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Childhood leukemia and residential proximity to industrial and urban sites

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ABSTRACT

Background: Few risk factors for the childhood leukemia are well established. While a small fraction of cases of childhood leukemia might be partially attributable to some diseases or ionizing radiation exposure, the role of industrial and urban pollution also needs to be assessed.
Objectives: To ascertain the possible effect of residential proximity to both industrial and urban areas on childhood leukemia, taking into account industrial groups and toxic substances released.
Methods: We conducted a population-based case–control study of childhood leukemia in Spain, covering 638 incident cases gathered from the Spanish Registry of Childhood Tumors and for those Autonomous Regions with 100% coverage (period 1990-2011), and 13,188 controls, individually matched by year of birth, sex, and autonomous region of residence. Distances were computed from the respective subject's residences to the 1068 industries and the 157 urban areas with $\geq$ 10,000 inhabitants, located in the study area. Using logistic regression, odds ratios (ORs) and 95% confidence intervals (95%CIs) for categories of distance to industrial and urban pollution sources were calculated, with adjustment for matching variables.
Results: Excess risk of childhood leukemia was observed for children living near ($\leq$ 2.5 km) industries (OR = 1.31; 95%CI = 1.03–1.67) – particularly glass and mineral fibers (OR = 2.42; 95%CI = 1.49–3.92), surface treatment using organic solvents (OR = 1.87; 95%CI = 1.24–2.83), galvanization (OR = 1.86; 95%CI = 1.07–3.21), production and processing of metals (OR = 1.69; 95%CI = 1.22–2.34), and surface treatment of metals (OR = 1.62; 95%CI = 1.22–2.15) – , and urban areas (OR = 1.36; 95%CI = 1.02–1.80).
Conclusions: Our study furnishes some evidence that living in the proximity of industrial and urban sites may be a risk factor for childhood leukemia.

1. Introduction

Childhood cancer is the leading cause of disease-related death in childhood affecting both sexes worldwide and, therefore, is an important concern for public health, medical care, and society (Peris-Bonet et al., 2010).

The main group is leukemia, with almost a third of all childhood cancers (Peris-Bonet et al., 2010). Insofar as the etiology of

Abbreviations: IPPC, Integrated Pollution Prevention and Control; E-PRTR, European Pollutant Release and Transfer Register; RETI-SEHOP, Spanish Registry of Childhood Tumors; UTM, Universal Transverse Mercator; ORs, odds ratios; 95%CIs, 95% confidence intervals; IARC, International Agency for Research on Cancer; VOCs, volatile organic compounds; POPs, persistent organic pollutants; PACs, polycyclic aromatic chemicals; Non-HPCs, non-halogenated phenolic chemicals; PAHs, polycyclic aromatic hydrocarbons

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this disease is concerned, few risk factors for the childhood leukemias are well established. There are evidences that Down syndrome (Mezei et al., 2014) and inherit cancer-predisposing conditions such as ataxia telangiectasia (Bielorai et al., 2013) substantially increase the risk of leukemias (specially for acute lymphoblastic leukemia and acute myeloid leukemia) but account for only a small fraction of cases (5%) (Ross et al., 2011). Investigations of other risk factors, as ionizing radiation (Wakeford et al., 2009), radon (Evrard and Hemon 2005; Tong et al., 2012) or infectious agents (Alexander et al., 1998; Greaves, 2002; Smith et al., 1998), have also indicated increased risk of childhood leukemias. With respect to environmental and parental occupational exposures, several studies have reported risks of leukemias among children whose parents have been occupational exposed to a high level of carcinogenic agents (Perez-Saldivar et al., 2008), pesticides (Ferreira et al., 2013) or involving social contact (Keegan et al., 2012), and some meta-analyses found associations between childhood leukemias and prenatal parental occupational pesticide exposure (Vinson et al., 2011; Wigle et al., 2009). Other exposure to chemicals, as benzene and some volatile organic compounds, has been associated with some type of leukemias (Best et al., 2001; Eden, 2010; Knox, 2005; Steffen et al., 2004), although a review of chemical risk factors and childhood leukemia revealed inconsistent associations (Infante-Rivard, 2008).

With regard to urban and residential traffic exposure, some authors have found associations between childhood leukemia and air pollutants (Boothe et al., 2014; Heck et al., 2014). Nevertheless, there are few studies on exposure to industrial pollution and childhood leukemia (Knox, 1994; Weng et al., 2008), even though industrial plants are known to release carcinogens, such as benzene, dioxins and metals. In relation to industrial sources, the European Commission passed the Integrated Pollution Prevention and Control (IPPC) in 2002 and the European Pollutant Release and Transfer Register (E-PRTR) in 2007. IPPC and E-PRTR records constitute an inventory of geo-located industries with health and environmental impact in Europe, which is a valuable resource for monitoring industrial pollution and, by extension, renders it possible for the association between residential proximity to such pollutants installations and health impacts, such as cancer, to be studied (Lopez-Cima et al., 2011; Lopez-Cima et al., 2013).

In this context, a Spanish population-based case–control study of incident childhood cancer was set in motion to furnish in-depth knowledge of the possible role of residential proximity to both industrial and urban areas as a risk factor for childhood leukemias. In this paper, we analyze the effects of exposure to industrial and urban areas and, including different industrial groups, groups of carcinogenic and other toxic substances, and specific pollutants, on childhood leukemia risk, by incorporating information on industries governed by the IPPC Directive and E-PRTR Regulation.

2. Materials and methods

2.1. Study area and subjects

We designed a population-based case–control study of childhood cancer in Spain. Cases were incident cases of childhood cancer (0–14 years) gathered from the Spanish Registry of Childhood Tumors (RETI-SEHOP) and for those Autonomous Regions with 100% coverage (Catalonia, the Basque Country, Aragon, and Navarre), for the period 1990–2011.

In this study, we select incident cases of childhood leukemia, and corresponded to diseases coded as leukemias, myeloproliferative diseases, and myelodysplastic diseases – code I (International Classification of Diseases for Oncology, 3rd revision) (Steliarova-Foucher et al., 2005). Controls were selected by simple random sampling from among all single live births registered in the Spanish National Statistics Institute between 1996 and 2011, individually matched to cases by year of birth, sex and autonomous region of residence. The final study population comprised 638 cases and 13,188 controls, and both cases and controls were ethnically homogeneous.

2.2. Residential locations

Each individual's last residence was geocoded using Google Map Javascript API v3 (Google Maps, 2015). The obtained latitude and longitude coordinates were projected into the ETRS89/UTM zone 30N (EPSG:25830) using QGIS software (Open Source Geospatial Foundation (OSGeo), 2015), and subsequently converted into the Universal Transverse Mercator (UTM) Zone 30 (ED50) coordinates. Then, we validated the coordinates and kept those where the address and the coordinates matched. For this validation process, we apply the inverse method, getting the addresses of the obtained coordinates and comparing these new addresses (town or city name, street name, and street number) to the original addresses. Lastly, in UTM coordinates of children's residences, the last digit of coordinates (*X*, *Y*) was assigned randomly in order to preserve their confidentiality.

With respect to cases, we successfully validated 87% of their addresses. The remaining 13% of cases were fairly uniformly distributed along the different regions and, therefore, we did not think the data were biased in this sense. On the other hand, only 2% of controls did not have valid coordinates. Having had a small number of failures we decided to select more controls to replace this 2%, and we geocoded and validated this last group to end up with more than 20 controls with valid coordinates for every case.

2.3. Industrial facility locations

We used the industrial database (industries governed by IPPC and facilities pertaining to industrial activities not subject to IPPC but included in the E-PRTR) provided by the Spanish Ministry for Agriculture, Food & Environment in 2009, which includes information on the geographic location and industrial pollution emissions of all industrial plants in Spain.

Each of the installations was classified into one of the 25 categories of industrial groups listed in Table 1. These groups were formed on the basis of the similarity of their pollutant emission patterns.

Owing to the presence of errors in the initial location of industries, the geographic coordinates of the industrial locations recorded in the IPPC+E-PRTR 2009 database were previously validated: every single address was thoroughly checked using Google Earth, the Spanish Agricultural Plots Geographic Information System (Spanish Ministry of Agriculture and Food and Environment, 2015), the "Yellow pages" web page, and the web pages of the industries themselves, to ensure that location of the industrial facility was exactly where it should be. We identified a total of 1068 industrial facilities: 1026 installations located in the four areas included in the study and 42 installations located in adjacent regions but very close to the individuals. Table 1 shows the distribution of the number of industrial facilities by industrial group and autonomous region.

2.4. Urban locations

In Spain, municipal centroids are computed by taking only the inhabited area of the designated town into account, and are situated in the center of the most populous zone where the town hall and the main church tend to be located. For the purposes of this study, we considered as urban areas those towns with more

Table 1
List of industrial groups, together with their E-PRTR categories, and number of installations by industrial group and autonomous region.

Industrial group	E-PRTR category	Autonomous regions					Total
		Catalonia	Basque Country	Aragon	Navarre	Other regions[a]	
Combustion installations	1.c	15	8	8	3	2	36
Refineries and coke ovens	1.a, 1.d	2	2	0	0	0	4
Production and processing of metals	2.a, 2.b, 2.c.i, 2.c.ii, 2.d, 2.e	15	70	11	10	0	106
Galvanization	2.c.iii	5	5	1	2	1	14
Surface treatment of metals and plastic	2.f	58	49	25	12	10	154
Mining industry	3.a, 3.b	18	0	5	6	1	30
Cement and lime	3.c, 3.d	13	5	4	3	1	26
Glass and mineral fibers	3.e, 3.f	9	3	1	2	0	15
Ceramic	3.g	39	3	15	4	6	67
Organic chemical industry	4.a	66	13	10	5	2	96
Inorganic chemical industry	4.b	20	9	14	0	1	44
Fertilizers	4.c	7	0	2	1	0	10
Biocides	4.d	9	0	3	0	0	12
Pharmaceutical products	4.e	30	0	2	0	0	32
Explosives and pyrotechnics	4.f	1	4	1	1	0	7
Hazardous waste	5.a, 5.b	32	11	3	3	2	51
Non-hazardous waste	5.c, 5.d	36	19	12	8	4	79
Disposal or recycling of animal waste	5.e	9	3	2	2	0	16
Urban waste-water treatment plants	5.f, 5.g	24	1	2	2	2	31
Paper and wood production	6.a, 6.b, 6.c	28	13	13	6	1	61
Food and beverage sector	8.a, 8.b, 8.c	66	7	29	22	3	127
Pre-treatment or dyeing of textiles	9.a	7	1	0	1	0	9
Tanning of hides and skins	9.b	2	0	0	0	0	2
Surface treatment using organic solvents	9.c	12	12	2	6	6	38
Production of carbon or electro-graphite	9.d	0	0	0	1	0	1
TOTAL	–	523	238	165	100	42	1068

[a] These adjacent regions include industries very close to the individuals.

than 10,000 inhabitants, where a total of 157 towns were identified in the areas under study.

2.5. Exposure coding and statistical analysis

For each subject, the following Euclidean distances were calculated: (a) industrial distance, i.e., the distance between the subject's residence and any of the previously mentioned 1068 industrial installations (using a purpose-designed distance matrix between all industrial facilities and subjects); and (b) urban distance, i.e., the distance between the subject's residence and the centroid of the town in which it resides.

Three types of statistical analysis, including mixed multiple unconditional logistic regression models, were performed to estimate odds ratios (ORs) and 95% confidence intervals (95%CIs), in order to:

(1) evaluate the possible relationship between childhood leukemia and residential proximity to any industrial installation (taking the following industrial distances '*D*' into account: 5, 4, 3, 2.5, 2, 1.5, and 1 km) and urban sites, where all models (7 independent models) included matching factors (year of birth, sex, and autonomous region of residence (as a random effect)). Each of the subjects was classified into one of the following 4 categories of exposure variable for each model: (a) residence in an "*industrial area*", defined in terms of proximity to industrial facilities, on the basis of the industrial distance '*D*'; (b) residence in the "*urban area*", taking the areas defined by the following urban distances, according to the size of the municipality: 10 km (if the towns have more than 2,000,000 inhabitants), 6 km (towns between 1,000,000 and 2,000,000 inhabitants), 4 km (towns between 500,000 and 1,000,000 inhabitants), 3 km (towns between 200,000 and 500,000 inhabitants), 2 km (towns between 100,000 and 200,000 inhabitants), 1 km (towns between 50,000 and 100,000 inhabitants), and 0.5 km (towns between 10,000 and 50,000 inhabitants); (c) residence in the intersection between industrial and urban areas ("*both*"); and, (d) residence within the "*reference area*", consisting of zones not included above and corresponding mainly to rural settings. If a subject resides at $\leq$ 'D' km from any industrial installation but far from towns with more than 10,000 inhabitants, is categorized as "*industrial area*"; if not, if it resides near towns with more than 10,000 inhabitants (in the circles above-defined for the urban distances) but far ($>$ '*D*' km) from any industrial installation, is categorized as "*urban area*"; if not, if it resides near towns with more than 10,000 inhabitants and $\leq$ '*D*' km from any facility, is categorized as "*both*"; otherwise, is categorized as "*reference area*". Figs. 1 (A) and 1 (B) depict two examples for the above-defined areas, for industrial distances of 1 and 2.5 km, respectively, in Barcelona City and its metropolitan area (Catalonia), which include 28 towns $\geq$ 10,000 inhabitants and 139 industrial facilities;

(2) evaluate the relationship between childhood leukemia and residential proximity to industries by different categories of industrial groups defined in Table 1, using the above-described mixed multiple unconditional logistic regression model for the industrial distance '*D*' which yielded the highest and statistically significant ORs for the three categories of exposure (industrial area (only), urban area (only), and both), where all models (25 independent models) included matching factors. To this end, we created an exposure variable for each model in which the subject was classified into one of the following categories: (a) residence near a specific "*industrial group*": children at $\leq$ '*D*' km from any installation belonging to the industrial group in question; (b) residence near "*other industrial groups*": children at $\leq$ '*D*' km from any industrial installation other than the group analyzed (intermediate area); (c) residence in the "*urban area*", defined as in the previous analysis; d) residence in the intersection between "*industrial group*" and "*urban*" areas; and (e) residence within the "*reference area*", consisting of zones not included above; and,

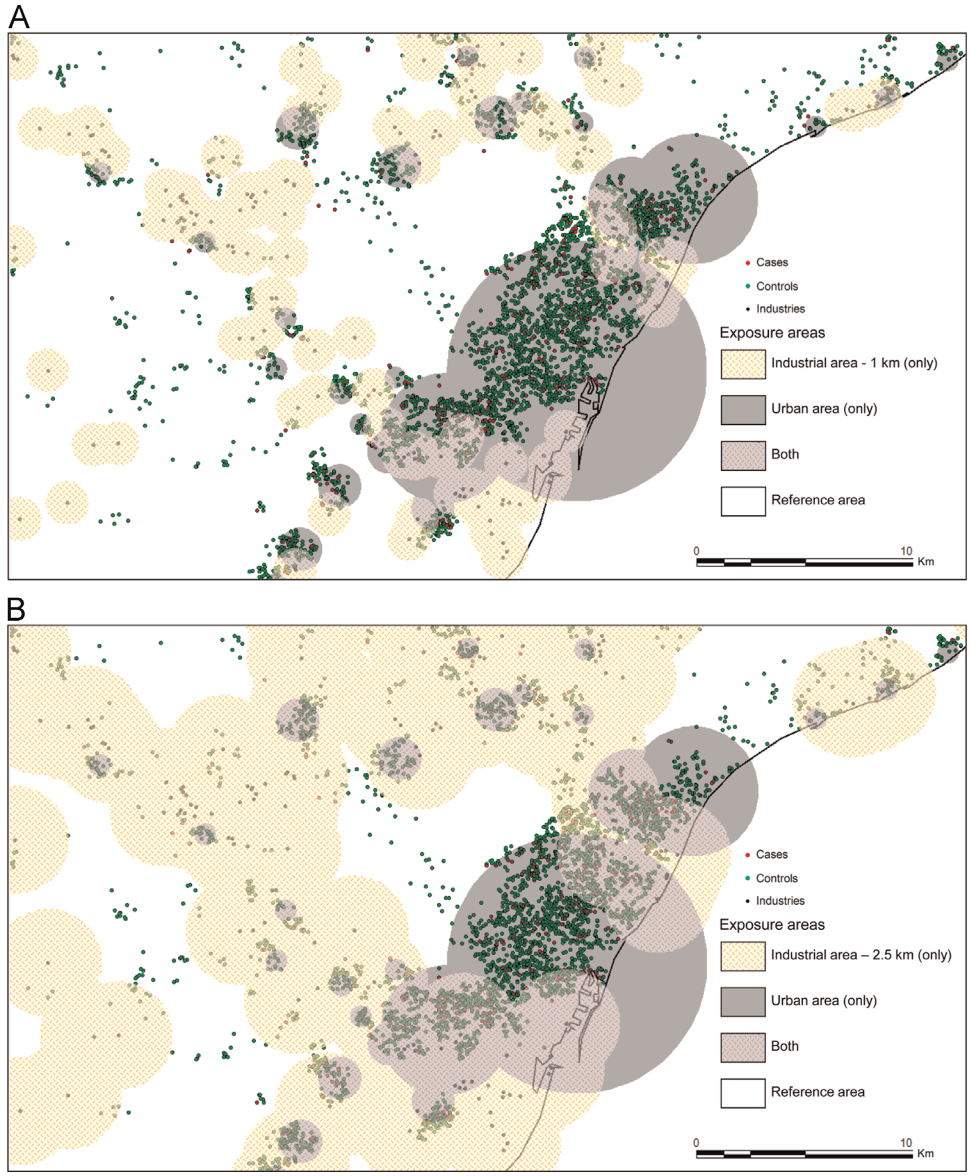

Fig. 1. Examples of exposure areas to industrial and urban sites, for industrial distances of 1 (A) and 2.5 km (B) in Barcelona City and its metropolitan area (Catalonia).

(3) assess the relationship between childhood leukemia and residential proximity to any industrial focus releasing substances classified by the International Agency for Research on Cancer (IARC) as carcinogenic (Group 1), probably carcinogenic (Group 2A) and possibly carcinogenic (Group 2B) to humans, and other toxic chemical substances (9 groups) – including metals, pesticides, polycyclic aromatic chemicals (PACs), non-halogenated phenolic chemicals (non-HPCs), plasticizers, persistent organic pollutants (POPs), volatile organic compounds (VOCs), solvents, and other. For this purpose, the industrial distance chosen in the previous phase was used to define an "exposed subject" as any child who lived close to any facility releasing the above-defined groups of carcinogenic and toxic substances, and specific pollutants, and we performed two different sub-analyses, according to groups of carcinogenic and toxic substances (12 independent models), and specific pollutants (72 independent models). To this end, we created an exposure variable for each model, analogous to the second analysis.

Since matching conditions, i.e., year of birth, sex, and autonomous region of residence, are very general and controls can fit the criteria for more than one case (the corresponding pair can be interchangeable), the standard methodology is to use unconditional logistic regression including the matched characteristics in the model.

Finally, to take into account the problem of multiple comparisons or multiple testing (which occurs when a set of statistical inferences is considered simultaneously), *p*-values were also suitably adjusted by controlling for the expected proportion of false positives (False Discovery Rate), as proposed by Benjamini (Benjamini and Hochberg, 1995; Benjamini and Yekutieli, 2001).

3. Results

The analysis covered 638 cases and 13,188 controls. Distribution by sex, year of birth, autonomous region, and histologic type

Table 2
Characteristics of childhood leukemias cases and controls.

Characteristic	n (%)	
	Cases (n=638)	Controls (n=13,188)
Sex		
Male	369 (57.8)	7387 (56.0)
Female	269 (42.2)	5801 (44.0)
Year of birth, mean (SD)	2001.5 (3.8)	2001.8 (4.0)
Autonomous region		
Catalonia	418 (65.5)	8866 (67.2)
Basque Country	119 (18.7)	2175 (16.5)
Aragon	60 (9.4)	1295 (9.8)
Navarre	41 (6.4)	852 (6.5)
Histologic type		
Lymphoid leukemias	520 (81.5)	
Acute myeloid leukemias	101 (15.8)	
Chronic myeloproliferative diseases	2 (0.3)	
Myelodysplastic syndrome and other myeloproliferative diseases	7 (1.1)	
Unspecified and other specified leukemias	8 (1.3)	

of case is summarized in Table 2. Catalonia was the autonomous region with the highest proportion of cases and controls (65.5% and 67.2%, respectively), and histologically, lymphoid leukemias (81.5%) was the main type of childhood leukemias.

In order to provide a global view of the different components of the study, Fig. 2 shows the locations of residences of cases and controls, industrial installations, and towns with more than 10,000 inhabitants.

Estimated ORs of childhood leukemias associated with residential proximity to industrial and urban sites using different industrial distances are shown in Table 3. An increased risk of childhood leukemia was observed for all distances analyzed, with this proving statistically significant for children living between 1.5 and 2.5 km, both of industrial (only) and urban (only) sites. Of these distances, 2.5 km (adjusted-OR=1.31; 95%CI=1.03–1.67 for industrial sites (only); adjusted-OR=1.36; 95%CI=1.02–1.80 for urban area (only)) also provided an excess risk, although non-statistically significant, for the intersection area between industrial and urban areas (adjusted-OR=1.07; 95%CI=0.84–1.36) and, therefore, this distance was used to define industrial proximity in subsequent analyses. This industrial distance of 2.5 km has the advantage of being able to better discriminate the risk and furnish a series of cases and controls which would have enough statistical power in the three categories of exposure analyzed (see Table 3).

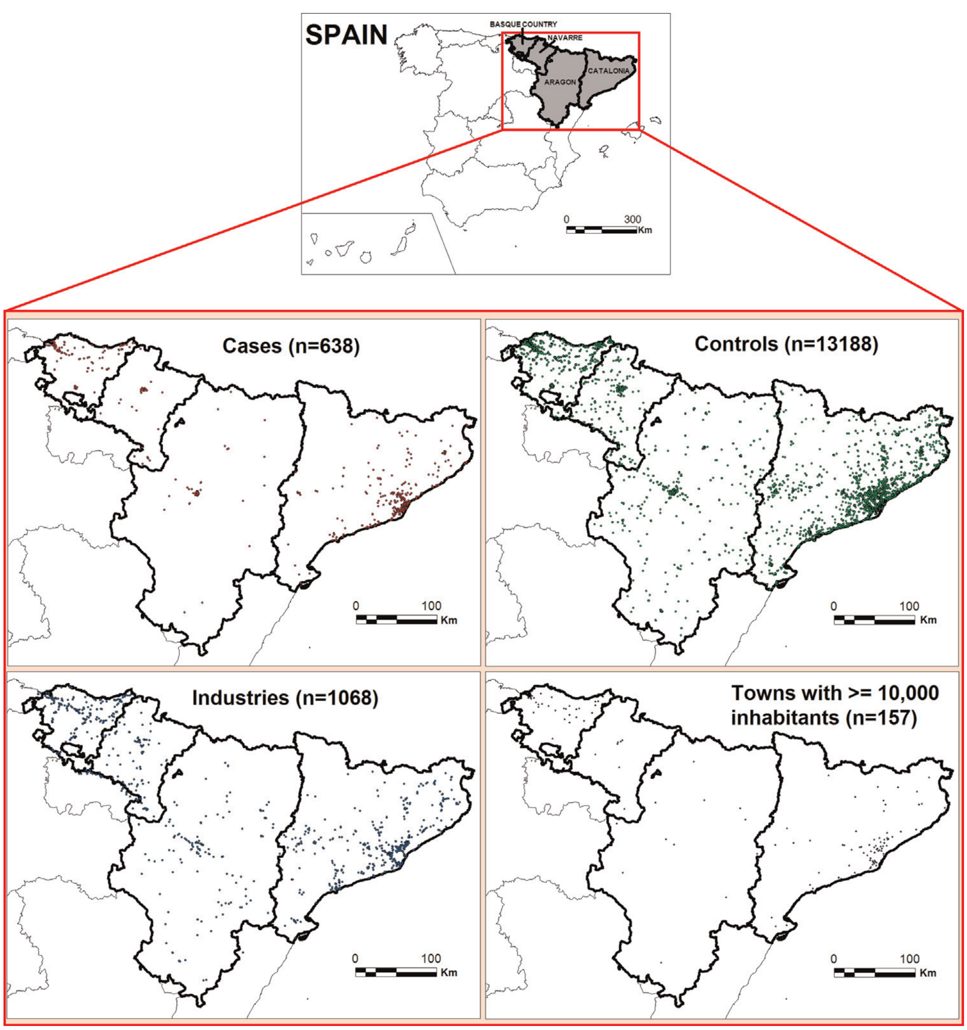

Fig. 2. Geographic distribution of cases, controls, industrial facilities, and towns with more than 10,000 inhabitants.

Table 3
Odds ratios of childhood leukemias by industrial distance and exposure category.

Industrial distance[a]	Exposure category	Controls (n)	Cases (n)	OR (95%CI)[b]
5 km				
	Reference	1059	47	–
	Industrial area - 5 km (only)	5314	267	1.13 (0.83–1.56)
	Urban area (only)	222	14	1.41 (0.76–2.61)
	Both[c]	6593	310	1.05 (0.77–1.44)
4 km				
	Reference	1372	56	–
	Industrial area – 4 km (only)	5001	258	1.26 (0.94–1.70)
	Urban area (only)	543	37	1.66 (1.08–2.55)
	Both[c]	6272	287	1.12 (0.83–1.50)
3 km				
	Reference	1936	81	–
	Industrial area – 3 km (only)	4437	233	1.26 (0.97–1.63)
	Urban area (only)	1217	66	1.29 (0.92–1.80)
	Both	5598	258	1.10 (0.85–1.42)
2.5 km				
	Reference	2378	98	–
	Industrial area – 2.5 km (only)	3995	216	1.31 (1.03–1.67)
	Urban area (only)	1901	107	1.36 (1.02–1.80)
	Both[c]	4914	217	1.07 (0.84–1.36)
2 km				
	Reference	3020	128	–
	Industrial area – 2 km (only)	3353	186	1.31 (1.04–1.65)
	Urban area (only)	2884	157	1.28 (1.00–1.62)
	Both[c]	3931	167	1.00 (0.79–1.26)
1.5 km				
	Reference	3738	159	–
	Industrial area – 1.5 km (only)	2635	155	1.38 (1.10–1.73)
	Urban area (only)	3939	209	1.24 (1.00–1.53)
	Both[c]	2876	115	0.94 (0.73–1.20)
1 km				
	Reference	4743	210	–
	Industrial area – 1 km (only)	1630	104	1.44 (1.13–1.84)
	Urban area (only)	5249	270	1.16 (0.96–1.39)
	Both[c]	1566	54	0.78 (0.57–1.05)

[a] Industrial distance referred to the industrial area (only) in the exposure category.
[b] ORs were estimated from various mixed multiple logistic regression models (an independent model for each of the categories of industrial distance), that included year of birth, sex, and autonomous region of residence (as a random effect).
[c] Intersection area between industrial area defined by the corresponding industrial distance and urban area (only).

Estimated ORs of childhood leukemias, both overall and by industrial group, are shown in Table 4. When type of industrial activity was taken into account, all industrial groups in the study area – with the exception of 'Refineries and coke ovens', 'Mining industry', 'Inorganic chemical industry', 'Fertilizers', and 'Tanning of hides and skins' – showed an increased risk of childhood leukemias in their environs, with this reaching statistically significance in the case of 'Glass and mineral fibers' (adjusted-OR = 2.42), 'Surface treatment using organic solvents' (adjusted-OR = 1.87), 'Galvanization' (adjusted-OR = 1.86), 'Production and processing of metals' (adjusted-OR = 1.69), 'Surface treatment of metals and plastics' (adjusted-OR = 1.62), 'Hazardous waste' (adjusted-OR = 1.55), and 'Pharmaceutical products' (adjusted-OR = 1.53). Detailed information on emission amounts by groups of substances, and type of specific pollutants released by the industrial groups analyzed is provided in Supplementary Data, S1 and S2, respectively.

Table 5 shows the estimated ORs of childhood leukemias by reference to groups of carcinogens and other toxic chemical substances released by industries. The results showed highest and statistically significant ORs in children living close ($\leq$ 2.5 km) to industrial facilities releasing carcinogenic substances (adjusted-ORs = 1.35 for facilities releasing Group-1 carcinogens, 1.48 for Group 2A, and 1.54 for Group 2B) and all groups of toxic substances, principally near non-HPCs (adjusted-OR = 1.71), plasticizers (adjusted-OR = 1.67), pesticides and solvents (adjusted-ORs = 1.61 in both cases), POPs (adjusted-OR = 1.58), PACs (adjusted-OR = 1.57), and metals (adjusted-OR = 1.40).

Lastly, Table 6 shows specific pollutants released by facilities, amounts in kg and number of industrial facilities reporting these releases, and estimated ORs of childhood leukemias in children living at $\leq$ 2.5 km from industries releasing these specific substances. Many pollutants (37 of 72) displayed high statistically significant results, including tetrachloromethane (adjusted-OR = 2.23), fluoranthene (adjusted-OR = 1.86), PAHs (adjusted-OR = 1.54), and arsenic or cadmium (adjusted-OR = 1.50 in both cases). Finally, it should be noted that some pollutants were released by virtually the same facilities; in fact, 100% of the population exposed to benzo(a)pyrene was also exposed to benzo(b) fluoranthene, benzo(k)fluoranthene, and indeno(1,2,3-cd)pyrene.

Table 4
Odds ratios of childhood leukemias by industrial group.

Industrial group (no. industries)	Individuals residing at $\leq$2.5 km					
	Controls (n)	Cases (n)	OR (95%CI)[a]	p-value[b]	p-BH[c]	p-BY[d]
Reference	2378	98	–	–	–	–
All industries (1068)	3995	216	1.31 (1.03–1.67)	0.030	0.106	0.406
Combustion installations (36)	342	19	1.35 (0.82–2.24)	0.239	0.392	1.000
Refineries and coke ovens (4)	117	3	0.61 (0.19–1.96)	0.407	0.599	1.000
Production and processing of metals (106)	915	64	1.69 (1.22–2.34)	0.002	0.013	0.049
Galvanization (14)	208	16	1.86 (1.07–3.21)	0.027	0.106	0.406
Surface treatment of metals and plastic (154)	1567	105	1.62 (1.22–2.15)	0.001	0.010	0.038
Mining industry (30)	53	2	0.92 (0.22–3.85)	0.912	0.992	1.000
Cement and lime (26)	311	14	1.09 (0.62–1.94)	0.761	0.906	1.000
Glass and mineral fibers (15)	219	22	2.42 (1.49–3.92)	0.000	0.008	0.032
Ceramic (67)	402	23	1.39 (0.87–2.22)	0.168	0.326	1.000
Organic chemical industry (96)	828	44	1.28 (0.89–1.85)	0.182	0.326	1.000
Inorganic chemical industry (44)	386	16	1.00 (0.58–1.71)	0.999	0.999	1.000
Fertilizers (10)	130	4	0.74 (0.27–2.04)	0.558	0.734	1.000
Biocides (12)	222	10	1.08 (0.56–2.10)	0.819	0.931	1.000
Pharmaceutical products (32)	460	29	1.53 (1.00–2.34)	0.051	0.159	0.607
Explosives and pyrotechnics (7)	48	2	1.03 (0.25–4.28)	0.971	0.999	1.000
Hazardous waste (51)	595	38	1.55 (1.06–2.28)	0.025	0.106	0.406
Non-hazardous waste (79)	439	25	1.38 (0.88–2.16)	0.166	0.326	1.000
Disposal or recycling of animal waste (16)	216	14	1.57 (0.88–2.79)	0.128	0.320	1.000
Urban waste-water treatment plants (31)	650	39	1.45 (0.99–2.12)	0.057	0.159	0.607
Paper and wood production (61)	611	32	1.27 (0.84–1.91)	0.251	0.392	1.000
Pre-treatment or dyeing of textiles (9)	89	5	1.34 (0.53–3.38)	0.535	0.734	1.000
Tanning of hides and skins (2)	70	2	0.69 (0.17–2.85)	0.606	0.757	1.000
Food and beverage sector (127)	1101	57	1.26 (0.90–1.75)	0.183	0.326	1.000
Surface treatment using organic solvents (38)	415	32	1.87 (1.24–2.83)	0.003	0.018	0.069
Production of electro-graphite (1)	0	0	–	–	–	–

[a] ORs were estimated from various mixed multiple logistic regression models (an independent model for each of the categories of industrial groups), that included year of birth, sex, and autonomous region of residence (as a random effect).
[b] p-value associated with hypothesis test for the mixed multiple logistic regression model.
[c] p-value adjusted by Benjamini & Hochberg's method.
[d] p-value adjusted by Benjamini & Yekutieli's method.

Other examples were the next: 84% of the population exposed to cadmium was also exposed to arsenic, and 69% of the population exposed to nickel was also exposed to arsenic and cadmium (data not shown).

4. Discussion

In this study, we investigated the effects of exposure to industrial and urban air pollutions on childhood leukemia risk in Spain, taking into account different industrial groups, groups of carcinogens and other toxic substances, and specific pollutants. Our findings support the hypothesis that air pollution might be a risk factor for childhood leukemia incidence. Indeed, our analyses show an excess of risk of childhood leukemia among children living in the proximity of industrial installations (in a radius of 2.5 km) and urban nuclei ($\geq$10,000 inhabitants) and, especially those living near plants involved in the metal sector (production and processing of metals, galvanization, and surface treatment of metals and plastics), glass and mineral fibers, pharmaceutical products, hazardous waste, and surface treatment using organic solvents, and facilities releasing, principally, carcinogens, non-HPCs, plasticizers, pesticides, solvents, POPs, PACs, metals, and VOCs.

Insofar as exposure to industrial pollution is concerned, the studies existing in the literature about childhood leukemia and industrial sectors are inconsistent. Whereas the results of a Taiwanese study showed that children who lived in municipalities with highest levels of petrochemical air pollution had a statistically significant higher risk of developing leukemia (Weng et al., 2008), and a review found increased risk of childhood leukemia with residential addresses near gas stations and nuclear power plants (Brender et al., 2011), other studies did not find evidence of risk of childhood leukemia in the vicinity of incinerators (Reeve et al., 2013) or petrochemicals (Yu et al., 2006).

With regard to the industrial groups of our study, our findings for the metal industry (production and processing of metals, galvanization, and surface treatment of metals and plastic) are consistent with a previous ecologic study carried out by our group about leukemia-related mortality in towns close to these installations, which suggested an association between risk of dying due to leukemia (in general population, including all age groups) and proximity to Spanish metal industries (Garcia-Perez et al., 2010). These types of installations release numerous carcinogenic substances into the environment, e.g., heavy metals, PAHs, asbestos, benzene or dioxins, which have been linked to leukemias. In this sense, a British study found childhood leukemia clusters near steelworks (Knox, 1994), whereas another study of the same author found relative excesses of leukemia and of solid cancers in children living near installations of production of aluminium, zinc, galvanizers and iron/steel foundries, although the authors did not distinguish the findings for leukemias and for solid cancers (Knox and Gilman, 1997). Insofar as the galvanizing sector is concerned, it is one of the main industrial activities that releases dioxins to air (Martinez et al., 2008), recognized by the IARC as carcinogens in humans (IARC, 2012) and related to increased risk of leukemias in general population (Consonni et al., 2008), a finding that could be related to the excess risk observed by us in the environs of this industrial group. Another noteworthy result is the excess risk found in the environs of installations for the surface treatment of metals and plastic, a group of metal industries that use mineral oils and metalworking fluids, a range of oils and other chemicals substances known to be carcinogens in humans (Savitz, 2003). In this connection, an Italian study detected increased risk of

Table 5
Odds ratios of childhood leukemias by groups of carcinogenic and toxic substances.

Groups of pollutants	Individuals residing at ≤2.5 km		
	Controls (n)	Cases (n)	OR (95%CI)[a]
Reference	2378	98	–
IARC groups[b]			
Group 1	3438	191	1.35 (1.05–1.73)
Group 2 A	2259	138	1.48 (1.13–1.93)
Group 2B	3541	192	1.54 (1.14–2.07)
Groups of toxic substances[c]			
Metals	3002	173	1.40 (1.08–1.80)
Pesticides	781	52	1.61 (1.14–2.27)
PACs	1309	85	1.57 (1.16–2.11)
Non-HPCs	765	54	1.71 (1.21–2.40)
Plasticizers	433	30	1.67 (1.10–2.55)
POPs	1588	104	1.58 (1.19–2.10)
VOCs	3100	177	1.38 (1.07–1.78)
Solvents	1492	99	1.61 (1.20–2.14)
Other	2862	162	1.37 (1.06–1.77)

[a] ORs were estimated from various mixed multiple logistic regression models (an independent model for each of the categories of groups of pollutants), that included year of birth, sex, and autonomous region of residence (as a random effect).

[b] IARC carcinogenic classification: Group 1: carcinogens to humans (arsenic and compounds, cadmium and compounds, chromium and compounds, nickel and compounds, dioxins+furans, polychlorinated biphenyls, trichloroethylene, vinyl chloride, benzene, ethylene oxide, polycyclic aromatic hydrocarbons, particulate matter (PM_{10}), total suspended particulate matter, and benzo(a)pyrene); Group 2A: probably carcinogenic to humans (lead and compounds, dichloromethane, tetrachloroethylene, and hexabromobiphenyl); Group 2B: possibly carcinogenic to humans (chlordane, DDT, 1,2-dichloroethane, dichloromethane, heptachlor, hexachlorobenzene, 1,2,3,4,5,6-hexachlorocyclohexane, lindane, mirex, pentachlorophenol, tetrachloromethane, trichloromethane, ethyl benzene, naphthalene, di-(2-ethyl hexyl) phthalate, cobalt and compounds, benzo(b)fluoranthene, benzo (k)fluoranthene, and indeno(1,2,3-cd)pyrene).

[c] Metals (arsenic and compounds, cadmium and compounds, chromium and compounds, copper and compounds, mercury and compounds, nickel and compounds, lead and compounds, zinc and compounds, thallium, antimony, cobalt, manganese, and vanadium); Pesticides (alachlor, aldrin, atrazine, chlordane, chlorfenvinphos, chlorpyrifos, DDT, dieldrin, diuron, endosulfan, endrin, heptachlor, lindane, mirex, pentachlorobenzene, pentachlorophenol, simazine, isoproturon, organotin compounds, tributyltin and compounds, triphenyltin and compounds, trifluralin, and isodrin); PACs: Polycyclic aromatic chemicals (anthracene, polycyclic aromatic hydrocarbons, fluoranthene, benzo(g,h,i)perylene, benzo(a)pyrene, benzo (b)fluoranthene, benzo(k)fluoranthene, and indeno(1,2,3-cd)pyrene); Non-HPCs: Non-halogenated phenolic chemicals (nonylphenol and nonylphenol ethoxylates, and octylphenols and octylphenol ethoxylates); Plasticizers (di-(2-ethyl hexyl) phthalate); POPs: Persistent organic pollutants (aldrin, chlordane, DDT, dieldrin, endosulfan, endrin, heptachlor, hexachlorobenzene, 1,2,3,4,5,6-hexachlorocyclohexane, lindane, mirex, dioxins+furans, pentachlorobenzene, polychlorinated biphenyls, brominated diphenylethers, organotin compounds, polycyclic aromatic hydrocarbons, hexabromobiphenyl, benzo(a)pyrene, benzo(b) fluoranthene, and benzo(k)fluoranthene); VOCs: Volatile organic compounds (non-methane volatile organic compounds, 1,2-dichloroethane, dichloromethane, hexachlorobutadiene, tetrachloroethylene, trichlorobenzenes, 1,1,1-trichloroethane, trichloroethylene, trichloromethane, vinyl chloride, benzene, ethyl benzene, ethylene oxide, and naphtalene); Solvents (1,2-dichloroethane, dichloromethane, tetrachloroethylene, trichlorobenzenes, 1,1,1-trichloroethane, trichloroethylene, trichloromethane, benzene, ethyl benzene, toluene, and xylenes); Other (tetrachloromethane, particulate matter (PM_{10}), and total suspended particulate matter).

childhood leukemia related to paternal exposure to mineral oils (Miligi et al., 2013). Lastly, it should be noted that the primary metal industry is a major environmental contributor of chlorinated solvents (dichloromethane, tetrachloroethylene, and trichloroethylene), which are potential chemical leukemogens (Shore et al., 1993) and known or suspected carcinogens. There are studies which have linked exposure to drinking water contaminated by tetrachloroethylene and trichloroethylene to an increase in incidence of some childhood leukemias (Cohn et al., 1994; Fagliano et al., 1990). In our study, we found statistically significant excess risks for tetrachloroethylene and dichloromethane, and a non-statistically significant excess risk for trichloroethylene (see Table 6).

In relation to other industrial groups, Knox and Gilman found relative excess risks of childhood leukemias and solid cancers near fiberglass fabricators (Knox and Gilman, 1997), a finding that could be related to the high statistically significant excess risk found by us in the proximity of installations for the production of glass and mineral fibers.

With regard to the specific groups of pollutants of our study, some papers have found associations between exposure to toxic pollutants and risk of childhood leukemia: an American study found an association between increased childhood leukemia rates and high exposure scores for 25 potentially carcinogenic hazardous air pollutants (including benzene, dioxins, tetrachloroethylene, and vinyl chloride) released from mobile, area, and point sources (Reynolds et al., 2003), whereas other authors detected increased risks of leukemia in relation to exposure to some ambient air toxics in pregnancy, specifically with PAHs, arsenic, benzene, lead, toluene, and xylenes (Heck et al., 2014). In our study, we have found high statistically significant excess risks in children living close to industrial installations releasing these pollutants, findings consistent with other studies about exposure to specific PAHs (Deziel et al., 2014; Miligi et al., 2013). With respect to other pollutants, a Canadian study found an association between exposure to zinc in drinking water and childhood leukemia (Infante-Rivard et al., 2001), whereas some studies have found associations between some types of childhood leukemia and parental occupational exposure to toluene (Infante-Rivard et al., 2005), and chromium and lead (Miligi et al., 2013).

In this paper, we have used several urban distances depending on the size of the municipality, from large cities to small towns. Our findings for exposure to urban air pollution are consistent with other studies (Boothe et al., 2014; Crosignani et al., 2004; Filippini et al., 2015; Vinceti et al., 2012), although some papers did not find any evidence of an association between traffic density and the risk of childhood leukemia (Langholz et al., 2002; Sun et al., 2014; Von Behren et al., 2008). One of the most surprising results is the inverse relationship between the excess risks in the urban areas and industrial distance (from OR-adjusted=1.16 for urban areas with industrial distance of 1 km to OR-adjusted=1.41 for urban areas in 5 km). A possible explanation for this could be that the increase in industrial distance entails reducing the urban and reference areas (see Fig. 1), something that allows for the establishment of a “cleaner” reference zone with increasing industrial distance (reference areas having no industry in a radius of 5 km will be “cleaner” than reference areas having no industry in a radius of 1 km, i.e., it is possible that many children included in the reference area for the example of industrial distance of 1 km are “actually exposed” to industrial pollution and, therefore, the estimated ORs for urban areas are lower than for industrial distance of 5 km).

One of this study’s limitations is the non-inclusion of possible confounding factors that might be associated with the distance, as socioeconomic variables or life-style-related factors, for their unavailability at an individual level. Moreover, this study uses distances to the pollution sources as a proxy of exposure, assuming an isotropic model, something that could introduce a problem of misclassification, since real exposure is critically dependent on prevailing winds, geographic landforms and releases into aquifers. Nevertheless, this problem would limit the capacity to find positive results but in no way invalidating the associations found. Lastly, we did not have any information about parental occupational exposures at an individual level.

It should be noted that we have the home address of the cases at the moment of diagnosis (i.e., residence at the time of incidence, because in childhood leukemia, the time difference between

Table 6
Specific pollutants released by facilities, amounts in kg and number of industrial facilities reporting these releases (in 2009), and estimated ORs of childhood leukemias in children living at $\leq$ 2.5 km from industries releasing these substances.

				Air		Water		Individuals residing at $\leq$ 2.5 km					
Pollutant	CAS no.[a]	IARC Group[b]	Chemical substance type	kg	Facilities	kg	Facilities	Controls (n)	Cases (*n*)	OR (95%CI)[c]	*p*-value[d]	*p*-BH[e]	*p*-BY[f]
1,1,1-trichloroethane	71-55-6		VOCs/Solvents	0.5	1	0	0	51	0	0 (0–inf)	0.971	0.975	1.000
1,2,3,4,5,6-hexachlorocyclohexane	608-73-1	2B	POPs	0.1	2	0.5	10	165	10	1.46 (0.75–2.86)	0.265	0.455	1.000
1,27-dichloroethane	107-06-2	2B	VOCs/Solvents	9870	3	379	23	579	32	1.34 (0.89–2.01)	0.164	0.338	1.000
Alachlor	15972-60-8		Pesticides	0	0	0.03	4	86	4	1.13 (0.41–3.12)	0.819	0.975	1.000
Aldrin	309-00-2		Pesticides/POPs	0	0	8	9	120	6	1.20 (0.52–2.80)	0.666	0.975	1.000
Anthracene	120-12-7		PACs	82	13	1	17	571	34	1.44 (0.96–2.14)	0.078	0.169	0.823
Antimony	7440-36-0		Metals	74	28	0	0	447	21	1.14 (0.70–1.85)	0.596	0.953	1.000
Arsenic and compounds	7440-38-2	1	Metals	943	136	1613	117	1833	114	1.50 (1.14–1.98)	0.004	0.030	0.146
Atrazine	1912-24-9		Pesticides	0	0	5	17	396	30	1.83 (1.20–2.80)	0.005	0.030	0.146
Benzene	71-43-2	1	VOCs/Solvents	44331	75	56	18	792	49	1.50 (1.05–2.13)	0.025	0.078	0.378
Benzo(a)pyrene	50-32-8	1	POPs/PACs	0	0	0.6	3	57	6	2.59 (1.09–6.16)	0.031	0.084	0.407
Benzo(b)fluoranthene	205-99-2		POPs/PACs	0	0	0.6	3	57	6	2.59 (1.09–6.16)	0.031	0.084	0.407
Benzo(g,h,i)perylene	191-24-2		PACs	0	0	2	13	304	22	1.76 (1.09–2.83)	0.021	0.069	0.337
Benzo(k)fluoranthene	207-08-9		POPs/PACs	0	0	0.6	3	57	6	2.59 (1.09–6.16)	0.031	0.084	0.407
Brominated diphenylethers			POPs	0	0	2	11	123	6	1.18 (0.51–2.73)	0.703	0.975	1.000
Cadmium and compounds	7440-43-9	1	Metals	637	144	301	119	1837	114	1.50 (1.14–1.98)	0.004	0.030	0.146
Chlordane	57-74-9	2B	Pesticides/POPs	0	0	0.1	7	103	4	0.94 (0.34–2.60)	0.905	0.975	1.000
Chlorfenvinphos	470-90-6		Pesticides	0	0	1	10	122	6	1.19 (0.51–2.75)	0.692	0.975	1.000
Chlorpyrifos	2921-88-2		Pesticides	0	0	0.9	9	105	4	0.92 (0.33–2.55)	0.877	0.975	1.000
Chromium and compounds	7440-47-3	1	Metals	4193	180	5077	208	2489	153	1.49 (1.15–1.93)	0.003	0.030	0.146
Cobalt and compounds	7440-48-4	2B	Metals	41	27	0	0	404	17	1.02 (0.60–1.73)	0.943	0.975	1.000
Copper and compounds	7440-50-8		Metals	5387	133	7529	207	2269	140	1.49 (1.15–1.95)	0.003	0.030	0.146
DDT	50-29-3	2B	Pesticides/POPs	0	0	0.02	5	102	4	0.95 (0.34–2.62)	0.920	0.975	1.000
Di-(2-ethyl hexyl) phthalate	117-81-7	2B	Plasticizers	759	12	6	12	433	30	1.67 (1.10–2.55)	0.017	0.061	0.296
Dichloromethane	75-09-2	2B	VOCs/Solvents	45229	17	37	9	516	35	1.65 (1.11–2.45)	0.014	0.058	0.280
Dieldrin	60-57-1		Pesticides/POPs	0	0	0.4	8	103	4	0.94 (0.34–2.60)	0.905	0.975	1.000
Diuron	330-54-1		Pesticides	0	0	173	17	468	35	1.80 (1.21–2.69)	0.004	0.030	0.146
Endosulfan	115-29-7		Pesticides/POPs	0	0	0.5	9	105	4	0.92 (0.33–2.55)	0.877	0.975	1.000
Endrin	72-20-8		Pesticides/POPs	0	0	0.4	8	103	4	0.94 (0.34–2.60)	0.905	0.975	1.000
Ethyl benzene	100-41-4	2B	VOCs/Solvents	0	0	8387	23	246	13	1.28 (0.71–2.31)	0.420	0.703	1.000
Ethylene oxide	75-21-8	1	VOCs	18159	3	0	0	52	2	0.94 (0.23–3.94)	0.936	0.975	1.000
Fluoranthene	206-44-0		PACs	0	0	10	31	468	36	1.86 (1.26–2.77)	0.002	0.030	0.146
Heptachlor	76-44-8	2B	Pesticides/POPs	0	0	0.4	7	89	4	1.09 (0.39–3.02)	0.870	0.975	1.000
Hexabromobiphenyl	36355-1-8		POPs	0	0	0.3	6	89	4	1.09 (0.39–3.02)	0.870	0.975	1.000
Hexachlorobenzene	118-74-1	2B	POPs	0.1	1	1	11	136	5	0.89 (0.36–2.22)	0.806	0.975	1.000
Hexachlorobutadiene	87-68-3		VOCs	0	0	2	11	122	6	1.19 (0.51–2.75)	0.692	0.975	1.000
Indeno(1,2,3-cd)pyrene	193-39-5	2B	PACs	0	0	0.6	3	57	6	2.59 (1.09–6.16)	0.031	0.084	0.407
Isodrin	465-73-6		Pesticides	0	0	0.01	4	100	4	0.97 (0.35–2.67)	0.949	0.975	1.000
Isoproturon	34123-59-6		Pesticides	0	0	2	4	154	10	1.57 (0.80–3.07)	0.189	0.377	1.000
Lead and compounds	7439-92-1	2A	Metals	7875	156	2622	158	2046	125	1.48 (1.13–1.94)	0.005	0.030	0.146
Lindane	58-89-9		Pesticides/POPs	0.1	1	0.5	4	156	10	1.55 (0.79–3.03)	0.202	0.382	1.000
Manganese and compounds	7439-96-5		Metals	344	34	0	0	411	20	1.18 (0.72–1.93)	0.512	0.837	1.000
Mercury and compounds	7439-97-6		Metals	889	123	86	85	1620	96	1.43 (1.07–1.91)	0.015	0.058	0.280
Mirex	2385-85-5	2B	Pesticides/POPs	0	0	0.01	4	100	4	0.97 (0.35–2.67)	0.949	0.975	1.000
Naphthalene	91-20-3	2B	VOCs	1010	20	113	19	621	38	1.48 (1.00–2.17)	0.048	0.115	0.561
Nickel and compounds	7440-02-0	1	Metals	18415	161	11279	214	2487	150	1.46 (1.12–1.89)	0.005	0.030	0.146
Non-methane volatile organic compounds			VOCs	24361743	522	0	0	2989	171	1.39 (1.07–1.79)	0.012	0.054	0.262
Nonylphenol and nonylphenol ethoxylates	25154-52-3		Non-HPCs	0	0	587	30	711	46	1.56 (1.09–2.24)	0.015	0.058	0.280
Octylphenols and octylphenol ethoxylates	1806-26-4		Non-HPCs	0	0	2028	32	660	46	1.69 (1.17–2.42)	0.005	0.030	0.146
Organotin compounds			Metals/Pesticides/POPs	0	0	198	23	397	23	1.39 (0.87–2.22)	0.164	0.338	1.000
Particulate matter (PM_{10})		1	Other	3135218	409	0	0	2513	138	1.33 (1.02–1.73)	0.036	0.089	0.433
PCDD + PCDF (dioxins + furans)		1	POPs	0.04	69	0.0005	11	1102	72	1.58 (1.16–2.16)	0.004	0.030	0.146

Pentachlorobenzene	608-93-5		Pesticides/POPs	0	0	1	10	118	6	1.23 (0.53–2.86)	0.629	0.975	1.000
Pentachlorophenol	87-86-5	2B	Pesticides	0	0	31	5	159	10	1.52 (0.78–2.98)	0.219	0.405	1.000
Polychlorinated biphenyls	1336-36-3	1	POPs	2	17	0.1	9	465	25	1.30 (0.83–2.04)	0.250	0.449	1.000
Polycyclic aromatic hydrocarbons		1	PACs/POPs	2506	73	777	64	1274	81	1.54 (1.14–2.08)	0.005	0.030	0.146
Simazine	122-34-9		Pesticides	0	0	8	22	423	29	1.66 (1.08–2.54)	0.020	0.069	0.337
Tetrachloroethylene	127-18-4	2A	VOCs/Solvents	419	5	54	18	587	40	1.65 (1.13–2.41)	0.010	0.047	0.229
Tetrachloromethane	56-23-5	2B	Other	2	3	43	2	218	20	2.23 (1.35–3.68)	0.002	0.030	0.146
Thallium	7440-28-0		Metals	36	13	0	0	271	12	1.07 (0.58–1.98)	0.825	0.975	1.000
Toluene	108-88-3		VOCs/Solvents	0	0	4982	30	516	33	1.55 (1.03–2.32)	0.036	0.089	0.433
Total suspended particulate matter		1	Other	4192306	153	0	0	1249	70	1.36 (0.99–1.83)	0.056	0.126	0.611
Tributyltin and compounds			Pesticides	0	0	0.6	5	98	4	0.98 (0.36–2.72)	0.975	0.975	1.000
Trichlorobenzenes	12002-48-1		VOCs/Solvents	0	0	1	11	192	9	1.13 (0.56–2.27)	0.732	0.975	1.000
Trichloroethylene	79-01-6	1	VOCs/Solvents	1489	8	4494	15	265	15	1.38 (0.79–2.41)	0.260	0.455	1.000
Trichloromethane	67-66-3	2B	VOCs/Solvents	31	6	145	28	542	25	1.11 (0.71–1.74)	0.645	0.975	1.000
Trifluralin	1582-09-8		Pesticides	0	0	0.004	3	86	4	1.13 (0.41–3.12)	0.819	0.975	1.000
Triphenyltin and compounds			Pesticides	0	0	0.03	3	86	4	1.13 (0.41–3.12)	0.819	0.975	1.000
Vanadium	7440-62-2		Metals	136	26	0	0	330	19	1.39 (0.84–2.31)	0.198	0.382	1.000
Vinyl chloride	75-01-4	1	VOCs	46065	6	907	11	194	7	0.87 (0.40–1.91)	0.736	0.975	1.000
Xylenes	1330-20-7		Solvents	0	0	71	21	422	27	1.55 (1.00–2.40)	0.050	0.117	0.569
Zinc and compounds	7440-66-6		Metals	94594	137	41684	302	2629	156	1.44 (1.11–1.86)	0.006	0.032	0.157

[a] Chemical Abstracts Service registry number. When the pollutant is a group of substances, the CAS is not specified.
[b] IARC carcinogenic classification.
[c] ORs were estimated from various mixed multiple logistic regression models (an independent model for each of the pollutants), that included year of birth, sex, and autonomous region of residence (as a random effect).
[d] *p*-value associated with hypothesis test for the mixed multiple logistic regression model.
[e] *p*-value adjusted by Benjamini & Hochberg's method.
[f] *p*-value adjusted by Benjamini & Yekutieli's method.

disease onset and diagnosis is usually very small), and the home address of the mother at birth for the controls. This difference could introduce bias in the analysis, but according to official data in Spain, only around 1% of the children change their residence to a different province (National Statistics Institute, 2015). Therefore, we considered that the home address at time of diagnosis is the same as the home address at birth for most of the cases.

One aspect addressed in the analyses is the problem of multiple comparisons (to find associations that are falsely positive by random chance). In the tables, we have provided adjusted *p*-values, though from an epidemiologic standpoint we have preferred to discuss the results in the light of a series of factors, namely, the magnitude of risk *per se*, the consistency of the associations observed, and biologic plausibility.

One of the main strengths of our study is the large control group (approximately 20 controls per case), that give a much more realistic image of the spatial distribution of the population at risk. The controls were randomly selected from birth certificates. This implies the possibility of having cases included in the control group, since the exclusion of the cases in that group could bias the results (Grimes and Schulz, 2005). The control group should give a clear view of the spatial distribution of the population at risk and should have the same risk of exposure as the cases. We matched the controls by sex, year of birth, and region of residence to account for the temporal and regional variation in the child population.

5. Conclusions

In conclusion, our study furnishes some evidence that living in the proximity of industrial and urban sites may be a risk factor for childhood leukemia. Specifically, children living near plants involved in the metal industry, glass and mineral fibers, pharmaceutical products, hazardous waste, and surface treatment using organic solvents showed an increased risk. In addition, analysis by group of substances showed a statistically significant excess risk of childhood leukemia in the proximity of installations releasing carcinogens, non-HPCs, plasticizers, pesticides, solvents, POPs, PACs, metals, and VOCs.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.envres.2015.05.014.

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