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Residential proximity to environmental pollution sources and risk of rare tumors in children

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Abbreviations:

RETI-SEHOP: Spanish Registry of Childhood Tumors

NSI: National Statistics Institute

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

Abstract

Background: Few epidemiologic studies have explored risk factors for rare tumors in children, and the role of environmental factors needs to be assessed.
Objectives: To ascertain the effect of residential proximity to both industrial and urban areas on childhood cancer risk, taking industrial groups into account.
Methods: We conducted a population-based case-control study of five childhood cancers in Spain (retinoblastoma, hepatic tumors, soft tissue sarcomas, germ cell tumors, and other epithelial neoplasms/melanomas), including 557 incident cases from the Spanish Registry of Childhood Tumors (period 1996-2011), and 3342 controls individually matched by year of birth, sex, and region of residence. Distances were computed from the residences to the 1271 industries and the 30 urban areas with ≥75,000 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 and socioeconomic confounders.
Results: Children living near industrial and urban areas as a whole showed no excess risk for any of the tumors analyzed. However, isolated statistical associations (OR; 95%CI) were found between retinoblastoma and proximity to industries involved in glass and mineral fibers (2.49; 1.01-6.12 at 3 km) and organic chemical industries (2.54; 1.10-5.90 at 2 km). Moreover, soft tissue sarcomas registered the lower risks in the environs of industries as a whole (0.59; 0.38-0.93 at 4 km).
Conclusions: We have found isolated statistical associations between retinoblastoma and proximity to industries involved in glass and mineral fibers and organic chemical industries.

Key Words: childhood cancer; rare tumor; industrial pollution; urban pollution; case-control study; residential proximity

1. Introduction

Childhood cancer is the main cause of disease-related death in childhood affecting both sexes in developed countries (National Cancer Institute, 2016; WHO, 2016). Although advances in diagnosis and treatment have improved 5-year survival rates for childhood cancer, which are now as high as 78-83% (Gatta et al., 2014; Howlader et al., 2015), children are at risk for short-and long-adverse effects of treatment: surgery-related complications, development of secondary tumors, and chronic health conditions (endocrine disorders and gonadal failure, orthopedic sequelae, cardiac disease and congestive heart failure, pulmonary complications, and neurosensory/neurologic adverse outcomes) (Diller et al., 2009; Friedman et al., 2016; Kaste et al., 2008; Madenci et al., 2015; Marques et al., 2016; Meadows et al., 2009; Mulrooney et al., 2016; Oeffinger et al., 2006; Versluys and Bresters, 2016).

The causes of childhood cancer are largely unknown. Few risk factors have been established – including genetic factors, congenital anomalies or ionizing radiation –, but they explain only a small proportion of childhood cancers (Ross and Spector, 2006; Ross and Swensen, 2000; Stiller, 2004; Wakeford et al., 2009). With respect to environmental exposures, several studies have analyzed the risk of frequent childhood cancers – such as leukemias, central nervous system or lymphomas –, and exposure to toxic substances (Carlos-Wallace et al., 2016; Vinson et al., 2011; Whitworth et al., 2008) or in the environs of pollution sources (Danysh et al., 2015; Knox and Gilman, 1997; Weng et al., 2008). However, there are no epidemiologic studies about the risk of rare tumors in children (cancers with an incidence rate ≤2 per million per year (Bisogno et al., 2012), such as retinoblastoma, hepatoblastoma or germ cell tumors) in the proximity of environmental pollution sources, such as industrial plants and urban areas with air pollution from traffic. Some authors have focused attention on occupational exposures (Abdolahi et al., 2013; Buckley et al., 1989; Chen et al., 2005; Grufferman et al., 2014) but the diverse diagnostic groups, clinical behaviors, and low numbers of cases limit the research in these rare cancers (Brecht et al., 2014; Rodriguez-Galindo et al., 2013). Therefore, epidemiologic science research is needed to ascertain whether residential proximity to environmental exposures might have an influence on the frequency of these childhood cancers.

In this paper, we analyze the possible association between residential proximity to environmental pollution sources (industrial plants – including different industrial groups and groups of carcinogenic/toxic substances –, and urban areas) and risk of five groups of rare tumors in children (retinoblastoma, hepatic tumors, soft tissue sarcomas, germ cell tumors, and other epithelial neoplasms and melanomas), in the context of the biggest population-based case-control study of incident childhood cancer carried out in Spain (Garcia-Perez et al., 2015; Garcia-Perez et al., 2016; Ramis et al., 2015).

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 rare tumors in children (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, according to the International Classification of Diseases for Oncology, 3^{rd} revision, as retinoblastoma (code V), hepatic tumors (code VII), soft tissue and other extraosseous sarcomas (code IX), germ cell tumors, trophoblastic tumors, and neoplasms of gonads (code X), and other malignant epithelial neoplasms and malignant melanomas (code XI) (Steliarova-Foucher et al., 2005). Six controls per case were selected by simple random sampling from among all live births registered in the Birth Registry of the Spanish National Statistics Institute (NSI) between 1996 and 2011, individually matched to cases by year of birth, sex, and autonomous region of residence. The final study population comprised 557 cases (139 of retinoblastoma, 58 of hepatic tumors, 200 of soft tissue sarcomas, 120 of germ cell tumors, and 40 of other epithelial neoplasms and melanomas) and 3342 controls.

2.2 Residential locations

Each individual's last residence was geocoded using Google Map Javascript API v3 and QGIS software (Open Source Geospatial Foundation, 2016), where the last digit of coordinates (X, Y) was assigned randomly in order to preserve their confidentiality.

We geocoded the home address of the cases at the moment of diagnosis (included in the RETI-SEHOP), and the home address of the mother at birth for the controls (included in the Birth Registry of the NSI).

2.3 Industrial facility and urban 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 Pollutant Release and Transfer Register (E-PRTR) – provided by the Spanish Ministry for Agriculture, Food & Environment in 2009, which includes information on the geographic location, previously validated (Garcia-Perez et al., 2015), and industrial pollution emissions of all industrial plants in Spain. We selected the 1271 industries that reported their releases to air and water in 2009, classified into one of the 25 categories of industrial groups listed in Supplementary Data, Table S1. Additionally, Supplementary Data, Figure S1 shows the distribution of the years of commencement of operations of the installations studied, by industrial group. The mean year of commencement of operations for industries as a whole was 1974.

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

2.4 Exposure coding and statistical analysis

For each subject, we calculated: a) industrial distance: the shortest Euclidean distance between the subject's residence and any of the 1271 industrial installations; and b) urban distance: the shortest Euclidean distance between the subject's residence and any of the 30 centroids of the towns.

Using the same methodology as in a previous paper of our group (Garcia-Perez et al., 2016), 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). All models included: matching factors (year of birth, sex, and autonomous region of residence); other potential confounders provided by the 2001 census at a census tract level (percentage of illiteracy, percentage of unemployed, and socioeconomic status); and percentage of total crop surface in a 1-km buffer around each individual's last residence (GCI_{ij}) as a proxy of exposure to pesticides, described in detail in (Gomez-Barroso et al., 2016). The exposure variables, the matching factors year and sex, and potential confounding covariates were fixed-effects in the models, whereas autonomous region was a random effect.

1) Analysis 1 (relationship between childhood tumors and proximity to industrial installations and urban sites as a whole). Taking into account several industrial distances 'D' (5, 4, 3, and 2 km), each subject was classified into one of the following 4 categories of exposure variable for each tumor and distance 'D' (4

independent models for each tumor): a) residence in the *"industrial area (only)"*, defined in terms of proximity to industrial facilities, on the basis of the distance 'D'; b) residence in the *"urban area (only)"*, taking the areas defined by urban distances according to the size and spatial characteristics of the municipalities in Spain; 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. Additionally, with the aim of introducing robustness in our analysis and controlling potential biases introduced by the use of home addresses of the cases at the moment of diagnosis instead of birth addresses, we performed a sensitivity analysis including only cases with the same address at the time of birth and at the moment of diagnosis. For this purpose, we used a matching strategy to find children with the addresses of the Birth Registry of the NSI matched to RETI-SEHOP.

2) Analysis 2 (relationship between childhood tumors and proximity to industries by category of industrial groups). Taking into account 25 categories of industrial groups defined in Supplementary Data, Table S1 (25 independent models for each tumor and distance 'D'), we created an exposure variable for each tumor and distance 'D', 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 industry and far from urban areas. The remaining variables were the same as in the above model.

3) Analysis 3 (relationship between childhood tumors and residential proximity to industries by groups of carcinogens according to the International Agency for Research on Cancer, and other toxic substances). To this end, we created an exposure variable for each tumor and distance 'D' (12 independent models for each tumor and distance 'D'), where each subject was categorized as resident near industries releasing the specific "*group of carcinogens or toxic substances"* or resident in the "*reference area"*, analogous to the previous analysis. The remaining variables were the same as in the first model.

As we have considered a frequency matched study, given that matching conditions 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).

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 main characteristics of the 577 cases and 3342 controls included in the analyses were depicted in Table 1. Retinoblastoma, and other epithelial neoplasms and melanomas were the two groups of childhood tumors with a higher distribution by sex in girls than boys (51.1% vs. 48.9%, and 60.0% vs. 40.0%, respectively). Moreover, Catalonia and Madrid Region were the autonomous regions with the highest proportion of cases and controls in the majority of tumors, and other epithelial neoplasms and melanomas was the diagnostic group with the highest age median at diagnosis (6 years).

Estimated ORs of childhood cancers associated with residential proximity to industrial and urban sites, using different industrial distances (analysis 1), are shown in Table 2. Children living near industrial areas (only) registered non-statistically significant excess risks of retinoblastoma, germ cell tumors, and other epithelial neoplasms and melanomas. The remaining childhood cancers showed no excess risks, and soft tissue sarcomas registered the lower risks, being statistically significant for all distances analyzed, suggesting a negative association between proximity to industries and this diagnostic group of cancer, i.e., children living in the reference area (mainly rural zones) showed a higher risk than children close to industries. On the other hand, children living near urban areas (only) registered excess risks of retinoblastoma, and germ cell tumors, although non-statistically significant. The remaining cancers showed no excess risks in the proximity of urban areas. Lastly, for the intersection area between industrial and urban areas, there was an excess risk of germ cell tumors in children for all industrial distances, although non-statistically significant. On the other hand, the sensitivity analysis including only the cases with the same address at birth and at the moment of diagnosis (Table 3) shows similar ORs than those showed in Table 2, except for the intersection area between industrial and urban areas in the case of soft tissue sarcomas (which now shows increased risks between 1.16 at 5 km and 1.78 at 2 km), and urban areas (only) in the case of retinoblastoma (with ORs lower than the unit at 5 and 4 km).

In relation to the analysis of proximity to industries by categories of industrial groups (analysis 2), retinoblastoma was the only diagnostic group that showed statistically significant excess risks and a number of cases>5 for the following industrial groups and distances (see Supplementary Data, Table S1): 'Glass and mineral fibers' (OR=2.49; 95%CI=1.01-6.12 at 3 km), and 'Organic chemical industry' (OR=2.54; 95%CI=1.10-5.90 at 2 km). These analyses were performed separately for each of the 25 categories of industrial groups, as were the corrections using multiple comparisons, in the case of retinoblastoma (see Supplementary Data, Table S1), germ cell tumors (see Supplementary Data, Table S2), and other epithelial neoplasms and melanomas (see Supplementary Data, Table S3).

In relation to the analysis of proximity to industries by categories of groups of carcinogens and other toxic substances released by the facilities (analysis 3), there were no statistically significant excess risk in any of the diagnostic groups analyzed. The results of this analysis for retinoblastoma, germ cell tumors, and other epithelial neoplasms and melanomas are included in Supplementary Data, Tables S4, S5, and S6, respectively.

Finally, Table 4 shows detailed information on emission amounts by specific pollutants released by the facilities included in our study. We have included the established threshold according to the E-PRTR for each pollutant, the chemical substance type, and those substances classified by the International Agency for Research on Cancer (IARC) as carcinogenic (Group 1), probably carcinogenic (Group 2A) and possibly carcinogenic (Group 2B).

4. Discussion

4.1 Summary

To our knowledge, this is the first study that analyzes the risk of rare tumors in children in the vicinity of environmental pollution sources, as industrial plants and urban areas, according to different industrial groups and groups of carcinogens and other toxic pollutants. Our results did not show increased risks with residential proximity to environmental pollution sources, albeit we have found isolated statistical associations between retinoblastoma and proximity to industries involved in glass and mineral fibers and organic chemical industries.

4.2 Retinoblastoma

There are few epidemiologic studies of retinoblastoma. Some authors have reported associations between this cancer and parental age, human papillomavirus, and paternal employment in the military and metal manufacturing (Bunin et al., 1990; Heck et al., 2012), whereas the results of other studies suggest a role for several maternal health and reproductive factors (Heck et al., 2015a), and maternal active smoking during pregnancy (Azary et al., 2016). Other suggested risk factors are paternal occupational exposures to non-welding metals and pesticides (Abdolahi et al., 2013). On the other hand, a recent study provided some evidence that maternal diet higher in fruits and lower in fried foods and cured meats may reduce the risk of retinoblastoma (Lombardi et al., 2015).

Insofar as environmental pollution exposures and retinoblastoma are concerned, we did not find epidemiologic studies about residential proximity to industrial installations, and there are very few papers focused on urban areas and/or specific pollutants. Two studies carried out in California (US) showed associations between risk of retinoblastoma and prenatal exposure to traffic-related air pollution during the first trimester (Ghosh et al., 2013; Heck et al., 2013), and average $PM_{2,5}$ concentrations during pregnancy (Heck et al., 2013). In our study, we have registered non-statistically significant excess risks of retinoblastoma near urban areas, as a proxy of exposure to traffic pollution. In relation to specific pollutants, another study carried out in California (US) found associations between increased risk of retinoblastoma and pregnancy exposure to some pollutants, such as benzene, chloroform, chromium, para-dichlorobenzene, nickel, toluene, 1,3-butadiene, ethyl benzene, xylenes, and acetaldehyde (Heck et al., 2015b). In our study, we only found significant associations between retinoblastoma and organotin compounds (OR=2.20; 95%CI=1.04-4.66 at 5 km), tetrachloromethane (OR=2.54; 95%CI=1.01-6.40 at 4 km), toluene (OR=3.18; 95%CI=1.29-7.82 at 2 km), and trichloroethylene (OR=5.98; 95%CI=1.62-22.04 at 2 km) (data not shown).

4.3 Germ cell tumors

Germ cell tumors are grouped by both location and cells of origin, and include, among others, gonadal tumors of the testes or ovaries. Due to its rarity, few epidemiologic studies have explored risk factor for malignant germ cell tumors in children. Cryptorchidism is one of the few established risk factors for testicular germ cell tumors (Strader et al., 1988), and other risk factors that may also be associated with germ cell tumors include in utero exposure to maternal endogenous hormones, radiation exposure during pregnancy, parental environmental exposures to chemicals or solvents, and maternal diseases and viral infections during pregnancy (Ross and Spector, 2006; Shu et al., 1995). A family history of cancer with onset <40 years could be associated with an increased risk among male cases (Poynter et al., 2010).

In relation to environmental pollution exposures, an American study did not show a strong association of increased germ cell tumor risk in offspring with parental or child-postnatal residential exposure to insecticides, certain chemicals (paints, stains, petroleum products, or hair dyes), metals (iron, nickel, copper, or mercury), engine exhaust fumes, and industrial dusts (Chen et al., 2006). In another paper, the same authors failed to find strong evidence in support of a relation between parental exposure to pesticides in the workplace and an increased risk of germ cell tumors in offspring (Chen et al., 2005). In this sense, the results of our study showed no association between increased risk of germ cell tumors and proximity to industries releasing metals or pesticides (see Supplementary Data, Table S6).

With regard to exposure to traffic pollution, Heck et al. (Heck et al., 2013) showed associations between risk of germ cell tumors and prenatal exposure to traffic-related air pollution during the first trimester. In our study, we found no association with proximity to urban areas with traffic pollution.

4.4 Other childhood tumors

With respect to other childhood tumors assessed in the present study, very few epidemiologic studies have explored environmental risk factors of these tumors due to the rarity and the heterogeneity of the different diagnostic groups. One of the most surprising results found in our investigation is the low risk of children with soft tissue sarcomas residing near industrial and urban sites, where the risk estimates obtained were less than unity and statistically significant (see Table 2). This means that the reference zone (principally, rural zones) showed higher risks than the remaining areas. In this sense, an English study found a higher incidence of soft tissue sarcomas in more rural than in less urban zones (McNally et al., 2003), and other authors found no associations between rhabdomyosarcoma (the largest homogeneous group of soft tissue sarcomas in children) and prenatal exposure to traffic-related air pollution during the first trimester (Heck et al., 2013), with risk estimators less than unity.

Another tumor in our study with low risks was hepatic cancer. Heck et al. (Heck et al., 2013) also found risk estimators less than unity in children with hepatoblastoma (the main histologic type of hepatic tumor in children) residing near traffic-related air pollution. However, Thompson et al. (Thompson et al., 2008) found elevated spatial risks of childhood hepatic tumors near hazardous air pollutant release facilities (OR=1.87), whereas our risk estimates in relation to industrial areas ranged between 0.60 and 0.65. On the other hand, in relation to occupational exposures and risk of hepatoblastoma, Buckeley et al. (Buckley et al., 1989) found further evidence that occupational exposures (metals, petroleum products, and paints or pigments) may increase the risk of this cancer in offspring.

4.5 Limitations and strengths

Aside from the limitations inherent to all case-control studies, in our case mention should also be made of the following: the small sample size and the exploratory nature of the study; 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 (though we included some socioeconomic variables at a census tract level, so we assigned to every subject the information of the corresponding census tract, as other similar studies (Mezei et al., 2006)); the use of 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 dependent on prevailing winds, geographic landforms, and releases into aquifers (though this would limit the capacity to find positive results, without invalidating the associations found); the non-inclusion of information about parental occupational exposures for their unavailability at an individual level; and the non-inclusion of some factors that could be potentially related to the misclassification of the exposure, such as confounding by indoor air pollution and the time actually spent inside the exposure areas.

It should be noted that we have the home address of the cases at the time of diagnosis, and the home address of the mother at birth for the controls. This difference could introduce some bias in the analysis. To control this bias, we carried out a sensitivity analysis including only cases with the same address at birth and at the moment of diagnosis. This reduces considerably the problem of misclassification in the exposure due to the residential mobility of children, inasmuch as this sub-analysis includes all children (cases and controls) with the same window of exposure.

Yet another limitation is that, for the cases, we used the residential location at time of diagnosis and at time of birth in a subset of cases, with the purpose of assessing the effects of exposure to pollutant sources, an approach that might not have adequately accounted for antecedent exposure due to changes of residence between the pregnancy and the time of diagnosis or the time of birth, and do not allow us to explore the effects of the latency period of the different diagnostic groups, thus inducing some degree of exposure misclassification (Ortega-Garcia et al., 2016; Vinceti et al., 2012).

In Spain, there is a low rate of local migration between provinces: according to official data, in Spain only around 1% of the children change their residence to a different province (National Statistics Institute, 2016). However, an important limitation is the possible residential mobility of children within the same province, something that could affect the accuracy of the exposure assessment. Regrettably, we have no data on migration within each province. In our case, however, this would amount to a non-differential bias which would limit the capacity to find positive results and, in turn, render the estimates of real risk greater than those found.

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 a similar risk of exposure as the cases (the null hypothesis of our study is that controls and cases have the same risk of exposure in industrial and urban areas). 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 group of carcinogenic and toxic substances, which provides a description more exhaustive of childhood cancer risk; the 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); and the lack of recall bias.

5. Conclusions

Our results did not show increased risks of rare tumors in children with residential proximity to environmental pollution sources, albeit we have found isolated statistical associations between retinoblastoma and proximity to industries involved in glass and mineral fibers and organic chemical industries.

However, it would be of great interest in the future 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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Table 1: Characteristics of cases of childhood tumors and controls.

	Retinoblastoma n (%)		Hepatic tumors n (%)		Soft tissue sarcomas n (%)		Germ cell tumors n (%)		Other epithelial neoplasms / melanomas n (%)	
Characteristic	Cases (n=139)	Controls (n=834)	Cases (n=58)	Controls (n=348)	Cases (n=200)	Controls (n=1200)	Cases (n=120)	Controls (n=720)	Cases (n=40)	Controls (n=240)
Sex										
Male	68 (48.9)	408 (48.9)	38 (65.5)	228 (65.5)	123 (61.5)	738 (61.5)	61 (50.8)	366 (50.8)	16 (40.0)	96 (40.0)
Female	71 (51.1)	426 (51.1)	20 (34.5)	38 (34.5)	77 (38.5)	462 (38.5)	59 (49.2)	354 (49.2)	24 (60.0)	144 (60.0)
Year of birth, mean (SD)	2004 (4)	2004 (4)	2003 (4)	2003 (4)	2002 (4)	2002 (4)	2002 (4)	2002 (4)	2001 (4)	2001 (4)
Autonomous region										
Catalonia	58 (41.7)	348 (41.7)	22 (37.9)	132 (37.9)	85 (42.5)	510 (42.5)	55 (45.8)	330 (45.8)	27 (67.5)	162 (67.5)
Madrid	51 (36.7)	306 (36.7)	23 (39.7)	138 (39.7)	69 (34.5)	414 (34.5)	44 (36.7)	264 (36.7)	6 (15.0)	36 (15.0)
Basque Country	10 (7.2)	60 (7.2)	7 (12.1)	42 (12.1)	25 (12.5)	150 (12.5)	6 (5.0)	36 (5.0)	5 (12.5)	30 (12.5)
Aragon	11 (7.9)	66 (7.9)	5 (8.6)	30 (8.6)	10 (5.0)	60 (5.0)	10 (8.3)	60 (8.3)	2 (5.0)	12 (5.0)
Navarre	9 (6.5)	54 (6.5)	1 (1.7)	6 (1.7)	11 (5.5)	66 (5.5)	5 (4.2)	30 (4.2)	0 (0.0)	0 (0.0)
Age at diagnosis (years), mean (SD)	1.5 (1.3)		2.6 (2.6)		4.6 (3.8)		4.2 (4.3)		6.2 (4.1)	
median (IQR)	1.0 (1.0)		2.0 (2.0)		4.0 (6.0)		2.0 (8.0)		6.0 (7.0)	
Unemployment, mean (SD)	10.7 (3.8)	11.1 (3.8)	10.1 (3.2)	11.2 (3.8)	10.8 (3.6)	11.1 (3.8)	10.1 (3.7)	10.8 (3.8)	11.3 (5.2)	10.7 (3.7)
Illiteracy, mean (SD)	9.5 (6.5)	10.0 (6.7)	7.9 (5.3)	10.4 (7.1)	9.2 (5.8)	9.7 (6.4)	8.9 (6.7)	10.0 (6.8)	10.1 (6.1)	9.7 (6.0)
Socioeconomic status, mean (SD)	1.1 (0.1)	1.1 (0.1)	1.1 (0.1)	1.1 (0.1)	1.1 (0.1)	1.1 (0.1)	1.1 (0.1)	1.1 (0.1)	1.1 (0.1)	1.1 (0.1)
Global crop index										
Reference: 0%	120 (86.3)	735 (88.1)	41 (70.7)	305 (87.6)	153 (76.5)	1068 (89.0)	87 (72.5)	625 (86.8)	31 (77.5)	192 (80.0)
1st quartile (Q1)	6 (4.3)	25 (3.0)	2 (3.5)	11 (3.2)	8 (4.0)	33 (2.8)	6 (5.0)	24 (3.3)	3 (7.5)	14 (5.8)
2nd quartile (Q2)	2 (1.5)	26 (3.1)	3 (5.2)	12 (3.4)	10 (5.0)	35 (2.9)	7 (5.8)	24 (3.3)	2 (5.0)	11 (4.6)
3rd quartile (Q3)	5 (3.6)	23 (2.8)	10 (17.2)	9 (2.6)	13 (6.5)	31 (2.5)	9 (7.5)	24 (3.3)	0 (0.0)	11 (4.6)
4th quartile (Q2)	6 (4.3)	25 (3.0)	2 (3.4)	11 (3.2)	16 (8.0)	33 (2.8)	11 (9.2)	23 (3.3)	4 (10.0)	12 (5.0)
Diagnostic group										
Retinoblastoma	139 (100.0)									
Hepatic tumors										
Hepatoblastoma			53 (91.4)							
Hepatic carcinomas			5 (8.6)							
Soft tissue sarcomas										
Rhabdomyosarcomas					105 (52.5)					
Fibrosarcomas, peripheral nerve sheath tumors and other fibrous neoplasms					20 (10.0)					
Other specified soft tissue sarcomas					60 (30.0)					
Unspecified soft tissue sarcomas					15 (7.5)					
Germ cell tumors										
Intracranial and instraspinal germ cell tumors							35 (29.2)			
Malignant extracranial and extragonadal germ cell tumors							45 (37.5)			
Malignant gonadal germ cell tumors							40 (33.3)			
Other epithelial neoplasms/melanomas										
Adrenocortical carcinomas									6 (15.0)	
Thyroid carcinomas									13 (32.5)	
Nasopharyngeal carcinomas									1 (2.5)	
Malignant melanomas									13 (32.5)	
Skin carcinomas									2 (5.0)	
Other and unspecified carcinomas									5 (12.5)	

Table 2: Odds ratios of childhood tumors by industrial distance and exposure category.

Industrial distance[a]	Exposure category	Retinoblastoma			Hepatic tumors			Soft tissue sarcomas		
		Controls (n)	Cases (n)	OR (95%CI)[b]	Controls (n)	Cases (n)	OR (95%CI)[b]	Controls (n)	Cases (n)	OR (95%CI)[b]
5 Km										
	Reference	102	15	-	28	10	-	121	35	-
	Industrial area - 5 km (only)	526	95	1.33 (0.73-2.44)	214	39	0.64 (0.26-1.57)	780	115	0.60 (0.39-0.93)
	Urban area (only)	13	4	2.08 (0.58-7.42)	7	2	1.19 (0.19-7.53)	26	0	0 (0-inf)
	Both[c]	193	25	0.94 (0.45-1.94)	99	7	0.33 (0.10-1.09)	273	50	0.81 (0.48-1.37)
4 Km										
	Reference	102	15	-	28	10	-	121	35	-
	Industrial area - 4 km (only)	504	89	1.31 (0.71-2.40)	203	34	0.60 (0.24-1.48)	743	108	0.59 (0.38-0.93)
	Urban area (only)	52	9	1.16 (0.46-2.92)	28	2	0.31 (0.06-1.75)	72	9	0.51 (0.23-1.17)
	Both[c]	154	20	0.96 (0.45-2.04)	78	7	0.45 (0.14-1.48)	227	41	0.81 (0.47-1.39)
3 Km										
	Reference	102	15	-	28	10	-	121	35	-
	Industrial area - 3 km (only)	465	82	1.31 (0.71-2.42)	184	31	0.60 (0.24-1.50)	671	103	0.64 (0.41-1.00)
	Urban area (only)	87	17	1.33 (0.60-2.93)	48	5	0.44 (0.12-1.66)	136	20	0.60 (0.31-1.15)
	Both[c]	119	12	0.76 (0.32-1.76)	58	4	0.36 (0.10-1.42)	163	30	0.86 (0.48-1.54)
2 Km										
	Reference	102	15	-	28	10	-	121	35	-
	Industrial area - 2 km (only)	332	61	1.38 (0.73-2.59)	131	23	0.65 (0.25-1.68)	520	77	0.62 (0.39-0.99)
	Urban area (only)	127	22	1.19 (0.57-2.52)	75	6	0.33 (0.10-1.16)	208	31	0.62 (0.35-1.11)
	Both[c]	79	7	0.69 (0.26-1.84)	31	3	0.60 (0.13-2.71)	91	19	1.02 (0.52-1.96)

Industrial distance[a]	Exposure category	Germ cell tumors			Other epithelial neoplasms / melanomas		
		Controls (n)	Cases (n)	OR (95%CI)[b]	Controls (n)	Cases (n)	OR (95%CI)[b]
5 Km							
	Reference	86	15	-	18	3	-
	Industrial area - 5 km (only)	447	76	1.28 (0.68-2.40)	185	33	1.24 (0.29-5.35)
	Urban area (only)	8	2	1.76 (0.33-9.52)	1	0	0 (0-inf)
	Both[c]	179	27	1.31 (0.62-2.76)	36	4	0.58 (0.09-3.63)
4 Km							
	Reference	86	15	-	18	3	-
	Industrial area - 4 km (only)	415	68	1.24 (0.65-2.34)	176	33	1.40 (0.32-6.14)
	Urban area (only)	39	5	0.98 (0.32-3.02)	7	0	0 (0-inf)
	Both[c]	148	24	1.43 (0.67-3.08)	30	4	0.73 (0.12-4.62)
3 Km							
	Reference	86	15	-	18	3	-
	Industrial area - 3 km (only)	377	61	1.23 (0.64-2.34)	157	31	1.45 (0.33-6.37)
	Urban area (only)	86	14	1.28 (0.55-3.00)	17	0	0 (0-inf)
	Both[c]	101	15	1.38 (0.60-3.18)	20	4	1.08 (0.17-6.93)
2 Km							
	Reference	86	15	-	18	3	-
	Industrial area - 2 km (only)	276	41	1.15 (0.59-2.26)	122	26	1.82 (0.39-8.44)
	Urban area (only)	136	21	1.23 (0.56-2.71)	25	2	0.44 (0.05-3.81)
	Both[c]	51	8	1.62 (0.61-4.32)	12	2	1.06 (0.12-9.09)

[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 total crop surface, 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 tumors by industrial distance and exposure category, including only cases with the same address at the time of birth and at the moment of diagnosis (sensitivity analysis).

		Retinoblastoma			Hepatic tumors			Soft tissue sarcomas		
Industrial distance[a]	Exposure category	Controls (n)	Cases (n)	OR (95%CI)[b]	Controls (n)	Cases (n)	OR (95%CI)[b]	Controls (n)	Cases (n)	OR (95%CI)[b]
5 Km										
	Reference	57	8	-	10	6	-	52	12	-
	Industrial area - 5 km (only)	297	55	1.38 (0.61-3.14)	127	19	0.28 (0.07-1.06)	354	53	0.78 (0.38-1.60)
	Urban area (only)	9	1	0.73 (0.08-6.70)	2	1	0.99 (0.06-16.19)	12	0	0 (0-inf)
	Both[c]	123	17	0.95 (0.37-2.45)	47	5	0.28 (0.06-1.44)	146	29	1.16 (0.52-2.63)
4 Km										
	Reference	57	8	-	10	6	-	52	12	-
	Industrial area - 4 km (only)	285	51	1.33 (0.58-3.04)	118	17	0.26 (0.07-1.02)	332	52	0.82 (0.40-1.71)
	Urban area (only)	33	4	0.80 (0.21-2.98)	12	1	0.18 (0.02-2.23)	36	5	0.83 (0.25-2.75)
	Both[c]	99	14	0.97 (0.36-2.58)	37	5	0.36 (0.07-1.80)	122	24	1.19 (0.51-2.75)
3 Km										
	Reference	57	8	-	10	6	-	52	12	-
	Industrial area - 3 km (only)	263	48	1.35 (0.59-3.11)	109	16	0.27 (0.07-1.06)	295	52	0.97 (0.46-2.03)
	Urban area (only)	57	10	1.18 (0.41-3.37)	23	3	0.31 (0.05-1.95)	67	10	0.93 (0.34-2.54)
	Both[c]	78	8	0.73 (0.25-2.18)	26	3	0.32 (0.05-1.92)	91	19	1.31 (0.55-3.16)
2 Km										
	Reference	57	8	-	10	6	-	52	12	-
	Industrial area - 2 km (only)	192	32	1.23 (0.52-2.90)	83	11	0.24 (0.06-1.02)	229	38	0.90 (0.42-1.92)
	Urban area (only)	85	15	1.19 (0.45-3.16)	35	3	0.19 (0.03-1.14)	113	16	0.84 (0.34-2.05)
	Both[c]	47	3	0.43 (0.10-1.80)	14	3	0.70 (0.11-4.37)	45	13	1.78 (0.68-4.66)

		Germ cell tumors			Other epithelial neoplasms / melanomas		
Industrial distance[a]	Exposure category	Controls (n)	Cases (n)	OR (95%CI)[b]	Controls (n)	Cases (n)	OR (95%CI)[b]
5 Km							
	Reference	42	7	-	6	2	-
	Industrial area - 5 km (only)	225	38	1.29 (0.52-3.20)	98	17	0.22 (0.02-2.25)
	Urban area (only)	6	2	2.35 (0.36-15.46)	1	0	0 (0-inf)
	Both[c]	99	15	1.36 (0.48-3.91)	21	2	0.09 (0.01-1.73)
4 Km							
	Reference	42	7	-	6	2	-
	Industrial area - 4 km (only)	208	31	1.13 (0.45-2.86)	95	17	0.27 (0.02-3.04)
	Urban area (only)	18	3	1.16 (0.25-5.48)	3	0	0 (0-inf)
	Both[c]	87	14	1.47 (0.51-4.28)	19	2	0.13 (0.01-2.49)
3 Km							
	Reference	42	7	-	6	2	-
	Industrial area - 3 km (only)	192	27	1.07 (0.42-2.74)	84	17	0.33 (0.03-3.78)
	Urban area (only)	46	8	1.31 (0.40-4.28)	10	0	0 (0-inf)
	Both[c]	59	9	1.46 (0.46-4.58)	12	2	0.23 (0.01-4.85)
2 Km							
	Reference	42	7	-	6	2	-
	Industrial area - 2 km (only)	143	19	1.02 (0.39-2.71)	65	14	0.31 (0.03-3.73)
	Urban area (only)	74	12	1.33 (0.44-4.02)	16	0	0 (0-inf)
	Both[c]	31	5	1.64 (0.45-6.05)	6	2	0.55 (0.02-13.07)

[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 total crop surface, 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 4: Description of the specific pollutants released by facilities, including their thresholds, 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	Threshold (Kg/year)[c]	Emission (Kg/year)	No. of facilities	Threshold (Kg/year)[c]	Emission (Kg/year)	No. of facilities
1,1,1-trichloroethane	71-55-6		VOCs/Solvents	100	0.5	1	-	0	0
1,2,3,4,5,6-hexachlorocyclohexane	608-73-1	2B	POPs	10	0.1	2	1	0.5	10
1,2-dichloroethane	107-06-2	2B	VOCs/Solvents	1000	9870	3	10	379	23
Alachlor	15972-60-8		Pesticides	-	0	0	1	0.03	4
Aldrin	309-00-2		Pesticides/POPs	1	0	0	1	8	9
Anthracene	120-12-7		PACs	50	82	14	1	1	17
Antimony	7440-36-0		Metals	NE[d]	122	36	-	0	0
Arsenic and compounds	7440-38-2	1	Metals	20	1053	171	5	1620	131
Atrazine	1912-24-9		Pesticides	-	0	0	1	5	17
Benzene	71-43-2	1	VOCs/Solvents	1000	48538	84	200	56	20
Benzo(a)pyrene	50-32-8	1	POPs/PACs	-	0	0	NE[d]	0.6	5
Benzo(b)fluoranthene	205-99-2	2B	POPs/PACs	-	0	0	NE[d]	0.6	8
Benzo(g,h,i)perylene	191-24-2		PACs	-	0	0	1	2	15
Benzo(k)fluoranthene	207-08-9	2B	POPs/PACs	-	0	0	NE[d]	0.6	4
Brominated diphenylethers			POPs	-	0	0	1	2	11
Cadmium and compounds	7440-43-9	1	Metals	10	781	181	5	306	129
Chlordane	57-74-9	2B	Pesticides/POPs	1	0	0	1	0.1	7
Chlorfenvinphos	470-90-6		Pesticides	-	0	0	1	1	10
Chlorpyrifos	2921-88-2		Pesticides	-	0	0	1	0.9	9
Chromium and compounds	7440-47-3	1	Metals	100	4870	227	50	5157	236
Cobalt and compounds	7440-48-4	2B	Metals	NE[d]	137	38	-	0	0
Copper and compounds	7440-50-8		Metals	100	6230	175	50	7776	249
DDT	50-29-3	2A	Pesticides/POPs	1	0	0	1	0.02	5
Di-(2-ethyl hexyl) phthalate	117-81-7	2B	Plasticizers	10	759	13	1	7	13
Dichloromethane	75-09-2	2A	VOCs/Solvents	1000	314621	20	10	49	13
Dieldrin	60-57-1		Pesticides/POPs	1	0	0	1	0.4	8
Diuron	330-54-1		Pesticides	-	0	0	1	173	17
Endosulfan	115-29-7		Pesticides/POPs	-	0	0	1	0.5	9
Endrin	72-20-8		Pesticides/POPs	1	0	0	1	0.4	8
Ethyl benzene	100-41-4	2B	VOCs/Solvents	-	0	0	200	8390	27
Ethylene oxide	75-21-8	1	VOCs	1000	18159	4	10	0	0
Fluoranthene	206-44-0		PACs	-	0	0	1	10	35
Heptachlor	76-44-8	2B	Pesticides/POPs	1	0	0	1	0.4	7
Hexabromobiphenyl	36355-1-8		POPs	0.1	0	0	0.1	0.3	6
Hexachlorobenzene	118-74-1	2B	POPs	10	4	3	1	1	11
Hexachlorobutadiene	87-68-3		VOCs	-	0	0	1	2	11
Indeno(1,2,3-cd)pyrene	193-39-5	2B	PACs	-	0	0	NE[d]	0.6	4
Isodrin	465-73-6		Pesticides	-	0	0	1	0.01	4
Isoproturon	34123-59-6		Pesticides	-	0	0	1	2	4
Lead and compounds	7439-92-1	2A	Metals	200	16184	200	20	2767	174
Lindane	58-89-9	1	Pesticides/POPs	1	0.1	1	1	0.5	4
Manganese and compounds	7439-96-5		Metals	NE[d]	463	48	-	0	0
Mercury and compounds	7439-97-6		Metals	10	946	162	1	93	99
Mirex	2385-85-5	2B	Pesticides/POPs	1	0	0	1	0.01	4
Naphthalene	91-20-3	2B	VOCs	100	1217	23	10	178	30
Nickel and compounds	7440-02-0	1	Metals	50	18897	211	20	11727	253
Non-methane volatile organic compounds			VOCs	100000	26514608	573	-	0	0
Nonylphenol and nonylphenol ethoxylates	25154-52-3		Non-HPCs	-	0	0	1	587	30
Octylphenols and octylphenol ethoxylates	1806-26-4		Non-HPCs	-	0	0	1	2028	32
Organotin compounds			Metals/Pesticides/POPs	-	0	0	50	198	26

Particulate matter (PM_{10})		1	Other	50000	3378846	444	-	0	0
PCDD + PCDF (dioxins + furans)		1	POPs	0.0001	0.05	86	0.0001	0.0005	13
Pentachlorobenzene	608-93-5		Pesticides/POPs	1	0	0	1	1	10
Pentachlorophenol	87-86-5	2B	Pesticides	10	0	0	0.1	31	5
Polychlorinated biphenyls	1336-36-3	1	POPs	0.1	2	19	0.1	0.1	9
Polycyclic aromatic hydrocarbons		1	PACs/POPs	50	3286	80	5	778	74
Simazine	122-34-9		Pesticides	-	0	0	1	8	22
Tetrachloroethylene	127-18-4	2A	VOCs/Solvents	2000	419	5	10	54	18
Tetrachloromethane	56-23-5	2B	Other	100	2	3	1	43	2
Thallium	7440-28-0		Metals	NE[d]	44	14	-	0	0
Toluene	108-88-3		VOCs/Solvents	-	0	0	200	4989	40
Total suspended particulate matter		1	Other	NE[d]	4530687	236	-	0	0
Tributyltin and compounds			Pesticides	-	0	0	1	0.6	5
Trichlorobenzenes	12002-48-1		VOCs/Solvents	10	0	0	1	1	11
Trichloroethylene	79-01-6	1	VOCs/Solvents	2000	1489	8	10	4494	15
Trichloromethane	67-66-3	2B	VOCs/Solvents	500	91731	7	10	146	34
Trifluralin	1582-09-8		Pesticides	-	0	0	1	0.004	3
Triphenyltin and compounds			Pesticides	-	0	0	1	0.03	3
Vanadium	7440-62-2		Metals	NE[d]	336	34	-	0	0
Vinyl chloride	75-01-4	1	VOCs	1000	46065	6	10	907	11
Xylenes	1330-20-7		Solvents	-	0	0	200	150	28
Zinc and compounds	7440-66-6		Metals	200	143770	189	100	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.
[c]Established emission threshold or limit value (in Kg/year) for each pollutant. Should any plant exceed this threshold, it must report the release of the pollutant.
[d]Not especified.

Supplementary Data

Title of the manuscript: "Residential proximity to environmental pollution sources and risk of rare tumors in children".

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

a) Table S1, showing the odds ratios of retinoblastoma by industrial distance and category of industrial group.

b) Table S2, showing the odds ratios of germ cell tumors in children by industrial distance and category of industrial group.

c) Table S3, showing the odds ratios of other epithelial neoplasms and melanomas in children by industrial distance and category of industrial group.

d) Table S4, showing the odds ratios of retinoblastoma by groups of carcinogenic and toxic substances.

e) Table S5, showing the odds ratios of germ cell tumors in children by groups of carcinogenic and toxic substances.

f) Table S6, showing the odds ratios of other epithelial neoplasms and melanomas in children by groups of carcinogenic and toxic substances.

g) 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 Material, Table S1: Odds ratios of retinoblastoma by industrial distance and category of industrial group.

	Individuals residing at ≤2 km						Individuals residing at ≤3 km						Individuals residing at ≤4 km						Individuals residing at ≤5 km					
Industrial group (no. industries)	Co[a]	Ca[b]	OR (95%CI)[c]	*p*-value[d]	*p*-BH[e]	*p*-BY[f]	Co[a]	Ca[b]	OR (95%CI)[c]	*p*-value[d]	*p*-BH[e]	*p*-BY[f]	Co[a]	Ca[b]	OR (95%CI)[c]	*p*-value[d]	*p*-BH[e]	*p*-BY[f]	Co[a]	Ca[b]	OR (95%CI)[c]	*p*-value[d]	*p*-BH[e]	*p*-BY[f]
Reference	102	15	-				102	15	-				102	15	-				102	15	-			
All sectors (1271)	332	61	1.38 (0.73-2.59)				465	82	1.31 (0.71-2.42)				504	89	1.31 (0.71-2.40)				526	95	1.33 (0.73-2.44)			
Combustion installations (42)	19	3	1.36 (0.34-5.39)	0.660	0.893	1.000	35	7	1.71 (0.62-4.74)	0.304	0.608	1.000	65	14	1.79 (0.78-4.14)	0.170	0.568	1.000	95	20	1.78 (0.82-3.87)	0.143	0.439	1.000
Refineries and coke ovens (4)	2	0	0 (0-inf)	0.990	0.990	1.000	8	1	0.96 (0.11-8.52)	0.969	0.992	1.000	11	1	0.72 (0.08-6.19)	0.764	0.955	1.000	15	2	1.07 (0.21-5.36)	0.937	0.976	1.000
Production and processing of metals (119)	57	16	2.10 (0.94-4.68)	0.071	0.531	1.000	104	25	1.84 (0.89-3.83)	0.101	0.521	1.000	142	33	1.82 (0.90-3.67)	0.094	0.568	1.000	193	39	1.54 (0.78-3.04)	0.211	0.439	1.000
Galvanization (19)	18	1	0.42 (0.05-3.41)	0.417	0.769	1.000	38	9	1.83 (0.72-4.63)	0.204	0.526	1.000	51	9	1.31 (0.53-3.27)	0.562	0.827	1.000	63	9	1.06 (0.43-2.62)	0.903	0.976	1.000
Surface treatment of metals and plastic (197)	165	27	1.26 (0.62-2.57)	0.525	0.820	1.000	267	46	1.31 (0.68-2.53)	0.422	0.778	1.000	328	60	1.40 (0.74-2.65)	0.307	0.603	1.000	354	66	1.43 (0.76-2.71)	0.266	0.475	1.000
Mining industry (39)	1	0	0 (0-inf)	0.989	0.990	1.000	7	1	0.95 (0.11-8.52)	0.964	0.992	1.000	13	2	1.11 (0.22-5.51)	0.901	0.990	1.000	23	5	1.67 (0.54-5.16)	0.377	0.555	1.000
Cement and lime (33)	14	1	0.52 (0.06-4.38)	0.546	0.820	1.000	34	4	0.85 (0.26-2.79)	0.790	0.992	1.000	50	10	1.50 (0.61-3.69)	0.372	0.664	1.000	74	18	1.85 (0.85-4.01)	0.122	0.439	1.000
Glass and mineral fibers (20)	18	4	1.92 (0.54-6.80)	0.311	0.726	1.000	42	12	2.49 (1.01-6.12)	0.048	0.513	1.000	76	16	1.72 (0.76-3.89)	0.196	0.568	1.000	99	23	1.88 (0.88-4.00)	0.104	0.439	1.000
Ceramic (86)	37	2	0.40 (0.09-1.85)	0.240	0.715	1.000	57	6	0.78 (0.28-2.13)	0.622	0.933	1.000	80	6	0.54 (0.20-1.48)	0.234	0.568	1.000	100	10	0.73 (0.31-1.73)	0.474	0.613	1.000
Organic chemical industry (106)	42	14	2.54 (1.10-5.90)	0.030	0.357	1.000	86	18	1.59 (0.73-3.43)	0.241	0.526	1.000	133	24	1.36 (0.66-2.81)	0.408	0.681	1.000	187	33	1.31 (0.66-2.61)	0.435	0.605	1.000
Inorganic chemical industry (46)	19	3	1.15 (0.30-4.44)	0.844	0.990	1.000	34	5	1.09 (0.36-3.29)	0.884	0.992	1.000	62	10	1.24 (0.51-3.00)	0.640	0.842	1.000	91	17	1.44 (0.66-3.15)	0.357	0.555	1.000
Fertilizers (10)	1	3	19.57 (1.87-204.44)	0.013	0.311	1.000	4	3	5.15 (1.01-26.20)	0.048	0.513	1.000	6	3	3.56 (0.78-16.33)	0.102	0.568	1.000	10	4	2.81 (0.76-10.44)	0.123	0.439	1.000
Biocides (12)	6	3	3.73 (0.82-16.95)	0.089	0.531	1.000	14	5	2.63 (0.81-8.58)	0.108	0.521	1.000	23	6	1.88 (0.64-5.54)	0.250	0.568	1.000	28	9	2.32 (0.89-6.04)	0.085	0.439	1.000
Pharmaceutical products (41)	43	10	1.75 (0.71-4.33)	0.224	0.715	1.000	79	21	2.04 (0.96-4.35)	0.064	0.513	1.000	113	26	1.77 (0.86-3.65)	0.123	0.568	1.000	152	33	1.64 (0.82-3.28)	0.165	0.439	1.000
Explosives and pyrotechnics (9)	2	0	0 (0-inf)	0.990	0.990	1.000	4	0	0 (0-inf)	0.986	0.992	1.000	5	0	0 (0-inf)	0.990	0.990	1.000	6	0	0 (0-inf)	0.989	0.989	1.000
Hazardous waste (60)	31	5	1.28 (0.42-3.93)	0.670	0.893	1.000	68	10	1.14 (0.47-2.79)	0.774	0.992	1.000	125	20	1.23 (0.58-2.62)	0.597	0.830	1.000	168	32	1.50 (0.74-3.02)	0.260	0.475	1.000
Non-hazardous waste (86)	10	3	2.37 (0.56-9.94)	0.239	0.715	1.000	37	7	1.45 (0.53-3.95)	0.469	0.805	1.000	73	10	1.05 (0.43-2.54)	0.922	0.990	1.000	99	19	1.47 (0.69-3.15)	0.322	0.536	1.000
Disposal or recycling of animal waste (18)	21	4	1.56 (0.45-5.40)	0.483	0.820	1.000	42	10	2.02 (0.80-5.12)	0.140	0.526	1.000	57	12	1.75 (0.73-4.21)	0.213	0.568	1.000	64	15	1.93 (0.84-4.42)	0.121	0.439	1.000
Urban waste-water treatment plants (53)	41	3	0.54 (0.15-2.02)	0.361	0.726	1.000	102	14	1.00 (0.45-2.24)	0.992	0.992	1.000	162	34	1.55 (0.78-3.06)	0.212	0.568	1.000	226	48	1.57 (0.82-3.02)	0.175	0.439	1.000
Paper and wood production (63)	38	6	1.19 (0.42-3.37)	0.741	0.936	1.000	67	15	1.71 (0.76-3.83)	0.194	0.526	1.000	104	24	1.79 (0.86-3.72)	0.120	0.568	1.000	137	32	1.88 (0.93-3.78)	0.079	0.439	1.000
Pre-treatment or dyeing of textiles (9)	5	0	0 (0-inf)	0.990	0.990	1.000	8	0	0 (0-inf)	0.987	0.992	1.000	9	0	0 (0-inf)	0.986	0.990	1.000	12	1	0.55 (0.06-4.63)	0.578	0.657	1.000
Tanning of hides and skins (2)	2	1	3.21 (0.26-39.47)	0.363	0.726	1.000	3	1	2.20 (0.21-23.59)	0.515	0.824	1.000	3	1	2.20 (0.21-23.59)	0.515	0.804	1.000	3	1	2.20 (0.21-23.59)	0.515	0.613	1.000
Food and beverage sector (145)	80	17	1.55 (0.72-3.34)	0.268	0.715	1.000	142	30	1.54 (0.77-3.05)	0.221	0.526	1.000	191	37	1.41 (0.72-2.73)	0.314	0.603	1.000	253	53	1.53 (0.81-2.89)	0.193	0.439	1.000
Surface treatment using organic solvents (50)	29	8	2.05 (0.77-5.48)	0.150	0.715	1.000	69	16	1.78 (0.80-3.97)	0.157	0.526	1.000	107	23	1.64 (0.78-3.42)	0.192	0.568	1.000	155	33	1.57 (0.79-3.13)	0.197	0.439	1.000
Production of electro-graphite (2)	0	0	-	-	-	-	0	0	-	-	-	-	1	0	0 (0-inf)	0.990	0.990	1.000	3	1	2.22 (0.21-23.67)	0.510	0.613	1.000

[a]Number of cases.
[b]Number of controls.
[c]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 total crop surface, percentage of illiteracy, percentage of unemployed, and socioeconomic status.
[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.

Supplementary Material, Table S2: Odds ratios of germ cell tumors in children by industrial distance and category of industrial group.

	Individuals residing at ≤2 km						Individuals residing at ≤3 km						Individuals residing at ≤4 km						Individuals residing at ≤5 km					
Industrial group (no. industries)	Co[a]	Ca[b]	OR (95%CI)[c]	*p*-value[d]	*p*-BH[e]	*p*-BY[f]	Co[a]	Ca[b]	OR (95%CI)[c]	*p*-value[d]	*p*-BH[e]	*p*-BY[f]	Co[a]	Ca[b]	OR (95%CI)[c]	*p*-value[d]	*p*-BH[e]	*p*-BY[f]	Co[a]	Ca[b]	OR (95%CI)[c]	*p*-value[d]	*p*-BH[e]	*p*-BY[f]
Reference	86	15	-				86	15	-				86	15	-				86	15	-			
All sectors (1271)	276	41	1.15 (0.59-2.26)				377	61	1.23 (0.64-2.34)				415	68	1.24 (0.65-2.34)				447	76	1.28 (0.68-2.40)			
Combustion installations (42)	13	1	0.76 (0.09-6.61)	0.802	0.990	1.000	29	2	0.66 (0.14-3.21)	0.606	0.839	1.000	50	2	0.36 (0.08-1.72)	0.201	0.914	1.000	71	6	0.79 (0.28-2.26)	0.662	0.948	1.000
Refineries and coke ovens (4)	2	1	8.54 (0.62-118.01)	0.109	0.990	1.000	11	2	1.92 (0.36-10.26)	0.448	0.839	1.000	13	2	1.66 (0.31-8.74)	0.553	0.990	1.000	14	2	1.52 (0.29-7.99)	0.620	0.948	1.000
Production and processing of metals (119)	44	10	1.98 (0.78-5.02)	0.149	0.990	1.000	99	21	1.84 (0.85-4.01)	0.124	0.782	1.000	124	28	1.95 (0.93-4.08)	0.076	0.914	1.000	162	29	1.48 (0.72-3.05)	0.292	0.948	1.000
Galvanization (19)	16	1	0.62 (0.08-5.22)	0.663	0.990	1.000	27	2	0.72 (0.15-3.46)	0.680	0.839	1.000	38	3	0.74 (0.20-2.78)	0.652	0.990	1.000	46	7	1.28 (0.47-3.48)	0.635	0.948	1.000
Surface treatment of metals and plastic (197)	128	20	1.35 (0.63-2.91)	0.445	0.990	1.000	214	33	1.30 (0.64-2.64)	0.463	0.839	1.000	262	45	1.51 (0.76-3.00)	0.239	0.914	1.000	291	50	1.50 (0.76-2.95)	0.240	0.948	1.000
Mining industry (39)	4	0	0 (0-inf)	0.987	0.990	1.000	10	0	0 (0-inf)	0.985	0.990	1.000	14	2	0.90 (0.18-4.63)	0.902	0.990	1.000	22	5	1.55 (0.48-4.97)	0.459	0.948	1.000
Cement and lime (33)	10	2	1.78 (0.33-9.51)	0.502	0.990	1.000	25	4	1.07 (0.31-3.72)	0.914	0.990	1.000	44	4	0.66 (0.20-2.20)	0.499	0.990	1.000	65	11	1.28 (0.53-3.08)	0.589	0.948	1.000
Glass and mineral fibers (20)	15	1	0.67 (0.08-5.75)	0.713	0.990	1.000	35	7	1.93 (0.68-5.49)	0.219	0.839	1.000	59	10	1.60 (0.63-4.05)	0.321	0.962	1.000	87	13	1.37 (0.58-3.23)	0.475	0.948	1.000
Ceramic (86)	31	4	0.86 (0.26-2.90)	0.810	0.990	1.000	50	9	1.20 (0.48-3.03)	0.699	0.839	1.000	62	9	0.96 (0.38-2.40)	0.926	0.990	1.000	72	11	1.01 (0.43-2.41)	0.977	0.990	1.000
Organic chemical industry (106)	46	6	1.11 (0.39-3.18)	0.848	0.990	1.000	80	11	1.20 (0.50-2.88)	0.689	0.839	1.000	127	20	1.35 (0.62-2.91)	0.448	0.990	1.000	167	23	1.18 (0.56-2.49)	0.666	0.948	1.000
Inorganic chemical industry (46)	23	4	1.33 (0.38-4.59)	0.656	0.990	1.000	41	7	1.31 (0.47-3.64)	0.600	0.839	1.000	53	10	1.43 (0.57-3.57)	0.445	0.990	1.000	75	12	1.23 (0.52-2.92)	0.639	0.948	1.000
Fertilizers (10)	4	1	1.27 (0.12-13.37)	0.842	0.990	1.000	7	2	1.75 (0.31-10.02)	0.528	0.839	1.000	10	2	1.04 (0.19-5.67)	0.964	0.990	1.000	12	2	0.91 (0.17-4.79)	0.907	0.990	1.000
Biocides (12)	7	0	0 (0-inf)	0.988	0.990	1.000	13	1	0.63 (0.07-5.43)	0.674	0.839	1.000	25	3	1.05 (0.27-4.13)	0.943	0.990	1.000	35	5	1.29 (0.41-4.05)	0.660	0.948	1.000
Pharmaceutical products (41)	49	6	1.07 (0.37-3.07)	0.898	0.990	1.000	85	6	0.59 (0.21-1.66)	0.315	0.839	1.000	113	13	1.01 (0.44-2.35)	0.973	0.990	1.000	147	18	1.03 (0.47-2.26)	0.933	0.990	1.000
Explosives and pyrotechnics (9)	1	0	0 (0-inf)	0.990	0.990	1.000	1	0	0 (0-inf)	0.990	0.990	1.000	2	0	0 (0-inf)	0.990	0.990	1.000	4	2	2.35 (0.36-15.36)	0.373	0.948	1.000
Hazardous waste (60)	29	1	0.29 (0.04-2.34)	0.243	0.990	1.000	63	2	0.26 (0.06-1.23)	0.089	0.782	1.000	104	7	0.57 (0.21-1.53)	0.267	0.914	1.000	144	14	0.82 (0.36-1.88)	0.638	0.948	1.000
Non-hazardous waste (86)	11	0	0 (0-inf)	0.990	0.990	1.000	36	1	0.20 (0.02-1.62)	0.130	0.782	1.000	54	6	0.79 (0.28-2.25)	0.657	0.990	1.000	79	10	0.94 (0.38-2.30)	0.889	0.990	1.000
Disposal or recycling of animal waste (18)	12	1	0.83 (0.10-7.22)	0.864	0.990	1.000	30	2	0.66 (0.14-3.20)	0.603	0.839	1.000	60	3	0.47 (0.12-1.77)	0.262	0.914	1.000	71	5	0.66 (0.22-2.02)	0.467	0.948	1.000
Urban waste-water treatment plants (53)	31	5	1.32 (0.42-4.15)	0.630	0.990	1.000	83	15	1.56 (0.68-3.55)	0.294	0.839	1.000	150	24	1.32 (0.63-2.78)	0.459	0.990	1.000	207	34	1.37 (0.68-2.78)	0.377	0.948	1.000
Paper and wood production (63)	37	2	0.39 (0.08-1.87)	0.237	0.990	1.000	71	4	0.46 (0.14-1.49)	0.194	0.839	1.000	101	11	0.87 (0.37-2.08)	0.758	0.990	1.000	117	15	1.04 (0.47-2.34)	0.917	0.990	1.000
Pre-treatment or dyeing of textiles (9)	6	0	0 (0-inf)	0.988	0.990	1.000	11	1	0.45 (0.05-4.07)	0.476	0.839	1.000	16	1	0.29 (0.03-2.52)	0.262	0.914	1.000	17	1	0.28 (0.03-2.39)	0.243	0.948	1.000
Tanning of hides and skins (2)	1	2	13.79 (1.14-167.36)	0.039	0.946	1.000	2	2	5.87 (0.70-48.97)	0.102	0.782	1.000	2	2	5.87 (0.70-48.97)	0.102	0.914	1.000	2	2	5.87 (0.70-48.97)	0.102	0.948	1.000
Food and beverage sector (145)	66	11	1.28 (0.53-3.08)	0.576	0.990	1.000	121	18	1.14 (0.53-2.47)	0.742	0.848	1.000	167	22	1.02 (0.49-2.13)	0.959	0.990	1.000	211	28	1.05 (0.52-2.13)	0.894	0.990	1.000
Surface treatment using organic solvents (50)	27	2	0.63 (0.13-2.99)	0.557	0.990	1.000	65	5	0.66 (0.22-1.97)	0.457	0.839	1.000	100	13	1.12 (0.49-2.60)	0.788	0.990	1.000	130	18	1.18 (0.54-2.57)	0.682	0.948	1.000
Production of electro-graphite (2)	0	0	-	-	-	-	0	0	-	-	-	-	0	0	-	-	-	-	2	0	0 (0-inf)	0.990	0.990	1.000

[a]Number of cases.
[b]Number of controls.
[c]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 total crop surface, percentage of illiteracy, percentage of unemployed, and socioeconomic status.
[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.

Supplementary Material, Table S3: Odds ratios of other epithelial neoplasms and melanomas in children by industrial distance and category of industrial group.

	Individuals residing at ≤2 km						Individuals residing at ≤3 km						Individuals residing at ≤4 km						Individuals residing at ≤5 km					
Industrial group (no. industries)	Co[a]	Ca[b]	OR (95%CI)[c]	*p*-value[d]	*p*-BH[e]	*p*-BY[f]	Co[a]	Ca[b]	OR (95%CI)[c]	*p*-value[d]	*p*-BH[e]	*p*-BY[f]	Co[a]	Ca[b]	OR (95%CI)[c]	*p*-value[d]	*p*-BH[e]	*p*-BY[f]	Co[a]	Ca[b]	OR (95%CI)[c]	*p*-value[d]	*p*-BH[e]	*p*-BY[f]
Reference	18	3	-				18	3	-				18	3	-				18	3	-			
All sectors (1271)	122	26	1.82 (0.39-8.44)				157	31	1.45 (0.33-6.37)				176	33	1.40 (0.32-6.14)				185	33	1.24 (0.29-5.35)			
Combustion installations (42)	7	5	4.60 (0.68-31.34)	0.119	0.997	1.000	17	7	2.73 (0.48-15.45)	0.255	0.997	1.000	28	9	2.08 (0.41-10.44)	0.375	0.998	1.000	38	12	2.29 (0.47-11.10)	0.306	0.998	1.000
Refineries and coke ovens (4)	3	0	0 (0-inf)	0.997	0.997	1.000	8	0	0 (0-inf)	0.994	0.997	1.000	9	1	0.98 (0.08-12.47)	0.985	0.998	1.000	12	3	2.41 (0.33-17.54)	0.387	0.998	1.000
Production and processing of metals (119)	18	4	1.72 (0.28-10.53)	0.557	0.997	1.000	34	6	1.34 (0.25-7.14)	0.734	0.997	1.000	47	7	1.06 (0.21-5.47)	0.942	0.998	1.000	58	13	1.68 (0.35-8.00)	0.518	0.998	1.000
Galvanization (19)	15	3	1.33 (0.19-9.55)	0.777	0.997	1.000	23	5	1.40 (0.23-8.41)	0.717	0.997	1.000	27	5	1.12 (0.19-6.68)	0.904	0.998	1.000	29	5	1.06 (0.18-6.29)	0.950	0.998	1.000
Surface treatment of metals and plastic (197)	49	17	2.66 (0.55-12.94)	0.227	0.997	1.000	90	24	2.19 (0.46-10.45)	0.324	0.997	1.000	115	27	2.08 (0.43-10.05)	0.363	0.998	1.000	125	27	1.86 (0.39-8.97)	0.440	0.998	1.000
Mining industry (39)	3	0	0 (0-inf)	0.997	0.997	1.000	6	0	0 (0-inf)	0.995	0.997	1.000	7	0	0 (0-inf)	0.995	0.998	1.000	11	1	0.60 (0.05-7.22)	0.690	0.998	1.000
Cement and lime (33)	7	0	0 (0-inf)	0.995	0.997	1.000	9	4	4.23 (0.67-26.82)	0.126	0.997	1.000	16	6	3.43 (0.62-18.97)	0.157	0.998	1.000	27	9	2.48 (0.50-12.22)	0.265	0.998	1.000
Glass and mineral fibers (20)	7	2	1.48 (0.15-14.94)	0.741	0.997	1.000	25	5	1.28 (0.21-7.95)	0.790	0.997	1.000	35	8	1.57 (0.29-8.63)	0.603	0.998	1.000	39	10	1.88 (0.35-10.10)	0.460	0.998	1.000
Ceramic (86)	13	0	0 (0-inf)	0.993	0.997	1.000	19	2	0.91 (0.12-7.25)	0.932	0.997	1.000	27	4	1.21 (0.20-7.47)	0.835	0.998	1.000	32	5	1.19 (0.21-6.68)	0.847	0.998	1.000
Organic chemical industry (106)	38	6	1.12 (0.21-6.12)	0.893	0.997	1.000	51	9	1.23 (0.25-6.19)	0.800	0.997	1.000	65	12	1.28 (0.27-6.11)	0.761	0.998	1.000	73	13	1.25 (0.26-5.95)	0.777	0.998	1.000
Inorganic chemical industry (46)	15	2	0.97 (0.12-7.67)	0.980	0.997	1.000	24	4	1.22 (0.21-7.15)	0.829	0.997	1.000	28	6	1.59 (0.30-8.51)	0.591	0.998	1.000	37	8	1.56 (0.31-7.82)	0.591	0.998	1.000
Fertilizers (10)	2	0	0 (0-inf)	0.997	0.997	1.000	2	0	0 (0-inf)	0.997	0.997	1.000	3	0	0 (0-inf)	0.997	0.998	1.000	7	0	0 (0-inf)	0.995	0.998	1.000
Biocides (12)	3	0	0 (0-inf)	0.997	0.997	1.000	7	0	0 (0-inf)	0.995	0.997	1.000	13	1	0.45 (0.04-5.77)	0.539	0.998	1.000	17	1	0.36 (0.03-4.59)	0.434	0.998	1.000
Pharmaceutical products (41)	21	3	0.81 (0.12-5.42)	0.825	0.997	1.000	39	8	1.22 (0.24-6.36)	0.810	0.997	1.000	57	11	1.15 (0.23-5.77)	0.866	0.998	1.000	73	16	1.48 (0.30-7.31)	0.632	0.998	1.000
Explosives and pyrotechnics (9)	0	0	-	-	-	-	0	0	-	-	-	-	1	0	0 (0-inf)	0.998	0.998	1.000	1	0	0 (0-inf)	0.998	0.998	1.000
Hazardous waste (60)	16	2	0.74 (0.09-6.14)	0.779	0.997	1.000	33	10	2.13 (0.43-10.61)	0.358	0.997	1.000	60	15	1.74 (0.37-8.17)	0.484	0.998	1.000	76	18	1.69 (0.36-7.80)	0.504	0.998	1.000
Non-hazardous waste (86)	9	1	0.92 (0.07-11.80)	0.947	0.997	1.000	22	1	0.30 (0.03-3.56)	0.340	0.997	1.000	34	5	1.04 (0.19-5.78)	0.966	0.998	1.000	48	8	1.20 (0.24-6.08)	0.824	0.998	1.000
Disposal or recycling of animal waste (18)	9	2	1.42 (0.16-12.41)	0.750	0.997	1.000	19	5	1.53 (0.26-9.16)	0.643	0.997	1.000	28	8	1.77 (0.33-9.48)	0.505	0.998	1.000	33	9	1.70 (0.33-8.73)	0.524	0.998	1.000
Urban waste-water treatment plants (53)	19	1	0.45 (0.04-5.37)	0.526	0.997	1.000	41	10	1.93 (0.39-9.62)	0.421	0.997	1.000	69	13	1.35 (0.29-6.36)	0.701	0.998	1.000	90	18	1.45 (0.31-6.71)	0.635	0.998	1.000
Paper and wood production (63)	9	3	2.73 (0.37-20.03)	0.325	0.997	1.000	19	5	1.88 (0.32-11.18)	0.487	0.997	1.000	32	8	1.69 (0.32-8.93)	0.538	0.998	1.000	43	8	1.20 (0.23-6.18)	0.824	0.998	1.000
Pre-treatment or dyeing of textiles (9)	4	1	1.16 (0.08-16.42)	0.913	0.997	1.000	6	2	1.68 (0.20-14.34)	0.637	0.997	1.000	7	2	1.48 (0.18-12.48)	0.719	0.998	1.000	9	2	1.13 (0.14-9.32)	0.910	0.998	1.000
Tanning of hides and skins (2)	0	0	-	-	-	-	0	0	-	-	-	-	0	0	-	-	-	-	0	0	-	-	-	-
Food and beverage sector (145)	29	5	1.40 (0.25-7.89)	0.704	0.997	1.000	51	6	0.89 (0.17-4.66)	0.891	0.997	1.000	63	10	1.19 (0.25-5.78)	0.826	0.998	1.000	82	12	1.09 (0.23-5.11)	0.917	0.998	1.000
Surface treatment using organic solvents (50)	9	2	1.32 (0.15-11.63)	0.802	0.997	1.000	24	3	0.81 (0.12-5.50)	0.833	0.997	1.000	32	10	2.21 (0.43-11.32)	0.340	0.998	1.000	49	14	2.19 (0.45-10.75)	0.333	0.998	1.000
Production of electro-graphite (2)	0	0	-	-	-	-	0	0	-	-	-	-	0	0	-	-	-	-	0	0	-	-	-	-

[a]Number of cases.
[b]Number of controls.
[c]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 total crop surface, percentage of illiteracy, percentage of unemployed, and socioeconomic status.
[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.

Supplementary Material, Table S4: Odds ratios of retinoblastoma by groups of carcinogenic and toxic substances

	Individuals residing at ≤2 km			Individuals residing at ≤3 km			Individuals residing at ≤4 km			Individuals residing at ≤5 km		
Groups of pollutants	Controls	Cases	OR (95%CI)[a]	Controls	Cases	OR (95%CI)[a]	Controls	Cases	OR (95%CI)[a]	Controls	Cases	OR (95%CI)[a]
Reference	102	15	-	102	15	-	102	15	-	102	15	-
IARC groups[b]												
Group 1	282	54	1.45 (0.76-2.76)	409	73	1.33 (0.72-2.48)	465	83	1.32 (0.71-2.44)	505	90	1.31 (0.71-2.41)
Group 2A	156	27	1.33 (0.65-2.69)	267	47	1.33 (0.69-2.56)	329	59	1.35 (0.71-2.55)	376	69	1.38 (0.74-2.59)
Group 2B	100	17	1.32 (0.61-2.87)	170	31	1.42 (0.71-2.85)	232	44	1.50 (0.77-2.91)	279	53	1.48 (0.77-2.82)
Groups of toxic substances[c]												
Metals	259	46	1.36 (0.71-2.62)	370	61	1.23 (0.65-2.31)	433	76	1.30 (0.70-2.41)	470	86	1.36 (0.74-2.52)
Pesticides	50	11	1.70 (0.70-4.13)	97	19	1.51 (0.70-3.27)	150	33	1.72 (0.85-3.48)	185	41	1.74 (0.88-3.43)
PACs	93	13	1.05 (0.46-2.38)	159	32	1.56 (0.78-3.12)	219	43	1.51 (0.78-2.95)	277	57	1.62 (0.85-3.10)
Non-HPCs	28	5	1.34 (0.44-4.15)	70	12	1.30 (0.55-3.05)	130	27	1.61 (0.78-3.32)	170	35	1.59 (0.79-3.18)
Plasticizers	19	3	1.24 (0.32-4.82)	42	7	1.28 (0.47-3.45)	67	14	1.65 (0.72-3.79)	90	20	1.75 (0.81-3.78)
POPs	126	21	1.28 (0.61-2.69)	216	36	1.28 (0.65-2.52)	276	49	1.35 (0.70-2.59)	317	61	1.48 (0.78-2.81)
VOCs	226	40	1.35 (0.69-2.63)	337	62	1.39 (0.74-2.62)	411	68	1.22 (0.65-2.28)	452	84	1.39 (0.75-2.57)
Solvents	110	23	1.64 (0.78-3.42)	198	36	1.40 (0.71-2.76)	255	48	1.45 (0.72-2.79)	319	60	1.44 (0.76-2.73)
Other	234	45	1.46 (0.76-2.82)	361	70	1.47 (0.79-2.74)	419	81	1.46 (0.79-2.71)	469	89	1.42 (0.77-2.62)

[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, heptachlor, hexachlorobenzene, 1,2,3,4,5,6-hexachlorocyclohexane, 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).

Supplementary Material, Table S5: Odds ratios of germ cell tumors in children by groups of carcinogenic and toxic substances

	Individuals residing at ≤2 km			Individuals residing at ≤3 km			Individuals residing at ≤4 km			Individuals residing at ≤5 km		
Groups of pollutants	Controls	Cases	OR (95%CI)[a]	Controls	Cases	OR (95%CI)[a]	Controls	Cases	OR (95%CI)[a]	Controls	Cases	OR (95%CI)[a]
Reference	86	15	-	86	15	-	86	15	-	86	15	-
IARC groups[b]												
Group 1	232	38	1.30 (0.66-2.58)	339	54	1.24 (0.65-2.40)	382	59	1.17 (0.61-2.24)	410	69	1.29 (0.68-2.45)
Group 2A	137	15	0.88 (0.39-1.97)	214	27	0.99 (0.48-2.03)	270	35	1.01 (0.51-2.02)	306	42	1.07 (0.54-2.10)
Group 2B	80	8	0.86 (0.33-2.22)	140	18	1.09 (0.50-2.39)	187	21	0.93 (0.44-1.99)	227	28	1.01 (0.49-2.08)
Groups of toxic substances[c]												
Metals	210	31	1.21 (0.60-2.46)	292	44	1.20 (0.61-2.35)	347	47	1.03 (0.53-2.00)	382	59	1.20 (0.63-2.30)
Pesticides	44	4	0.76 (0.23-2.56)	84	11	1.12 (0.46-2.72)	127	13	0.88 (0.38-2.03)	162	17	0.87 (0.39-1.91)
PACs	67	8	1.01 (0.39-2.63)	120	15	1.02 (0.46-2.30)	177	22	1.00 (0.47-2.11)	229	31	1.11 (0.55-2.26)
Non-HPCs	30	2	0.57 (0.12-2.78)	65	9	1.18 (0.46-3.02)	117	12	0.84 (0.36-1.98)	149	16	0.89 (0.40-1.98)
Plasticizers	15	2	1.20 (0.24-6.08)	30	6	1.79 (0.60-5.36)	47	9	1.82 (0.69-4.82)	68	13	1.86 (0.77-4.47)
POPs	98	13	1.12 (0.49-2.60)	175	24	1.16 (0.56-2.43)	236	30	1.05 (0.51-2.13)	272	39	1.19 (0.60-2.36)
VOCs	193	27	1.10 (0.54-2.24)	276	41	1.16 (0.59-2.28)	336	49	1.14 (0.59-2.22)	372	54	1.13 (0.59-2.17)
Solvents	92	13	1.23 (0.53-2.87)	156	23	1.25 (0.59-2.63)	210	25	0.98 (0.47-2.04)	257	33	1.05 (0.52-2.13)
Other	205	34	1.38 (0.68-2.77)	318	51	1.28 (0.66-2.48)	364	57	1.22 (0.63-2.33)	392	69	1.38 (0.73-2.61)

[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, heptachlor, hexachlorobenzene, 1,2,3,4,5,6-hexachlorocyclohexane, 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).

Supplementary Material, Table S6: Odds ratios of other epithelial neoplasms and melanomas in children by groups of carcinogenic and toxic substances

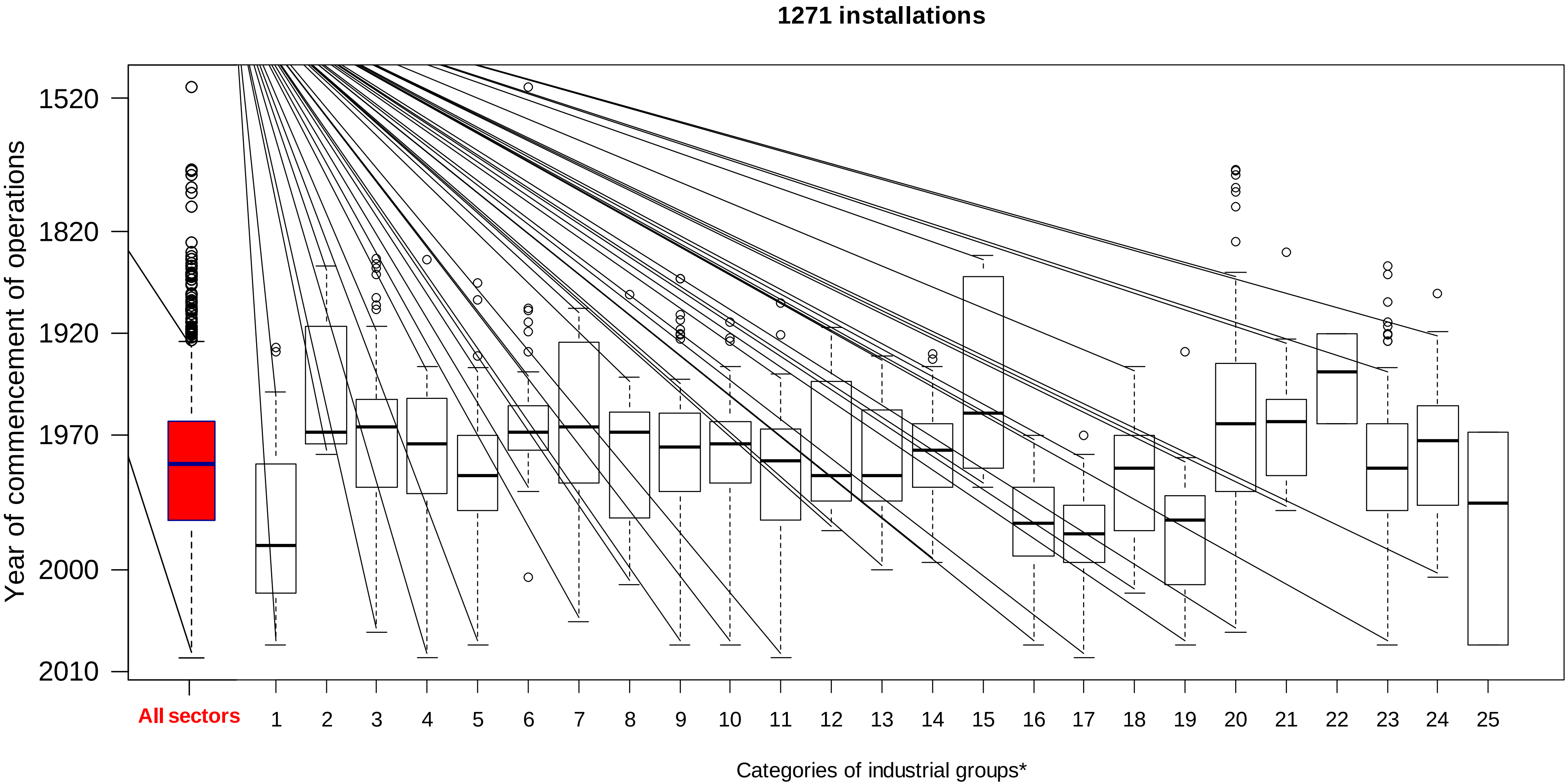
	Individuals residing at ≤2 km			Individuals residing at ≤3 km			Individuals residing at ≤4 km			Individuals residing at ≤5 km		
Groups of pollutants	Controls	Cases	OR (95%CI)[a]	Controls	Cases	OR (95%CI)[a]	Controls	Cases	OR (95%CI)[a]	Controls	Cases	OR (95%CI)[a]
Reference	18	3	-	18	3	-	18	3	-	18	3	-
IARC groups[b]												
Group 1	110	22	1.66 (0.36-7.76)	147	31	1.70 (0.38-7.70)	165	33	1.69 (0.37-7.75)	176	33	1.50 (0.33-6.71)
Group 2A	69	13	1.41 (0.29-6.82)	110	22	1.48 (0.32-6.76)	135	27	1.50 (0.33-6.76)	151	28	1.40 (0.31-6.35)
Group 2B	45	7	1.10 (0.21-5.87)	68	15	1.70 (0.35-8.13)	90	18	1.46 (0.32-6.76)	112	23	1.58 (0.34-7.27)
Groups of toxic substances[c]												
Metals	93	21	1.85 (0.39-8.74)	130	27	1.60 (0.35-7.27)	149	29	1.42 (0.32-6.33)	162	30	1.37 (0.31-6.10)
Pesticides	31	11	2.66 (0.53-13.33)	48	17	2.63 (0.55-12.53)	68	22	2.52 (0.54-11.80)	86	24	2.27 (0.48-10.67)
PACs	39	9	1.93 (0.38-9.89)	65	18	2.13 (0.46-9.88)	91	21	1.70 (0.37-7.67)	116	24	1.52 (0.34-6.80)
Non-HPCs	25	2	0.60 (0.08-4.59)	44	9	1.59 (0.32-8.02)	68	16	1.80 (0.38-8.50)	90	21	1.86 (0.40-8.70)
Plasticizers	6	1	1.31 (0.10-17.71)	9	3	2.61 (0.36-18.94)	16	6	3.74 (0.62-22.51)	30	9	2.39 (0.47-12.25)
POPs	61	15	2.09 (0.43-10.17)	94	24	1.82 (0.40-8.32)	115	25	1.63 (0.36-7.34)	129	25	1.41 (0.32-6.29)
VOCs	99	17	1.19 (0.26-5.52)	133	26	1.39 (0.32-6.09)	156	30	1.36 (0.31-5.93)	166	32	1.37 (0.31-5.97)
Solvents	48	6	0.82 (0.15-4.49)	77	17	1.71 (0.36-7.99)	97	21	1.63 (0.36-7.51)	123	22	1.26 (0.27-5.82)
Other	98	19	1.52 (0.33-7.08)	138	28	1.60 (0.35-7.27)	157	30	1.48 (0.33-6.63)	168	32	1.54 (0.34-6.96)

[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, heptachlor, hexachlorobenzene, 1,2,3,4,5,6-hexachlorocyclohexane, 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).

Supplementary Material, 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.