Association between residential proximity to environmental pollution sources and childhood renal tumors

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<u>Abbreviations</u>:

PAHs: Polycyclic aromatic hydrocarbons

RETI-SEHOP: Spanish Registry of Childhood Tumors

IPPC: Integrated Pollution Prevention and Control

E-PRTR: European Pollutant Release and Transfer Register

ORs: Odds ratios

95%CIs: 95% confidence intervals

IARC: International Agency for Research on Cancer

PACs: Polycyclic aromatic chemicals

Non-HPCs: Non-halogenated phenolic chemicals

POPs: Persistent organic pollutants

VOCs: Volatile organic compounds

Abstract

Background: Few risk factors for childhood renal tumors are well established. While a small fraction of cases might be attributable to susceptibility genes and congenital anomalies, the role of environmental factors needs to be assessed.

Objectives: To explore the possible association between residential proximity to environmental pollution sources (industrial and urban areas, and agricultural crops) and childhood renal cancer, taking into account industrial groups and toxic substances released.

Methods: We conducted a population-based case-control study of childhood renal cancer in Spain, including 213 incident cases gathered from the Spanish Registry of Childhood Tumors (period 1996-2011), and 1278 controls individually matched by year of birth, sex, and region of residence. Distances were computed from the respective subject's residences to the 1271 industries, the 30 urban areas with ≥75,000 inhabitants, and the agricultural crops located in the study area. Using logistic regression, odds ratios (ORs) and 95% confidence intervals (95%CIs) for categories of distance to pollution sources were calculated, with adjustment for matching variables and socioeconomic confounders.

Results: Excess risk (OR; 95%CI) of childhood renal tumors was observed for children living near (≤2.5 km) industrial installations as a whole (1.97; 1.13-3.42) – particularly glass and mineral fibers (2.69; 1.19-6.08), galvanization (2.66; 1.14-6.22), hazardous waste (2.59; 1.25-5.37), ceramic (2.35; 1.06-5.21), surface treatment of metals (2.25; 1.24-4.08), organic chemical industry (2.22; 1.15-4.26), food and beverage sector (2.19; 1.18-4.07), urban and waste-water treatment plants (2.14; 1.07-4.30), and production and processing of metals (1.98; 1.03-3.82) –, and in the proximity of agricultural crops (3.16; 1.54-8.89 for children with percentage of crop surface ≥24.35% in a 1-km buffer around their residences).

Conclusions: Our study provides some epidemiological evidence that living near certain industrial areas and agricultural crops may be a risk factor for childhood renal cancer.

Key Words: childhood renal tumors; industrial pollution; urban pollution; crops; case-control study; residential proximity

1. Introduction

Childhood renal tumors account for approximately 6-7% of cancer cases among children less than 15 years of age, and the main histologic type is Wilms' tumor, or nephroblastoma, which comprises approximately 90-95% of all diagnosed renal cancers (Bernstein et al., 1999; Parkin et al., 1998). Incidence rates of Wilms' tumor (and other non-epithelial renal tumors) among children under the age of 15 years are higher in the more developed regions, as Canada and the US (8.0 per million), Europe (8.2 per million), and Australia and New Zealand (9.0 per million), whereas lower rates have been observed in developing regions, as East Asia (2-4 per million), Central and South America (3-8 per million), and Africa (4-8 per million) (Chu et al., 2010; Howlader et al., 2011).

Although advances in diagnosis and treatment have improved 5-year survival rates, which are now as high as 85-90% (Howlader et al., 2011; Pastore et al., 2006; Shrestha et al., 2014), children treated for Wilms' tumor are at risk of short- and long-term adverse effects of treatment, specifically, surgery-related complications (intraoperative ruptures, bowel obstruction, and extensive hemorrhage), congestive heart failure due to treatment with doxorubicin, radiation-induced pulmonary compromise, radiation pneumonitis, chemotherapy-induced nephrotoxicity, development of malignant second neoplasms, orthopedic sequelae, and gonadal failure (Dome et al., 2013; Green et al., 2001; Kaste et al., 2008). On the other hand, even though most cases of Wilms' tumor cannot be linked to a specific cause, the etiology of this tumor is under constant research (Hohenstein et al., 2015). Taking into account that roughly only 2% of Wilms' tumor cases have another relative who has had the same type of cancer, investigation has been based on the study of constitutional syndromes, e.g., aniridia, genitourinary anomalies, and Beckwith-

Wiedemann syndrome, in which Wilms' tumors appear at an elevated rate (Hohenstein et al., 2015).

In contrast with these advances on genetic susceptibility, little is known about environmental agents that might play a key role either as mutagens or in the epigenetic mechanisms presumptively involved in childhood renal cancer (Hohenstein et al., 2015). The sporadic nature of occurrence in the majority of cases (98-99%) and the high incidence in the first few years of life suggest that other perinatal and early childhood factors may be etiologically important (Crump et al., 2014; Ruteshouser and Huff, 2004; Shrestha et al., 2014). However, few environmental risk factors for childhood renal tumors display great consistency. Most studies refer to Wilms' tumor, and several authors have reported increased risks of this tumor with parental exposure to pesticides (e.g., insecticides) (Chu et al., 2010; Sharpe et al., 1995), paternal occupation with exposure to inorganic compounds (Bunin et al., 1989) and known or suspected carcinogens, as hydrocarbons (e.g., polycyclic aromatic hydrocarbons (PAHs)) and metals (e.g., lead) (Chu et al., 2010; Colt and Blair, 1998; Shrestha et al., 2014), or exposures to the mother during pregnancy or birth, as use of coffee or tea, hair dye, and medications (Ross and Spector, 2006). Moreover, an American study found positive associations between Wilms' tumor in children and exposure during the third trimester of pregnancy to formaldehyde, acetaldehyde, perchloroethylene, and PAHs, all known carcinogens (Shrestha et al., 2014). On the other hand, other studies revealed inconsistent associations between paternal occupational or maternal hormonal exposures during pregnancy and risk of Wilms' tumor (Breslow et al., 1993) or do not support the hypothesis that Wilms' tumor is associated with residing near toxic waste sites (Tsai et al., 2006). However, there are no epidemiologic studies that have analyzed the risk of childhood renal cancers in the vicinity of industrial plants (by industrial group), urban areas, and agricultural crops, in the same paper. Accordingly, it would seem appropriate to ascertain whether residential proximity to these environmental pollutant sources might have an influence on the frequency of these tumors.

In this paper, we analyze the association between residential proximity to environmental pollution sources (industrial plants – including different industrial groups, and groups of carcinogenic and other toxic substances –, urban areas, and agricultural crops) and childhood renal cancer risk, in the context of an ongoing population-based case control study of incident cancer in Spain (Garcia-Perez et al., 2015; Ramis et al., 2015).

2. Materials and methods

2.1 Study area and subjects

We designed a population-based case-control study of childhood renal cancer in Spain. Cases were incident cases of childhood renal cancer (0-14 years), gathered from the Spanish Registry of Childhood Tumors (RETI-SEHOP) for those Autonomous Regions with 100% coverage (Catalonia, the Basque Country, Aragon, and Navarre, for the period 1996-2011, and Autonomous Region of Madrid, for the period 2000-2011), and corresponded to diseases coded as nephroblastoma and other non-epithelial renal tumors, renal carcinomas, and unspecified malignant renal tumors – code VI (International Classification of Diseases for Oncology, 3rd revision) (Steliarova-Foucher et al., 2005). Six controls per case 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 213 cases and 1278 controls.

2.2 Residential locations

Each individual’s last residence was geocoded using Google Map Javascript API v3 (Google Maps, 2015) and QGIS software (Open Source Geospatial Foundation, 2016), and converted into the Universal Transverse Mercator Zone 30 (ED50) coordinates, where the last digit of coordinates (X, Y) was assigned randomly in order to preserve their confidentiality.

With respect to cases, we successfully validated 98% of their addresses. The remaining 2% of cases were fairly uniformly distributed along the different regions and, therefore, we did not think that data were biased in this sense. With respect to controls, 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 6 controls with valid coordinates for every case.

2.3 Industrial facility locations

We used the industrial database – industries governed by the Integrated Pollution Prevention and Control (IPPC) Directive and facilities pertaining to industrial activities not subject to IPPC but included in the European Pollution Release and Transfer Register (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 Supplementary Data, Table S1. These groups were formed on the basis of the similarity of their pollutant emission patterns. Additionally, Supplementary Data, Figure S1 shows the distribution of the years of commencement of operations of the 1271 installations studied, by industrial group. The mean year of commencement of operations for industries as a whole was 1974.

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 (Garcia-Perez et al., 2015). We selected the 1271 industrial facilities that reported their releases to air and water in 2009, and Supplementary Data, Table S1 shows the distribution of the number of industrial facilities by industrial group and autonomous region.

2.4 Urban locations

For the purposes of this study, we considered as urban areas those towns with more than 75,000 inhabitants (named “big cities” by the Spanish Act 57/2003) according to 2001 census, where a total of 30 towns were identified in the areas under study.

2.5 Global Crop Index

Because of lack of data about individual exposure to pesticides and specific pesticides that were used in the Spanish crop fields, we estimated that individual exposure by means of a variable named “Global Crop Index”. To build this index, we calculated the percentage of total crop surface in a 1-km buffer around each individual’s last residence, using the Corine Land Cover 2006 inventory (European Environment Agency, 2015). More detailed information on this index is provided by Gomez-Barroso et al (Gomez-Barroso et al., 2016).

2.6 Exposure coding and statistical analysis

For each subject, the following Euclidean distances were calculated: a) industrial distance: distance between the subject's residence and any of the previously mentioned 1271 industrial installations; and b) urban distance: distance between the subject's residence and the centroid of the town in which it resides (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 or the main church tend to be located).

Four types of statistical analysis, including mixed multiple unconditional logistic regression models, were performed to estimate odds ratios (ORs) and 95% confidence intervals (95%CIs). All models included matching factors (year of birth, sex, and autonomous region of residence (as a random effect)), and other potential confounders provided by the 2001 census at a census tract level, such as percentage of illiteracy, percentage of unemployed, and socioeconomic status:

1) Analysis 1: in a first phase, we evaluated the possible relationship between childhood renal tumors 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), urban sites – as a proxy of residential traffic exposure –, and agricultural crops – as a proxy of pesticides exposure – (7 independent models). For the *industrial and urban areas* analysis (sub-analysis 1.a), 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 (only) – D km"*, defined in terms of proximity to industrial facilities, on the basis of the industrial distance 'D'; b) residence in the *"urban area (only)"*, taking the areas defined by the following urban distances, according to the size of the municipality: 8 km (for towns ≥2,000,000 inhabitants), 4 km (between 1,500,000 and 1,999,999 inhabitants), 2 km (between

1,000,000 and 1,499,999 inhabitants), 1.5 km (between 500,000 and 999,999 inhabitants), 1.25 km (between 300,000 and 499,999 inhabitants), 1 km (between 200,000 and 299,999 inhabitants), 0.75 km (between 150,000 and 199,999 inhabitants), 0.5 km (between 100,000 and 149,999 inhabitants), and 0.25 km (between 75,000 and 99,999 inhabitants); c) residence in the intersection between industrial and urban areas (*"both"*); and, d) residence within the *"reference"* area, consisting of zones with children having no (IPPC+E-PRTR)-registered industry within 5 km of their residences and far from urban areas. For the *global crop index* analysis (sub-analysis 1.b), we categorized every subject into one of the following 5 categories, according to the distribution of those percentages with value >0 among the control group: *0* (0% of crop surface, *reference* group), *Q1* (1^{st} quartile), *Q2* (2^{nd} quartile), *Q3* (3^{rd} quartile), and *Q4* (4^{th} quartile);

2) Analysis 2: we evaluated the relationship between childhood renal tumors and residential proximity to industries by different categories of industrial groups defined in Supplementary Data, Table S1, using the above-described mixed multiple unconditional logistic regression model for the industrial distance 'D' which yield stabilized ORs for the three categories of exposure in the *industrial and urban areas* analysis (industrial area (only), urban area (only), and both) (25 independent models). To this end, we created an exposure variable for each model in which the subject was classified as resident near a specific *"industrial group"*, if it resides at ≤'D' km from any installation belonging to the industrial group in question, and resident in the *"reference area"*, if it resides at >5 km from any (IPPC+E-PRTR)-registered industry and far from urban areas;
3) Analysis 3: we assessed the relationship between childhood renal tumors 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 second analysis 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 (12 independent models). To this end, we created an exposure variable for each model, analogous to the second analysis; and,

4) Analysis 4: finally, we performed an additional analysis to assess the risk gradient in the vicinity of industrial installations, described in detail in Supplementary Data, Appendix A.

Regression equations of the models for the first three analyses are shown in Supplementary Data, Appendix B.

As we have considered a frequency matched study, given that 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 (Rothman et al., 2008).

3. Results

The analysis covered 213 cases and 1278 controls. Distribution by sex, year of birth, autonomous region, percentages of unemployment and illiteracy, socioeconomic status, global crop index, and histologic type of case is summarized in Table 1. Distribution by sex was slightly higher in girls (52.6%) than boys (47.4%). Moreover, Catalonia was the autonomous region with the highest proportion of cases and controls (44.6%), and histologically, nephroblastoma (94.8%) was the main type of childhood renal cancer.

In order to provide a global view of the different components of the study, Figure 1 shows the locations of residences of cases and controls, industrial installations, and towns with more than 75,000 inhabitants.

Estimated ORs of childhood renal tumors associated with residential proximity to industrial and urban areas, and agricultural crops, using different industrial distances, are shown in Table 2. With respect to the *industrial and urban areas* analysis, a statistically significant increased risk of childhood renal tumors was observed near industrial areas (only) for all distances analyzed, from 1 km (OR=2.05; 95%CI=1.12-3.73) to 5 km (OR=1.85; 95%CI=1.07-3.18). On the other hand, children living near urban areas (only) registered an excess risk of childhood renal cancer, although non-statistically significant, for all industrial distances, from 1 km (OR=1.69; 95%CI=0.89-3.21) to 5 km (OR=1.28; 95%CI=0.35-4.75). For the intersection area between industrial and urban areas, however, there was a statistically significant risk of childhood renal tumors for all industrial distances, from 1 km (OR=3.95; 95%CI=1.36-3.21) to 5 km (OR=1.90; 95%CI=1.00-3.59), with this being higher than industrial area (only) and urban area (only) separately (synergic effect). Insofar as the *global crop index* analysis is concerned, children with percentages of total crop surface >7.64% (category Q3) and >24.35% (category

Q4) in a 1-km buffer around their residences showed high excess risks of childhood renal tumors. Moreover, a statistically significant trend was detected in the four categories for the global crop index (*p*-value <0.001 for all industrial distances analyzed). Lastly, the industrial distance of 2.5 km was used to define industrial proximity in subsequent analyses, inasmuch as it yielded stabilized ORs for the three categories of exposure in the *industrial and urban areas* analysis, and 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 in the *industrial and urban areas* analysis (see Table 2).

Estimated ORs of childhood renal tumors, both overall and by industrial group, are shown in Table 3. An increased risk was observed for all sectors as a whole (OR=1.97). When type of industrial activity was taken into account, all industrial groups in the study area – with the exception of 'Mining industry' – showed an increased risk of childhood renal cancer in their environs (≤2.5 km), with this reaching statistically significance in the case of 'Pre-treatment or dyeing of textiles' (OR=4.12, although only with 4 cases) , 'Glass and mineral fibers' (OR=2.69), 'Galvanization' (OR=2.66), 'Hazardous waste' (OR=2.59), 'Ceramic' (OR=2.35), 'Surface treatment of metals and plastics' (OR=2.25), 'Organic chemical industry' (OR=2.22), 'Food and beverage sector' (OR=2.19), 'Urban and waste-water treatment plants' (OR=2.14), and 'Production and processing of metals' (OR=1.98). 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, Table S2 and Table S3, respectively.

Table 4 shows the estimated ORs of childhood renal tumors by reference to groups of carcinogens and other toxic chemical substances released by industries. The results showed high and statistically significant ORs in children living close (≤2.5 km) to industrial facilities releasing carcinogenic substances (ORs=2.02 for facilities releasing Group-1 carcinogens, 2.13 for Group 2A, and 2.26 for Group 2B), and all groups of toxic substances – with the exception of 'Plasticizers' –, principally near 'Pesticides' (OR=2.88), 'POPs' (OR=2.51), 'Solvents' (OR=2.37), 'non-HPCs' (OR=2.18), and 'PACs' (OR=2.16). Detailed information on emission amounts by specific pollutants released by facilities is provided in Supplementary Data, Table S4.

Finally, Supplementary Data, Table S5 shows the ORs of childhood renal tumors for ever-decreasing radiuses within a 50-kilometer area surrounding each facility, both overall and by industrial group (risk gradient analysis), and we detected statistically significant radial effects in all sectors as a whole (OR=1.16, *p*-trend=0.0067), especially near 'Surface treatment of metals and plastic' (OR=1.18, *p*-trend=0.0120), 'Urban waste-water treatment plants' (OR=1.19, *p*-trend=0.0338), 'Food and beverage sector' (OR=1.15, *p*-trend=0.0399), and 'Glass and mineral fibers' (OR=1.28, *p*-trend=0.0463).

4. Discussion

Childhood cancer is an important concern for public health, medical care, and society (Peris-Bonet et al., 2010), but regrettably, little is known about its etiology (including childhood renal tumors). To our knowledge, this is the first study that analyzes the effects of exposure to environmental pollution sources, as industrial plants, urban areas, and agricultural crops, on childhood renal tumors (including Wilms' tumor and other histologic types), according to different industrial groups, and groups of carcinogens and other toxic pollutants. Our findings support the hypothesis that industrial pollution and proximity to agricultural crops – which are, generally, treated with pesticides – might be a risk factor for childhood renal cancer incidence.

Indeed, our analyses show an excess of risk of childhood renal tumors among children living in the proximity of industrial installations (between 1 and 5 km) and their intersections with urban nuclei (≥75,000 inhabitants), and agricultural crops (in a radius of 1 km), inasmuch as the statistical analysis about proximity to pollution sources detected higher risk due to these tumors for various industrial and toxic substances groups, and the risk gradient analysis detected statistically significant radial effects.

With respect to the results broken down by industrial group, attention should be drawn to the ORs registered in children 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, ceramic, organic chemical industry, hazardous waste, urban waste-water treatment plants, pre-treatment or dyeing of textiles, and food and beverage sector, and facilities releasing, principally, carcinogens, pesticides, POPs, solvents, non-HPCs, PACs, metals, and VOCs.

The study of childhood cancer in areas surrounding environmental pollution sources is beginning to assume growing importance (Boothe et al., 2014; Danysh et al., 2016; Heck et al., 2013; Weng et al., 2008), and industrial pollution emission registers, such as E-PRTR, afford a very useful tool for the surveillance and monitoring of possible effects of industrial pollution on the health of the children (Wine et al., 2014).

Insofar as environmental exposures and childhood renal tumors are concerned, the studies existing in the literature are almost exclusively focused on Wilms' tumor, and, especially, about parental exposures. Some papers have examined the relationship between risk of Wilms' tumor and maternal smoking, alcohol, coffee or tea consumption, with inconsistent results (Chu et al., 2010; Ross and Spector, 2006), whereas other studies have found associations between Wilms' tumor and paternal occupations with exposure to toxic substances (Colt and Blair, 1998; Sharpe et al., 1995; Sharpe and Franco, 1995). However, an English study suggested that it is unlikely that paternal occupational exposure is an important etiological factor for Wilms' tumor (Fear et al., 2009).

With regard to the specific groups of industrial pollutants of our study, few papers have analyzed childhood renal cancer and residential proximity to toxic substances, excluding occupational studies: a case-control study analyzed prenatal air toxics exposure and Wilms' tumor in children <6 years residing within a 15-mile radius of an air monitoring site and found a statistically significant increased risk in children exposed during the third trimester of pregnancy to some carcinogens, as formaldehyde, acetaldehyde, perchloroethylene, and PAHs (Shrestha et al., 2014). In our study, we have found high statistically significant excess risks in children living close to industrial installations releasing perchloroethylene and PAHs (data not shown). However, another American case-control study examined the association between risk of Wilms' tumor and residential exposures to hazardous chemicals commonly found at toxic waste sites, located within a distance of 1 mile, and the findings did not support that hypothesis (Tsai et al., 2006). It is known that some metals and PAHs have been implicated in DNA damage in fetuses and also been associated with increased risk of kidney cancer or kidney damage in adults (IARC, 1990; IARC, 2006; IARC, 2012; Perera et al., 1999), a finding that could be related to the high excess risk found by us in the proximity of installations which release these groups of pollutants. It is possible that these substances also increase susceptibility to childhood renal tumors, especially during the early life since this developmental period is believe to be more vulnerable to DNA damage and to higher absorption of toxics than in adulthood (Shrestha et al., 2014).

Insofar as exposure to pesticides and Wilms' tumor is concerned, the studies existing in the literature focused on parental or residential exposures are inconsistent. On the one hand, a meta-analysis for the association between maternal exposure to pesticides and Wilms' tumor revealed a significantly increased risk (Chu et al., 2010), and several reviews found increased risks for exposure to pesticides for child and parental exposures (Chu et al., 2010; Infante-Rivard and Weichenthal, 2007; Sharpe and Franco, 1995). However, other studies did not find evidence of major risk of childhood renal cancer associated with parental (Nasterlack, 2007) or residential exposure to pesticides (Cooney et al., 2007). With respect to agricultural pesticides and risk of childhood renal tumors, the studies are not conclusive: in a study of Wilms' tumor in Brazil, risk increased with frequency of parental agricultural use of pesticides (Sharpe et al., 1995), whereas other studies did not confirm associations between risk of childhood renal tumors with proximity of birth residence to agricultural use land (Carozza et al., 2009) or paternal occupation in agriculture at the time of birth (Pearce and Parker, 2000). Specific pesticides, such as organochlorine insectides (e.g.: aldrin, dieldrin, chlordane, and lindane), are highly lipid soluble and are sequestered in body tissues with a high lipid content, such as kidneys. In our study, we have found high ORs in children living near industries releasing pesticides (OR=2.88) and in the proximity of agricultural crops (OR=3.16 for children with percentage of crop surface ≥24.35% in a 1-km buffer around their residences).

Insofar as exposure to other chemicals is concerned, some studies have found increased risks of Wilms' tumors with paternal exposure to hydrocarbons, metals – such as lead –, and inorganic compounds (Chu et al., 2010; Colt and Blair, 1998; Shrestha et al., 2014). This finding could be related to the excess risk observed by us in the environs of industries releasing metals, PACs, and POPs (see Table 4).

In relation to the industrial groups of our study, there are no epidemiologic studies about residential proximity to these types of installations and childhood renal cancer risk. However, occupational studies have suggested an increased risk of Wilms' tumor in children whose fathers have been employed as welder or mechanic (Clapp et al., 2005). In this sense, one of the most noteworthy results of our study is the high excess risks found in children in the proximity of the metal industry (production and processing of metals, galvanization, and surface treatment of metals and plastics), a finding that could be related with occupational exposure of fathers who live close to the factories. Emissions from metal sector installations arouse great social concern due to the health problems that may be generated among their workers and the surrounding population. According to the IARC, a number of substances released by such installations, including metals (arsenic, cadmium, and chromium), PACs (PAHs), POPs (dioxins), and solvents (benzene, tetrachloroethylene, and trichloroethylene), are recognized as known or suspected carcinogens. Moreover, it should be stressed that effluents from the metal industries are genotoxic: they induce cytogenetic damage, mutations, and DNA damage in repair process (Houk, 1992). Lastly, residential proximity to metal industries has been associated with other childhood tumors, as childhood leukemia (Garcia-Perez et al., 2015).

Another important result of our study is the increased risk of childhood renal cancer found in the environs of urban waste-water treatment plants. This industrial group was the main emitter of pesticides released to water, and the second emitter of metals released to air and water (see Supplementary Data, Table S2). In this case, two possible routes of exposure to the pollution released by these installations are considered: direct exposure to pollutants released to air; and indirect exposure, both to pollutants and liquid effluents which are released to water and can then pass into the soil and aquifers, and pollutants which are released to air and then settle on plants.

In such cases, the toxins may pass into the trophic chain, affecting the population, including children.

One aspect to consider is the problem of multiple comparisons or multiple testing (to find associations that are falsely positive by random chance). We estimated that for α=0.05, random chance would account for 0.6 positive associations (number of comparisons x percentage of statistically significant ORs>1 expected under the null hypothesis, i.e., 2.5%) for the analysis by category of industrial group shown in Table 3, a figure lower than the number of associations observed. From an epidemiologic point of view, 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 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, and other possible confounders, as high fetal growth, maternal smoking or constitutional syndromes (Crump et al., 2014; Hohenstein et al., 2015; Stjernfeldt et al., 1986), for their unavailability at an individual level. However, we included some socioeconomic variables at a census tract level – such as percentages of illiteracy and unemployed, and status socioeconomic –, so we assigned to every subject the information of the corresponding census tract, as other similar studies (Mezei et al., 2006; Shrestha et al., 2014). 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. In our case, however, this problem would amount to a non-differential bias (it would affect children in both exposed and unexposed areas) which 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. In this sense, workers can carry hazardous substances home from work on their clothes, bodies, tools, and other items. Workers can unknowingly expose their families to these substances, causing various health effects.

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 renal cancer, the time difference between 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 children change their residence to a different province (National Statistics Institute, 2016). Therefore, we considered that the home address at time of diagnosis is the same as the home address at birth for the most of the cases.

One of the main strengths of our study is the large control group (6 controls per case, which were randomly selected from birth certificates). In this sense, 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.

Further advantages of the study are: the stratification of the risk by industrial group and groups of carcinogenic and toxic substances, which provides a description more exhaustive of childhood renal cancer risk; and inclusion of the same reference area (children having no industry within 5 km of their residences and far from urban areas) in the analyses for all industrial distances analyzed, something that allows for the establishment of a “cleaner” reference zone than other similar case-control studies (Garcia-Perez et al., 2015).

5. Conclusions

In conclusion, our study provides some epidemiological evidence that living in the proximity of industrial areas and agricultural crops may be a risk factor for childhood renal cancer. Specifically, children living near plants involved in the metal industry, glass and mineral fibers, ceramic, organic chemical industry, hazardous waste, urban waste-water treatment plants, and food and beverage sector showed an increased risk. In addition, analysis by group of substances showed a statistically significant excess risk of childhood renal tumors in the proximity of installations releasing carcinogens, pesticides, POPs, solvents, non-HPCs, PACs, metals, and VOCs.

These findings support the need for more detailed exposure assessment and health risk analysis of certain toxic substances by these types of industries. It would be of great interest to assess the possibility of using better exposure markers, such as biomarkers, for studying what is happening in the environs of each specific installation.

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Figure legends

Figure 1: Geographic distribution of cases, controls, industrial facilities, and towns with more than 75,000 inhabitants.

Table 1: Characteristics of cases of childhood renal tumors and controls.

	n (%)	
Characteristic	Cases (n=213)	Controls (n=1278)
Sex		
Male	101 (47.4)	606 (47.4)
Female	112 (52.6)	672 (52.6)
Year of birth, mean (SD)	2003.4 (4.0)	2003.4 (4.0)
Autonomous Region		
Catalonia	95 (44.6)	570 (44.6)
Madrid	68 (31.9)	408 (31.9)
Basque Country	21 (9.9)	126 (9.9)
Aragon	18 (8.4)	108 (8.4)
Navarre	11 (5.2)	66 (5.2)
Unemployment, mean (SD)	10.9 (4.0)	11.1 (3.9)
Illiteracy, mean (SD)	9.5 (6.7)	9.6 (6.3)
Socioeconomic status, mean (SD)	1.1 (0.1)	1.1 (0.1)
Global crop index		
Reference: 0%	162 (76.1)	1126 (88.1)
1st quartile (Q1): (0-1.91]	9 (4.2)	40 (3.1)
2nd quartile (Q2): (1.91-7.64]	7 (3.3)	37 (2.9)
3rd quartile (Q3): (7.64-24.35]	22 (10.3)	37 (2.9)
4th quartile (Q2): (24.35-100]	13 (6.1)	38 (2.9)
Histologic type		
Nephroblastoma	202 (94.8)	
Rhaboid renal tumor	6 (2.8)	
Kidney sarcomas	4 (1.9)	
Renal carcinomas	1 (0.5)	

Table 2: Odds ratios of childhood renal tumors by industrial distance and exposure category. Statistically significant results are in bold.

Industrial distance[a]	Exposure category	Controls (n)	Cases (n)	OR (95%CI)[b]	*p*-value for trend
5 Km					
	Industrial and urban areas				
	Reference	147	19	-	
	Industrial area - 5 km (only)	831	149	**1.85 (1.07-3.18)**	
	Urban area (only)	28	3	1.28 (0.35-4.75)	
	Both[c]	272	42	**1.90 (1.00-3.59)**	
	Global crop index (%)				
	Reference: [0]	1126	162	-	
	Q1: (0-1.91]	40	9	1.67 (0.78-3.57)	
	Q2: (1.91-7.64]	37	7	1.40 (0.60-3.26)	
	Q3: (7.64-24.35]	37	22	**4.83 (2.69-8.68)**	
	Q4: (24.35-100]	38	13	**3.00 (1.47-6.12)**	**<0.001**
4 Km					
	Industrial and urban areas				
	Reference	147	19	-	
	Industrial area - 4 km (only)	784	144	**1.91 (1.11-3.29)**	
	Urban area (only)	81	11	1.65 (0.71-3.81)	
	Both[c]	219	34	**1.92 (1.00-3.71)**	
	Global crop index (%)				
	Reference: [0]	1126	162	-	
	Q1: (0-1.91]	40	9	1.67 (0.78-3.56)	
	Q2: (1.91-7.64]	37	7	1.40 (0.60-3.27)	
	Q3: (7.64-24.35]	37	22	**4.89 (2.72-8.79)**	
	Q4: (24.35-100]	38	13	**3.03 (1.49-6.19)**	**<0.001**
3 Km					
	Industrial and urban areas				
	Reference	147	19	-	
	Industrial area - 3 km (only)	722	134	**1.96 (1.13-3.39)**	
	Urban area (only)	150	14	1.12 (0.52-2.43)	
	Both[c]	150	31	**2.62 (1.34-5.12)**	
	Global crop index (%)				
	Reference: [0]	1126	162	-	
	Q1: (0-1.91]	40	9	1.66 (0.78-3.56)	
	Q2: (1.91-7.64]	37	7	1.45 (0.62-3.38)	
	Q3: (7.64-24.35]	37	22	**4.91 (2.73-8.84)**	
	Q4: (24.35-100]	38	13	**3.17 (1.55-6.49)**	**<0.001**
2.5 Km					
	Industrial and urban areas				
	Reference	147	19	-	
	Industrial area - 2.5 km (only)	659	122	**1.97 (1.13-3.42)**	
	Urban area (only)	184	21	1.38 (0.67-2.81)	
	Both[c]	116	24	**2.62 (1.30-5.30)**	
	Global crop index (%)				
	Reference: [0]	1126	162	-	
	Q1: (0-1.91]	40	9	1.68 (0.79-3.60)	
	Q2: (1.91-7.64]	37	7	1.41 (0.61-3.29)	
	Q3: (7.64-24.35]	37	22	**4.94 (2.74-8.89)**	
	Q4: (24.35-100]	38	13	**3.16 (1.54-6.46)**	**<0.001**
2 Km					
	Industrial and urban areas				
	Reference	147	19	-	
	Industrial area - 2 km (only)	552	106	**2.02 (1.16-3.52)**	
	Urban area (only)	219	25	1.37 (0.69-2.73)	
	Both[c]	81	20	**3.14 (1.50-6.58)**	
	Global crop index (%)				
	Reference: [0]	1126	162	-	
	Q1: (0-1.91]	40	9	1.69 (0.79-3.62)	
	Q2: (1.91-7.64]	37	7	1.43 (0.61-3.33)	
	Q3: (7.64-24.35]	37	22	**4.84 (2.69-8.70)**	
	Q4: (24.35-100]	38	13	**3.10 (1.52-6.32)**	**<0.001**
1.5 Km					
	Industrial and urban areas				
	Reference	147	19	-	
	Industrial area - 1.5 km (only)	428	79	**1.92 (1.09-3.40)**	
	Urban area (only)	247	31	1.52 (0.78-2.95)	
	Both[c]	53	14	**3.35 (1.49-7.55)**	
	Global crop index (%)				
	Reference: [0]	1126	162	-	
	Q1: (0-1.91]	40	9	1.70 (0.80-3.64)	
	Q2: (1.91-7.64]	37	7	1.42 (0.61-3.30)	
	Q3: (7.64-24.35]	37	22	**4.83 (2.69-8.68)**	
	Q4: (24.35-100]	38	13	**3.06 (1.50-6.23)**	**<0.001**

Industrial distance[a]	Exposure category	Controls (n)	Cases (n)	OR (95%CI)[b]	*p*-value for trend
1 Km					
	Industrial and urban areas				
	Reference	147	19	-	
	Industrial area - 1 km (only)	242	49	**2.05 (1.12-3.73)**	
	Urban area (only)	281	39	1.69 (0.89-3.21)	
	Both[c]	19	6	**3.95 (1.36-11.47)**	
	Global crop index (%)				
	Reference: [0]	1126	162	-	
	Q1: (0-1.91]	40	9	1.69 (0.79-3.61)	
	Q2: (1.91-7.64]	37	7	1.42 (0.61-3.31)	
	Q3: (7.64-24.35]	37	22	**4.80 (2.67-8.64)**	
	Q4: (24.35-100]	38	13	**3.01 (1.48-6.14)**	**<0.001**

[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, autonomous region of residence (as a random effect), percentage of illiteracy, percentage of unemployed, and socioeconomic status.

[c] Intersection area between industrial area defined by the corresponding industrial distance and urban area (only).

Table 3: Odds ratios of childhood renal tumors by category of industrial group. Statistically significant results are in bold.

	Individuals residing at ≤2.5 km		
Industrial group (no. industries)	Controls (n)	Cases (n)	OR (95%CI)[a]
Reference	147	19	-
All sectors (1271)	659	122	**1.97 (1.13-3.42)**
Combustion installations (42)	66	9	1.37 (0.56-3.32)
Refineries and coke ovens (4)	14	2	1.73 (0.35-8.53)
Production and processing of metals (119)	160	30	**1.98 (1.03-3.82)**
Galvanization (19)	49	11	**2.66 (1.14-6.22)**
Surface treatment of metals and plastic (197)	341	66	**2.25 (1.24-4.08)**
Mining industry (39)	8	1	0.93 (0.10-8.35)
Cement and lime (33)	35	5	1.29 (0.43-3.83)
Glass and mineral fibers (20)	66	14	**2.69 (1.19-6.08)**
Ceramic (86)	57	13	**2.35 (1.06-5.21)**
Organic chemical industry (106)	151	31	**2.22 (1.15-4.26)**
Inorganic chemical industry (46)	60	10	1.75 (0.74-4.14)
Fertilizers (10)	6	2	3.33 (0.58-19.11)
Biocides (12)	25	3	1.33 (0.35-5.02)
Pharmaceutical products (41)	133	22	1.98 (0.98-4.01)
Explosives and pyrotechnics (9)	6	1	1.99 (0.22-17.97)
Hazardous waste (60)	88	20	**2.59 (1.25-5.37)**
Non-hazardous waste (86)	59	10	1.94 (0.81-4.62)
Disposal or recycling of animal waste (18)	45	7	1.87 (0.71-4.95)
Urban waste-water treatment plants (53)	112	23	**2.14 (1.07-4.30)**
Paper and wood production (63)	92	11	1.32 (0.58-3.01)
Pre-treatment or dyeing of textiles (9)	7	4	**4.12 (1.01-16.85)**
Tanning of hides and skins (2)	3	0	0 (0-inf)
Food and beverage sector (145)	188	41	**2.19 (1.18-4.07)**
Surface treatment using organic solvents (50)	83	13	1.75 (0.79-3.86)
Production of electro-graphite (2)	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, autonomous region of residence (as a random effect), percentage of illiteracy, percentage of unemployed, socioeconomic status, and global crop index.

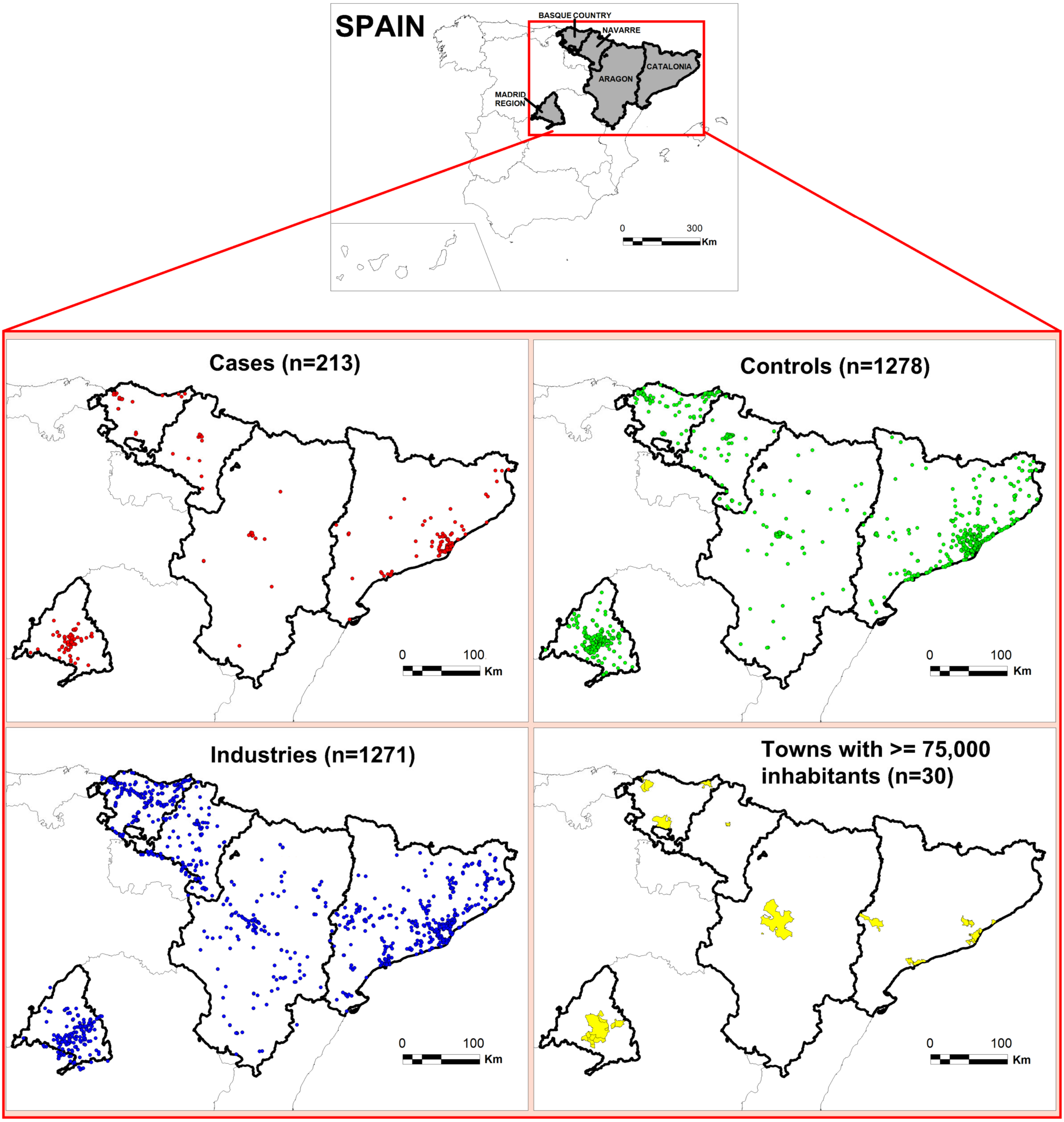
Table 4: Odds ratios of childhood renal tumors by groups of carcinogenic and toxic substances.

	Individuals residing at ≤2.5 km		
Groups of pollutants	Controls (n)	Cases (n)	OR (95%CI)[a]
Reference	147	19	-
IARC groups[b]			
Group 1	586	110	2.02 (1.15-3.52)
Group 2A	382	74	2.13 (1.19-3.81)
Group 2B	241	48	2.26 (1.22-4.19)
Groups of toxic substances[c]			
Metals	504	93	2.05 (1.16-3.63)
Pesticides	123	31	2.88 (1.46-5.65)
PACs	214	43	2.16 (1.16-4.03)
Non-HPCs	105	22	2.18 (1.07-4.45)
Plasticizers	67	8	1.32 (0.53-3.29)
POPs	291	64	2.51 (1.38-4.56)
VOCs	507	91	1.90 (1.08-3.35)
Solvents	279	58	2.37 (1.30-4.34)
Other	530	100	2.04 (1.16-3.59)

[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, autonomous region of residence (as a random effect), percentage of illiteracy, percentage of unemployed, socioeconomic status, and global crop index.

[b] IARC carcinogenic classification: Group 1: carcinogens to humans (arsenic and compounds, cadmium and compounds, chromium and compounds, nickel and compounds, lindane, 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, DDT, and hexabromobiphenyl); Group 2B: possibly carcinogenic to humans (chlordane, 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 naphthalene); 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).



Cases (n=213)

Controls (n=1278)

Industries (n=1271)

Towns with >= 75,000 inhabitants (n=30)

Supplementary Data

Title of the manuscript: “Association between residential proximity to environmental pollution sources and childhood renal tumors”.

This document is available as supplementary data for inclusion as online documentation. It includes:

a) Appendix A, showing the description of the risk gradient analysis.
b) Appendix B, showing the description of regression equations of the models for the analyses 1-3.
c) Table S1, showing the list of industrial groups, together with their E-PRTR categories, and number of installations by industrial group and autonomous region.
d) Table S2, showing the industrial groups and amounts (in kg) released by facilities in 2009, by groups of carcinogenic substances (IARC classification) and other groups of toxic substances.
e) Table S3, showing the specific pollutants released by industrial groups, both to air and water.
f) Table S4, showing the specific pollutants released by facilities, and amounts in kg and number of industrial facilities reporting these releases (in 2009).
g) Table S5, showing the Odds ratios of childhood renal tumors for ever-decreasing radiuses within a 50-kilometer area surrounding each facility, both overall and by industrial group (risk gradient analysis, with categorical and continuous variables).
h) Figure S1, showing the box-and-whisker plots with the years of commencement of operations of the 1271 industries studied, according to the industrial group.

Supplementary Data, Appendix A.

Analysis 4: Risk gradient analysis

The risk gradient analysis in the vicinity of installations was confined to an area of 50 km surrounding each installation, and the ORs were estimated using mixed multiple unconditional logistic regression models, as follows:

a) *All industries as a whole (all sectors)*: for each subject, we calculated a new variable, "$minimum\ distance_i$", defined as:

$$\text{minimum distance}_\text{i} = min\{\text{industrial distance}_\text{ij}\}_\text{j}$$

i=1, …, 1491 children, j=1, …, 1271 facilities

where $industrial\ distance_{ij}$ is the distance between child i and facility j. This new explanatory variable was categorized in concentric rings (0-1, 1-2, 2-3, 3-4, 4-5; and 5-50 km as reference). This was included in the models as both a categorical and a continuous variable, thereby making it possible for: the effect of the respective distances to be estimated by the former; the existence of radial effects to be ascertained by the latter (rise in OR with increasing proximity to an installation); and, by applying the likelihood ratio test, the statistical significance of such minimum distance-related effects to be computed.

b) *By industrial group*: for each subject and industrial group, we calculated 25 new variables, "$minimum\ distance\_industrial\ group_{ik}$", defined as:

$$\text{minimum distance\_industrial group}_\text{ik} = min\{\text{industrial group distance}_\text{ij}\}_\text{j}$$

i=1, …, 1491 children, k=1, …, 25 industrial groups, j=1, …, no. of facilities of industrial group k,

where $industrial\ group\ distance_{ij}$ is the distance between child i and facility j belonging to industrial group k. These new explanatory variables were categorized in concentric rings (0-1, 1-2, 2-3, 3-4, 4-5; and 5-50 km as reference). These were included in the models as categorical and continuous variables, and children that had some industry other than the group analyzed within a radius of 5 km of the municipal centroid were excluded.

Supplementary Data, Appendix B.

Regression equations of the models for the analyses 1-3:

Analysis 1:

$$logit = \log\left(\frac{P(Y=1)}{1-P(Y=1)}\right) = \beta_0 + \beta_1 IndusUrban_{iD} + \beta_2 GCI_i + \beta_3 year_i + \beta_4 sex_i + \beta_5 ill_i + \beta_6 unem_i + \beta_7 SES_i + r_i$$

$i = 1, \dots, 1491\ children, \quad D = 1, \dots, 7\ industrial\ distances$ (7 independent models)

where Y is the case-control status (1=case, 0=control); $IndusUrban_{iD}$ is the exposure variable in the *industrial and urban areas* analysis (sub-analysis 1.a), categorized into 4 levels (*industrial area (only) – D km*, *urban area (only)*, *both*, and *reference* area); GCI_i is the exposure variable in the *global crop index* analysis (sub-analysis 1.b), categorized into 5 levels (*Q1*, *Q2*, *Q3*, *Q4*, and *reference* group); $year_i$ is the year of birth; sex_i is the sex; ill_i is the percentage of illiteracy; $unem_i$ is the percentage of unemployed; SES_i is the socioeconomic status; and, r_i is the autonomous region of residence as a random effect. The variables of "exposure" in the two sub-analyses, the matching factors $year_i$ and sex_i, and potential confounding covariates were fixed-effects in the models.

Analysis 2:

$$logit = \log\left(\frac{P(Y=1)}{1-P(Y=1)}\right) = \beta_0 + \beta_1 IndusGroup_{ij} + \beta_2 GCI_i + \beta_3 year_i + \beta_4 sex_i + \beta_5 ill_i + \beta_6 unem_i + \beta_7 SES_i + r_i$$

$i = 1, \dots, 1491\ children, \quad j = 1, \dots, 25\ industrial\ groups$ (25 independent models)

where $IndusGroup_{ij}$ is the exposure variable, categorized as residence near the specific *industrial group* j or residence in the *reference area*. The remaining variables are the same as the above model.

Analysis 3:

$$logit = \log\left(\frac{P(Y=1)}{1-P(Y=1)}\right) = \beta_0 + \beta_1 SubstanceGroup_{ik} + \beta_2 GCI_i + \beta_3 year_i + \beta_4 sex_i + \beta_5 ill_i + \beta_6 unem_i + \beta_7 SES_i + r_i$$

$i = 1, \dots, 1491\ children, \quad k = 1, \dots, 12\ groups\ of\ toxic\ substances$ (12 independent models)

where $SubstanceGroup_{ik}$ is the exposure variable, categorized as residence near industries releasing the *group of toxic substances* k or resident in the *reference area*. The remaining variables are the same as the first model.

Supplementary Data, Table S1: list of industrial groups, together with their E-PRTR categories, and number of installations by industrial group and autonomous region.

		Autonomous regions						
Industrial group	E-PRTR category	Catalonia	Madrid Region	Basque Country	Aragon	Navarre	Other regions[a]	TOTAL
Combustion installations	1.c	15	5	8	8	3	3	42
Refineries and coke ovens	1.a, 1.d	2	0	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	9	70	11	10	4	119
Galvanization	2.c.iii	5	5	5	1	2	1	19
Surface treatment of metals and plastic	2.f	58	36	49	25	12	17	197
Mining industry	3.a, 3.b	18	8	0	5	6	2	39
Cement and lime	3.c, 3.d	13	6	5	4	3	2	33
Glass and mineral fibers	3.e, 3.f	9	1	3	1	2	4	20
Ceramic	3.g	39	8	3	15	4	17	86
Organic chemical industry	4.a	66	7	13	10	5	5	106
Inorganic chemical industry	4.b	20	2	9	14	0	1	46
Fertilizers	4.c	7	0	0	2	1	0	10
Biocides	4.d	9	0	0	3	0	0	12
Pharmaceutical products	4.e	30	9	0	2	0	0	41
Explosives and pyrotechnics	4.f	1	1	4	1	1	1	9
Hazardous waste	5.a, 5.b	32	7	11	3	3	4	60
Non-hazardous waste	5.c, 5.d	36	7	19	12	8	4	86
Disposal or recycling of animal waste	5.e	9	2	3	2	2	0	18
Urban waste-water treatment plants	5.f, 5.g	24	22	1	2	2	2	53
Paper and wood production	6.a, 6.b, 6.c	28	2	13	13	6	1	63
Pre-treatment or dyeing of textiles	9.a	7	0	1	0	1	0	9
Tanning of hides and skins	9.b	2	0	0	0	0	0	2
Food and beverage sector	8.a, 8.b, 8.c	66	17	7	29	22	4	145
Surface treatment using organic solvents	9.c	12	11	12	2	6	7	50
Production of carbon or electro-graphite	9.d	0	0	0	0	1	1	2
TOTAL		523	165	238	165	100	80	1271

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

Supplementary Data, Table S2: industrial groups and amounts (in kg) released by facilities in 2009, by groups of carcinogenic substances (IARC classification) and other groups of toxic substances.

	IARC groups[a]			Groups of toxic substances[b]								
Industrial group	Group 1	Group 2A	Group 2B	Metals	Pesticides	PACs	Non-HPCs	Plasticizers	POPs	VOCs	Solvents	Other
Combustion installations	1311336	275	0	5029	0	548	0	0	548	333457	1676	1307481
Refineries and coke ovens	443462	206	22	18556	0	315	0	0	315	2810616	5177	422599
Production and processing of metals	1172280	12911	34	160275	35	2212	2	0	2223	830065	33221	1132947
Galvanization	4389	95	0	1085	0	0.02	0	0	0.02	719	0	4367
Surface treatment of metals and plastic	68828	580	206	10290	87	12	0	200	99	2898336	1490	63145
Mining industry	1246894	0	0	0	0	0	0	0	0	48613	0	1246894
Cement and lime	1429626	331	1085	1777	0	415	0	560	334	304099	6405	1422443
Glass and mineral fibers	419668	1715	91.7	3980	0	5	0.001	0	5	2506147	870	417528
Ceramic	560042	262	2	2543	0	0.02	0	0	0.02	109861	410	558235
Organic chemical industry	375168	432	19137	3221	0.1	472	2042	0.2	465	2758750	22757	308124
Inorganic chemical industry	56575	77	18	1249	3	0.1	0	0	4	16041	19	55957
Fertilizers	23512	0	2	537	0	0	0	0	0	59	0	23512
Biocides	4601	81	0.2	21	0	0	0	0	0	2860	81	4601
Pharmaceutical products	2561	314238	91882	436	0	0.01	0	0	0.01	3252059	406243	2480
Explosives and pyrotechnics	111	374	0	395	0	0	0	0	0	454	0	101
Hazardous waste	29578	417	70	1976	0.4	95	0	0	96	54009	259	28718
Non-hazardous waste	18551	331	64	8490	54	0.3	17	6	33	138044	357	16210
Disposal or recycling of animal waste	23136	0	0	2	0	0.8	0	0	0.8	5397	0	23135
Urban waste-water treatment plants	10834	1432	80	43128	174	49	554	0	48	173123	107	172
Paper and wood production	547721	146	1	1863	11	0.4	0	0.02	11	1372034	4494	542628
Pre-treatment or dyeing of textiles	2278	0	0	60	0	0	0	0	0	6238	0	2274
Tanning of hides and skins	18	0	0	18	0	0	0	0	0	139	0	0
Food and beverage sector	244617	1	0.01	377	0	0.04	0	0	0.01	593932	0.3	244539
Surface treatment using organic solvents	63019	193	203	2964	67	0.01	0	0	67	8837821	1812	62608
Production of carbon or electro-graphite	18917	0	0	0	0	37	0	0	37	8500	0	18880
TOTAL	8077722	334095	112899	268272	431	4162	2615	766	4287	27061375	485378	7909578

[a] IARC carcinogenic classification: Group 1: carcinogens to humans (arsenic and compounds, cadmium and compounds, chromium and compounds, nickel and compounds, lindane, 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, DDT, and hexabromobiphenyl); Group 2B: possibly carcinogenic to humans (chlordane, 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).

[b] 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 naphthalene); 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).

Supplementary Data, Table S3: specific pollutants released by industrial groups, both to air and water.

	Pollutants released by industrial groups	
Industrial group	Air	Water
Combustion installations	NMVOC[a], arsenic, cadmium, chromium, copper, mercury, nickel, lead, zinc, dioxins+furans, trichloroethylene, benzene, PAHs[b], PM_{10}[c], TSP[d], manganese, vanadium	Arsenic, cadmium, chromium, copper, mercury, nickel, lead, zinc, dioxins+furans, PAHs[b], toluene, fluoranthene, benzo(g,h,i)perylene
Refineries and coke ovens	NMVOC[a], arsenic, cadmium, chromium, copper, mercury, nickel, lead, zinc, dioxins+furans, polychlorinated biphenyls, 1,1,1-trichloroethane, trichloromethane, anthracene, benzene, naphthalene, PAHs[b], PM_{10}[c], TSP[d], antimony, cobalt, manganese, vanadium, ethyl benzene	Arsenic, cadmium, chromium, copper, mercury, nickel, lead, zinc, dioxins+furans, benzene, PAHs[b], toluene, xylenes, fluoranthene, benzo(g,h,i)perylene
Production and processing of metals	NMVOC[a], arsenic, cadmium, chromium, copper, mercury, nickel, lead, zinc, hexachlorobenzene, lindane, dioxins+furans, polychlorinated biphenyls, anthracene, benzene, naphthalene, PAHs[b], PM_{10}[c], TSP[d]	Arsenic, cadmium, chromium, copper, mercury, nickel, lead, zinc, pentachlorophenol, anthracene, nonylphenol, naphthalene, organotin compounds, PAHs,[b] octylphenols, fluoranthene, benzo(g,h,i)perylene, benzo(a)pyrene, benzo(b)fluoranthene, benzo(k)fluoranthene, indeno(1,2,3-cd)pyrene
Galvanization	NMVOC[a], arsenic, cadmium, chromium, copper, nickel, lead, zinc, dioxins+furans, PM_{10}[c], TSP[d]	Arsenic, cadmium, chromium, copper, nickel, lead, zinc, PAHs[b]
Surface treatment of metals and plastic	NMVOC[a], cadmium, chromium, copper, mercury, nickel, lead, zinc, benzene, dichloromethane, 1,2,3,4,5,6-hexachlorocyclohexane, tetrachloroethylene, trichloroethylene, di-(2-ethyl hexyl) phtalate, PAHs[b], PM_{10}[c], TSP[d], manganese, vanadium	Arsenic, cadmium, chromium, copper, mercury, nickel, lead, zinc, anthracene, naphthalene, organotin compounds, di-(2-ethyl hexyl) phtalate, PAHs[b], fluoranthene, trichloromethane, toluene, benzo(b)fluoranthene, ethyl benzene, xylenes
Mining industry	NMVOC[a], PM_{10}[c], TSP[d]	
Cement and lime	NMVOC[a], arsenic, cadmium, chromium, copper, mercury, nickel, lead, zinc, dioxins+furans, polychlorinated biphenyls, anthracene, benzene, naphthalene, di-(2-ethyl hexyl) phtalate, PAHs[b], PM_{10}, TSP[d], thallium, antimony, cobalt, manganese, vanadium	Copper, zinc
Glass and mineral fibers	NMVOC[a], arsenic, cadmium, chromium, copper, mercury, nickel, lead, zinc, dioxins+furans, polychlorinated biphenyls, benzene, PAHs[b], PM_{10}[c], TSP[d], manganese, vanadium	Arsenic, cadmium, chromium, copper, mercury, nickel, lead, zinc, benzene, ethyl benzene, toluene, xylenes, octylphenols
Ceramic	NMVOC[a], arsenic, cadmium, chromium, copper, mercury, nickel, lead, zinc, benzene, PAHs[b], PM_{10}[c], TSP[d], thallium, antimony, cobalt, manganese, vanadium	Arsenic, cadmium, chromium, copper, mercury, nickel, lead, zinc, trichloromethane, naphthalene
Organic chemical industry	NMVOC[a], arsenic, cadmium, chromium, copper, mercury, nickel, lead, zinc, 1,2-dichloroethane, dichloromethane, dioxins+furans, tetrachloroethylene, tetrachloromethane, trichloromethane, vinyl chloride, anthracene, benzene, ethylene oxide, naphthalene, PAHs[b], PM_{10}[c], TSP[d], antimony, cobalt, manganese, vanadium	Arsenic, cadmium, chromium, copper, mercury, nickel, lead, zinc, aldrin, atrazine, chlordane, chlorfenvinphos, chlorpyrifos, DDT, 1,2-dichloroethane, dichloromethane, dieldrin, endosulfan, endrin, hexachlorobenzene, hexachlorobutadiene, 1,2,3,4,5,6-hexachlorociclohexane, mirex, dioxins+furans, simazine, tetrachloroethylene, trichlorobenzenes, trichloroethylene, trichloromethane, vinyl chloride, anthracene, benzene, brominated diphenylethers, nonylphenol, ethyl benzene, naphthalene, organotin compounds, di-(2-ethyl hexyl) phtalate, PAHs[b], toluene, tributyltin, xylenes, octylphenols, fluoranthene, isodrin, benzo(b)fluoranthene, indeno(g,h,i)perylene
Inorganic chemical industry	NMVOC[a], arsenic, cadmium, chromium, copper, mercury, nickel, lead, zinc, dichloromethane, dioxins+furans, tetrachloromethane, trichloromethane, PM_{10}[c], TSP[d], antimony	Arsenic, cadmium, chromium, copper, mercury, nickel, lead, zinc, hexachlorobenzene, dioxins+furans, trichloromethane, organotin compounds, PAHs[b], fluoranthene
Fertilizers	NMVOC[a], zinc, PM_{10}[c], TSP[d], cobalt	
Biocides	NMVOC[a], dichloromethane, PM_{10}[c]	Copper, zinc, ethyl benzene, xylenes
Pharmaceutical products	NMVOC[a], arsenic, cadmium, chromium, copper, mercury, nickel, lead, zinc, 1,2-dichloroethane, dichloromethane, tetrachloromethane, trichloromethane, PM_{10}[c],	Chromium, copper, mercury, lead, zinc, 1,2-dichloroethane, dichloromethane, tetrachloroethylene, tetrachloromethane, trichloroethylene, trichloromethane,

	Pollutants released by industrial groups	
Industrial group	Air	Water
	TSP[d], thallium, antimony, cobalt, manganese, vanadium	benzene, ethyl benzene, toluene, xylenes, naphthalene, PAHs[b], fluoranthene, benzo(a)pyrene, benzo(b)fluoranthene, benzo(k)fluoranthene
Explosives and pyrotechnics	NMVOC[a], lead, PM_{10}[c]	Arsenic, cadmium, chromium, copper, mercury, nickel, lead, zinc
Hazardous waste	NMVOC[a], arsenic, cadmium, chromium, copper, mercury, nickel, lead, zinc, hexachlorobenzene, dioxins+furans, tetrachloroethylene, trichloroethylene, benzene, PAHs[b], PM_{10}[c], TSP[d], thallium, antimony, cobalt, manganese, vanadium	Arsenic, cadmium, chromium, copper, mercury, nickel, lead, zinc, dichloromethane, benzene, polychlorinated biphenyls, tetrachloroethylene, trichloroethylene, trichloromethane, ethyl benzene, naphthalene, organotin compounds, PAHs[b], toluene, xylenes
Non-hazardous waste	NMVOC[a], arsenic, cadmium, chromium, copper, mercury, nickel, lead, zinc, dioxins+furans, dichloromethane, tetrachloroethylene, tetrachloromethane, trichloroethylene, vinyl chloride, PM_{10}[c], TSP[d], antimony, cobalt, manganese, vanadium	Arsenic, cadmium, chromium, copper, mercury, nickel, lead, zinc, alachlor, aldrin, atrazine, chlordane, chlorfenvinphos, chlorpyrifos, DDT, 1,2-dichloroethane, dichloromethane, dieldrin, diuron, endosulfan, endrin, heptachlor, hexachlorobenzene, hexachlorobutadiene, 1,2,3,4,5,6-hexachlorociclohexane, lindane, mirex, dioxins+furans, pentachlorobenzene, pentachlorophenol, polychlorinated biphenyls, simazine, tetrachloroethylene, trichlorobenzenes, trichloroethylene, trichloromethane, vinyl chloride, anthracene, benzene, brominated diphenylethers, nonylphenol, ethyl benzene, isoproturon, naphthalene, organotin compounds, di-(2-ethyl hexyl) phtalate, PAHs[b], toluene, tributyltin, triphenyltin, trifluralin, xylenes, octylphenols, flouranthene, isodrin, hexabromobiphenyl
Disposal or recycling of animal waste	NMVOC[a], PAHs[b], dioxins+furans, PAHs[b], PM_{10}[c], TSP[d]	Zinc, dioxins+furans
Urban waste-water treatment plants	NMVOC[a], cadmium, chromium, copper, mercury, nickel, lead, dioxins+furans, PM_{10}[c]	Arsenic, cadmium, chromium, copper, mercury, nickel, lead, zinc, atrazine, 1,2-dichloroethane, diuron, lindane, pentachlorophenol, simazine, tetrachloroethylene, tetrachloromethane, trichloromethane, anthracene, benzene, nonylphenol, ethyl benzene, isoproturon, naphthalene, organotin compounds, di-(2-ethyl hexyl) phtalate, PAHs[b], toluene, tributyltin, xylenes, octylphenols, fluoranthene, benzo(g,h,i)perylene, benzo(a)pyrene, benzo(b)fluoranthene, benzo(k)fluoranthene, indeno(1,2,3-cd)pyrene
Paper and wood production	NMVOC[a], arsenic, cadmium, chromium, copper, mercury, nickel, lead, zinc, di-(2-ethyl hexyl) phtalate, PM_{10}[c], TSP[d]	Arsenic, cadmium, chromium, copper, mercury, nickel, lead, zinc, tetrachloroethylene, trichlorobenzenes, trichloroethylene, trichloromethane, organotin compounds, di-(2-ethyl hexyl) phtalate, PAHs[b], toluene
Pre-treatment or dyeing of textiles	NMVOC[a], PM_{10}[c]	Chromium, copper, mercury, nickel, zinc,
Tanning of hides and skins	NMVOC[a]	Chromium
Food and beverage sector	NMVOC[a], arsenic, cadmium, chromium, copper, mercury, nickel, dioxins+furans, PM_{10}[c], TSP[d]	Chromium, copper, mercury, nickel, lead, zinc, naphthalene, PAHs[b], toluene, fluoranthene, benzo(g,h,i)perylene, benzo(a)pyrene, benzo(b)fluoranthene
Surface treatment using organic solvents	NMVOC[a], chromium, copper, nickel, lead, zinc, dichloromethane, naphthalene, PAHs[b], PM_{10}[c], TSP[d]	Arsenic, cadmium, chromium, copper, mercury, nickel, lead, zinc, 1,2-dichloroethane, trichloroethylene, trichloromethane, organotin compounds, toluene, naphthalene, PAHs[b]
Production of carbon or electro-graphite	NMVOC[a], PAHs[b], PM_{10}[c], TSP[d]	

[a] Non-methane volatile organic compounds.

[b] Polycyclic aromatic hydrocarbons.

[c] Particulate matter.

[d] Total suspended particulate matter.

Supplementary Data, Table S5: specific pollutants released by facilities, and amounts in kg and number of industrial facilities reporting these releases (in 2009).

				Air		Water	
Pollutant	CAS No.[a]	IARC Group[b]	Chemical substance type	Kg	Facilities	Kg	Facilities
1,1,1-trichloroethane	71-55-6		VOCs/Solvents	0.5	1	0	0
1,2,3,4,5,6-hexachlorocyclohexane	608-73-1	2B	POPs	0.1	2	0.5	10
1,2-dichloroethane	107-06-2	2B	VOCs/Solvents	9870	3	379	23
Alachlor	15972-60-8		Pesticides	0	0	0.03	4
Aldrin	309-00-2		Pesticides/POPs	0	0	8	9
Anthracene	120-12-7		PACs	82	14	1	17
Antimony	7440-36-0		Metals	122	36	0	0
Arsenic and compounds	7440-38-2	1	Metals	1053	171	1620	131
Atrazine	1912-24-9		Pesticides	0	0	5	17
Benzene	71-43-2	1	VOCs/Solvents	48538	84	56	20
Benzo(a)pyrene	50-32-8	1	POPs/PACs	0	0	0.6	5
Benzo(b)fluoranthene	205-99-2		POPs/PACs	0	0	0.6	8
Benzo(g,h,i)perylene	191-24-2		PACs	0	0	2	15
Benzo(k)fluoranthene	207-08-9		POPs/PACs	0	0	0.6	4
Brominated diphenylethers			POPs	0	0	2	11
Cadmium and compounds	7440-43-9	1	Metals	781	181	306	129
Chlordane	57-74-9	2B	Pesticides/POPs	0	0	0.1	7
Chlorfenvinphos	470-90-6		Pesticides	0	0	1	10
Chlorpyrifos	2921-88-2		Pesticides	0	0	0.9	9
Chromium and compounds	7440-47-3	1	Metals	4870	227	5157	236
Cobalt and compounds	7440-48-4	2B	Metals	137	38	0	0
Copper and compounds	7440-50-8		Metals	6230	175	7776	249
DDT	50-29-3	2A	Pesticides/POPs	0	0	0.02	5
Di-(2-ethyl hexyl) phthalate	117-81-7	2B	Plasticizers	759	13	7	13
Dichloromethane	75-09-2	2A	VOCs/Solvents	314621	20	49	13
Dieldrin	60-57-1		Pesticides/POPs	0	0	0.4	8
Diuron	330-54-1		Pesticides	0	0	173	17
Endosulfan	115-29-7		Pesticides/POPs	0	0	0.5	9
Endrin	72-20-8		Pesticides/POPs	0	0	0.4	8
Ethyl benzene	100-41-4	2B	VOCs/Solvents	0	0	8390	27
Ethylene oxide	75-21-8	1	VOCs	18159	4	0	0
Fluoranthene	206-44-0		PACs	0	0	10	35
Heptachlor	76-44-8	2B	Pesticides/POPs	0	0	0.4	7
Hexabromobiphenyl	36355-1-8		POPs	0	0	0.3	6
Hexachlorobenzene	118-74-1	2B	POPs	4	3	1	11
Hexachlorobutadiene	87-68-3		VOCs	0	0	2	11
Indeno(1,2,3-cd)pyrene	193-39-5	2B	PACs	0	0	0.6	4
Isodrin	465-73-6		Pesticides	0	0	0.01	4
Isoproturon	34123-59-6		Pesticides	0	0	2	4
Lead and compounds	7439-92-1	2A	Metals	16184	200	2767	174
Lindane	58-89-9	1	Pesticides/POPs	0.1	1	0.5	4
Manganese and compounds	7439-96-5		Metals	463	48	0	0
Mercury and compounds	7439-97-6		Metals	946	162	93	99
Mirex	2385-85-5	2B	Pesticides/POPs	0	0	0.01	4
Naphthalene	91-20-3	2B	VOCs	1217	23	178	30
Nickel and compounds	7440-02-0	1	Metals	18897	211	11727	253
Non-methane volatile organic compounds			VOCs	26514608	573	0	0
Nonylphenol and nonylphenol ethoxylates	25154-52-3		Non-HPCs	0	0	587	30
Octylphenols and octylphenol ethoxylates	1806-26-4		Non-HPCs	0	0	2028	32
Organotin compounds			Metals/Pesticides/POPs	0	0	198	26
Particulate matter (PM_{10})		1	Other	3378846.475	444	0	0
PCDD + PCDF (dioxins + furans)		1	POPs	0.05	86	0.0005	13
Pentachlorobenzene	608-93-5		Pesticides/POPs	0	0	1	10
Pentachlorophenol	87-86-5	2B	Pesticides	0	0	31	5
Polychlorinated biphenyls	1336-36-3	1	POPs	2	19	0.1	9
Polycyclic aromatic hydrocarbons		1	PACs/POPs	3286	80	778	74
Simazine	122-34-9		Pesticides	0	0	8	22
Tetrachloroethylene	127-18-4	2A	VOCs/Solvents	419	5	54	18
Tetrachloromethane	56-23-5	2B	Other	2	3	43	2
Thallium	7440-28-0		Metals	44	14	0	0
Toluene	108-88-3		VOCs/Solvents	0	0	4989	40
Total suspended particulate matter		1	Other	4530687.311	236	0	0
Tributyltin and compounds			Pesticides	0	0	0.6	5
Trichlorobenzenes	12002-48-1		VOCs/Solvents	0	0	1	11
Trichloroethylene	79-01-6	1	VOCs/Solvents	1489	8	4494	15
Trichloromethane	67-66-3	2B	VOCs/Solvents	91731	7	146	34
Trifluralin	1582-09-8		Pesticides	0	0	0.004	3
Triphenyltin and compounds			Pesticides	0	0	0.03	3
Vanadium	7440-62-2		Metals	336	34	0	0
Vinyl chloride	75-01-4	1	VOCs	46065	6	907	11
Xylenes	1330-20-7		Solvents	0	0	150	28
Zinc and compounds	7440-66-6		Metals	143770	189	44991	370

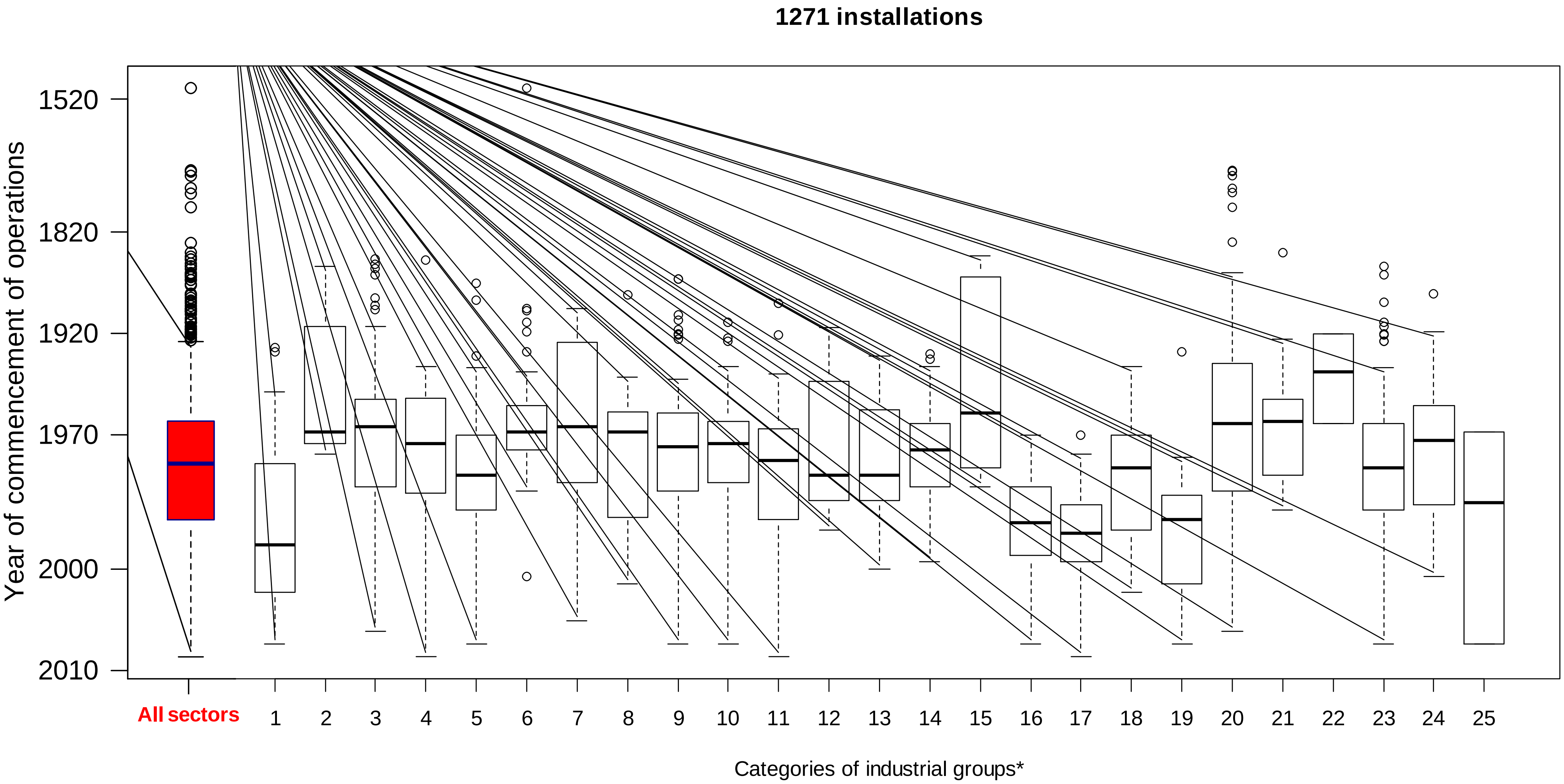
[a] Chemical Abstracts Service registry number. When the pollutant is a group of substances, the CAS is not specified.

[b] IARC carcinogenic classification.

Supplementary Data, Table S5: Odds ratios of childhood renal tumors for ever-decreasing radiuses within a 50-kilometer area surrounding each facility, both overall and by industrial group (risk gradient analysis, with categorical and continuous variables).

	Categorical variables																	Continuous variables	
	[0-1 km)			[1-2 km)			[2-3 km)			[3-4 km)			[4-5 km)			Reference: [5-50 km]			
Industrial group	Controls	Cases	OR (95%CI)	Controls	Cases	OR (95%CI)	Controls	Cases	OR (95%CI)	Controls	Cases	OR (95%CI)	Controls	Cases	OR (95%CI)	Controls	Cases	OR	p-trend
All sectors	242	49	2.07 (1.13-3.78)	310	57	1.96 (1.09-3.54)	170	28	1.74 (0.90-3.35)	62	10	1.53 (0.65-3.58)	47	5	0.99 (0.35-2.86)	156	19	1.16	0.0067
Combustion installations	8	2	2.97 (0.49-18.01)	41	4	0.99 (0.29-3.37)	35	5	1.31 (0.42-4.06)	43	7	1.58 (0.57-4.42)	36	6	1.40 (0.47-4.17)	134	19	1.07	0.5550
Refineries and coke ovens	0	0	-	7	1	-	13	5	-	6	1	-	2	2	-	19	0	-	-
Production and processing of metals	40	5	1.31 (0.43-4.04)	75	12	1.51 (0.64-3.56)	92	23	2.19 (1.04-4.62)	68	14	1.75 (0.75-4.04)	38	8	1.69 (0.64-4.48)	109	16	1.09	0.2867
Galvanization	13	1	0.38 (0.04-3.44)	21	6	1.65 (0.55-4.96)	23	10	2.72 (0.99-7.47)	20	4	1.21 (0.35-4.27)	34	7	1.16 (0.42-3.27)	84	16	1.08	0.4536
Surface treatment of metals and plastic	82	23	2.60 (1.27-5.33)	157	31	1.92 (0.98-3.77)	171	26	1.39 (0.70-2.76)	107	18	1.53 (0.73-3.21)	47	9	1.60 (0.66-3.88)	128	18	1.18	0.0120
Mining industry	2	0	0 (0-inf)	2	1	3.39 (0.25-46.31)	7	0	0 (0-inf)	6	1	1.20 (0.12-12.23)	23	5	1.46 (0.43-4.90)	115	18	0.95	0.8392
Cement and lime	6	1	0.99 (0.10-9.92)	16	3	1.42 (0.33-6.20)	24	5	1.67 (0.50-5.55)	35	12	3.05 (1.18-7.92)	54	6	1.06 (0.34-3.27)	104	18	1.14	0.2761
Glass and mineral fibers	8	2	3.43 (0.54-21.76)	30	9	5.28 (1.63-17.12)	57	6	1.19 (0.39-3.60)	35	6	1.69 (0.56-5.11)	36	7	1.93 (0.67-5.56)	98	14	1.28	0.0463
Ceramic	16	6	1.68 (0.48-5.83)	32	8	1.79 (0.68-4.67)	24	5	1.45 (0.48-4.44)	23	4	1.21 (0.37-3.97)	37	9	1.67 (0.67-4.15)	126	19	1.11	0.2476
Organic chemical industry	25	6	2.28 (0.78-6.64)	87	16	1.62 (0.76-3.49)	81	14	1.60 (0.73-3.54)	63	18	2.78 (1.28-6.05)	60	15	2.19 (2.99-4.86)	131	19	1.09	0.2592
Inorganic chemical industry	4	0	0 (0-inf)	36	5	1.18 (0.37-3.72)	47	7	1.15 (0.41-3.28)	29	15	4.88 (1.93-12.30)	49	7	1.73 (0.58-5.20)	104	14	1.04	0.7362
Fertilizers	1	0	0 (0-inf)	3	2	4.50 (0.37-54.84)	4	0	0 (0-inf)	2	2	3.79 (0.33-43.98)	10	1	0.46 (0.04-5.55)	37	6	1.31	0.3314
Biocides	4	0	0 (0-inf)	12	2	1.36 (0.19-9.65)	13	1	0.90 (0.08-10.37)	25	6	1.44 (0.31-6.71)	19	2	0.81 (0.12-5.59)	37	5	1.04	0.8557
Pharmaceutical products	22	4	1.25 (0.35-4.38)	72	10	1.14 (0.46-2.83)	70	13	1.49 (0.63-3.54)	60	7	0.97 (0.35-2.67)	59	11	1.37 (0.57-3.29)	103	15	1.04	0.6833
Explosives and pyrotechnics	2	0	0 (0-inf)	1	1	4.44 (0.23-85.46)	4	0	0 (0-inf)	4	0	0 (0-inf)	3	2	3.52 (0.45-27.80)	61	15	0.86	0.6097
Hazardous waste	9	1	1.16 (0.13-10.44)	47	8	1.46 (0.57-3.75)	62	19	2.65 (1.23-5.71)	98	12	1.06 (0.46-2.44)	70	15	1.92 (0.85-4.32)	127	18	1.13	0.1975
Non-hazardous waste	5	0	0 (0-inf)	26	5	2.04 (0.62-6.72)	51	10	1.82 (0.70-4.74)	57	9	1.40 (0.53-3.69)	42	8	1.87 (0.70-5.00)	142	18	1.14	0.2804
Disposal or recycling of animal waste	6	2	2.08 (0.36-12.01)	17	1	0.34 (0.04-2.84)	34	10	1.88 (0.62-5.67)	49	3	0.40 (0.10-1.60)	13	4	1.96 (0.53-7.33)	96	15	1.02	0.8734
Urban waste-water treatment plants	13	3	2.35 (0.57-9.69)	51	12	2.23 (0.95-5.28)	104	19	1.89 (0.88-4.07)	112	27	2.35 (1.15-4.78)	116	16	1.46 (0.67-3.18)	130	18	1.19	0.0338
Paper and wood production	16	2	1.03 (0.20-5.16)	41	6	1.21 (0.43-3.46)	62	4	0.46 (0.14-1.50)	57	13	1.90 (0.81-4.49)	51	9	1.44 (0.56-3.74)	135	19	0.97	0.7540
Pre-treatment or dyeing of textiles	1	2	inf (0-inf)	0	2	inf (0-inf)	9	0	0 (0-inf)	4	0	0 (0-inf)	2	0	0 (0-inf)	31	6	1.38	0.2522
Tanning of hides and skins	2	0	0 (0-inf)	1	0	0 (0-inf)	0	0	-	0	0	-	0	0	-	13	3	-	-
Food and beverage sector	37	11	2.45 (1.04-5.80)	113	23	1.86 (0.93-3.72)	67	12	1.62 (0.72-3.69)	57	7	1.11 (0.43-2.88)	103	18	1.65 (0.78-3.48)	140	19	1.15	0.0399
Surface treatment using organic solvents	11	2	1.54 (0.30-7.93)	40	8	1.73 (0.66-4.58)	56	9	1.45 (0.57-3.71)	68	10	1.30 (0.53-3.18)	51	15	2.40 (1.05-5.51)	110	16	1.08	0.4561
Production of carbon or electro-graphite	0	0	-	0	0	-	0	0	-	1	0	0 (0-inf)	2	1	3.38 (0.16-73.00)	31	11	1.12	0.9180

Supplementary Data, Figure S1: box-and-whisker plots with the years of commencement of operations of the 1271 industries studied, according to the industrial group.



*1=Combustion installations. 2=Refineries and coke ovens. 3=Production and processing of metals. 4=Galvanization. 5=Surface treatment of metals and plastic. 6=Mining industry. 7=Cement and lime. 8=Glass and mineral fibers. 9=Ceramic. 10=Organic chemical industry. 11=Inorganic chemical industry. 12=Fertilizers. 13=Biocides. 14=Pharmaceutical products. 15=Explosives and pyrotechnics. 16=Hazardous waste. 17=Non-hazardous waste. 18=Disposal or recycling of animal waste. 19=Urban waste-water treatment plants. 20=Paper and wood production. 21=Pre-treatment or dyeing of textiles. 22=Tanning of hides and skins. 23=Food and beverage sector. 24=Surface treatment using organic solvents. 25=Production of carbon or electro-graphite.