acute leukemia					Acute lymphoblastic leukemia				
				O	E	SIRR <sup>3</sup>	CI	P <sup>4</sup>	O	E	SIRR <sup>3</sup>	CI	P <sup>4</sup>
Geographic area	Paris excluded	20.6	2.1	9572	9572	1.03	1.00-1.06	0.04	7943	7943	1.03	1.00-1.06	0.02
	North-West of France	15.7	0.5	2293	2293	1.08	0.97-1.19	0.08	1918	1918	1.08	0.97-1.21	0.09
	North-East of France	20.9	0.6	2811	2811	1.03	0.98-1.07	0.13	2302	2302	1.02	0.93-1.11	0.34
	South-East of France	22.3	5.9	2752	2752	1.01	0.98-1.04	0.27	2752	2752	1.02	0.98-1.06	0.15
	South-West of France	19.9	3.5	1432	1432	1.00	0.94-1.07	0.50	1208	1208	1.01	0.95-1.09	0.35
Age	0-6 years old	20.6	1.7	7411	7411	1.03	0.99-1.06	0.07	6257	6257	1.03	0.99-1.07	0.09
	7-14 years old	20.6	1.7	4076	4076	1.03	0.99-1.08	0.07	3231	3231	1.06	1.00-1.11	0.02
Period	1990-1994	21.1	2.0	2225	2225	1.01	0.95-1.08	0.37	1831	1831	1.03	0.97-1.10	0.16
	1995-2004	20.9	1.7	4508	4508	1.05	1.01-1.10	0.01	3686	3686	1.05	1.01-1.10	0.02
	2005-2014	20.1	1.6	4754	4754	1.02	0.97-1.07	0.24	3971	3971	1.02	0.97-1.07	0.20

O: Observed number of cases; E: expected number of cases; CI: 95% Confidence Interval

<sup>1</sup> Average of the viticulture density in each stratum, weighted by the pediatric population at risk living in the municipalities of the category

<sup>2</sup> % pediatric population living in a municipality with 25% or more viticulture density (25% = limit value of the third quartile of the viticulture density distribution in the qualitative model)

<sup>3</sup> SIRR (for  $\Delta x = 10\%$ ) = Relative Standardized Incidence Ratio with 95% confidence limits: Multiplicative variation of the SIR for a 10% increase in the crop density derived from a log-linear Poisson regression model, where the outcome is the observed number of cases by municipality x period; the offset is the expected number of cases; and the independent covariate is the crop density.

<sup>4</sup> p-value of the tests (chi-square test of heterogeneity between categories of agricultural density, departure from log-linearity test, one-sided test of the regression coefficient in the semi-quantitative model ( $H_0$ : slope = 0 vs  $H_1$ : slope >0))