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Risk of neuroblastoma and residential proximity to industrial and urban sites: a case-control study

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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

PAHs: Polycyclic aromatic hydrocarbons

EDCs: Endocrine disrupting chemicals

Abstract

Background: Neuroblastoma is the most common extracranial solid tumor in children but its etiology is not clearly understood. While a small fraction of cases might be attributable to genetic factors, the role of environmental pollution factors needs to be assessed.

Objectives: To ascertain the effect of residential proximity to both industrial and urban areas on neuroblastoma risk, taking into account industrial groups and toxic substances released.

Methods: We conducted a population-based case-control study of neuroblastoma in Spain, including 398 incident cases gathered from the Spanish Registry of Childhood Tumors (period 1996-2011), and 2388 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 and the 30 urban areas with $\geq 75,000$ inhabitants located in the study area. Using logistic regression, odds ratios (ORs) and 95% confidence intervals (95% CIs) for categories of distance (from 1 km to 5 km) to industrial and urban pollution sources were calculated, with adjustment for matching variables and socioeconomic confounders.

Results: Excess risk (OR; 95% CI) of neuroblastoma was detected for the intersection between industrial and urban areas: (2.52; 1.20-5.30) for industrial distance of 1 km, and (1.99; 1.17-3.37) for industrial distance of 2 km. By industrial groups, excess risks were observed near 'Production of metals' (OR=2.05; 95% CI=1.16-3.64 at 1.5 km), 'Surface treatment of metals' (OR=1.89; 95% CI=1.10-3.28 at 1 km), 'Mines' (OR=5.82; 95% CI=1.04-32.43 at 1.5 km), 'Explosives/pyrotechnics' (OR=4.04; 95% CI=1.31-12.42 at 4 km), and 'Urban waste-water treatment plants' (OR=2.14; 95% CI=1.08-4.27 at 1.5 km).

Conclusions: These findings support the need for more detailed exposure assessment of certain substances released by these industries.

Key Words: neuroblastoma; industrial pollution; urban pollution; case-control study; residential proximity; Pollutant Release and Transfer Register

1. Introduction

Neuroblastoma is the most common extracranial solid tumor in children – accounting for 8-10% of all childhood cancers (Colon and Chung, 2011; Park et al., 2010) – and the most common tumor diagnosed during the first year of life in developed countries (Ries et al., 1999), with an estimated annual incidence of 10.9 cases per million children (<15 years of age) in Europe and 10.2 cases/million in the US (Maris, 2010; Spix et al., 2006).

The etiology of neuroblastoma is not clearly understood: whereas known genetic factors, including mutations of the anaplastic lymphoma kinase oncogene, account for 7-8% of cases, the high incidence in early childhood would suggest that factors occurring in pregnancy are likely important in its development (Azarova et al., 2011; Esiashvili et al., 2009). However, studies existing in the literature provide inconsistent and/or inconclusive results: although several factors – including birth weight, maternal smoking or alcohol consumption during pregnancy, prenatal hormone exposure, maternal medication use during pregnancy, and hair dye – have been explored as potential risk factors associated with neuroblastoma (Heck et al., 2009; Mullassery et al., 2009; Parodi et al., 2014; Ross and Spector, 2006), little is known about their mechanisms involved in neuroblastoma's etiopathogenesis and the role of such factors in the etiology of this cancer (Zhu et al., 2010). With regard to environmental and parental occupational exposures, several authors have analyzed the risk of neuroblastoma and exposure to pesticides (Daniels et al., 2001), different types of chemicals – such as metals or hydrocarbons (De Roos et al., 2001; Parodi et al., 2014) –, and ambient air toxics (Heck et al., 2013a; Heck et al., 2013b), with findings that need to be confirmed with other studies.

In this paper, we examine the effects of exposure to pollutant industries and urban areas, including different industrial groups and specific toxic substances, on neuroblastoma risk, in the

context of an ongoing population-based case-control study of incident childhood cancer in Spain (Garcia-Perez et al., 2015b; 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 neuroblastoma in Spain. Cases were incident cases of neuroblastoma (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 neuroblastoma and other peripheral nervous cell tumors – code IV (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 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 398 cases and 2388 controls, and both cases and controls were ethnically homogeneous.

2.2 Residential locations

Each individual's last residence was geocoded using Google Map Javascript API v3 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).

With respect to the cases, we successfully validated 98% of their addresses. The remaining 2% of cases were fairly uniformly distributed through the different regions and, therefore, we concluded that data were not biased in this sense. With respect to the controls, only 2% of controls did not have valid coordinates. Given that this number of failures was small, 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 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., 2015b), 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.

Finally, for the purposes of this study, we considered as urban areas the 30 towns with more than 75,000 inhabitants (big cities, according to the Spanish Act 57/2003) 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: Euclidean distance between the subject's residence and the centroid of the town in which it resides.

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)), 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 as a proxy of exposure to pesticides, described in detail in (Gomez-Barroso et al., 2016). In a first phase, we evaluated the relationship between neuroblastoma and residential proximity to any industrial installation (taking the following industrial distances 'D' into account: 5, 4, 3, 2.5, 2, 1.5, and 1 km) and urban sites (7 independent models). 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)*", 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 and spatial characteristics of the municipalities in Spain: 8 km (for towns $\geq 2,000,000$ 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).

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. In a second phase, we evaluated the relationship between neuroblastoma and residential proximity to industries by categories of industrial groups defined in Supplementary Data, Table S1 (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 \leq ‘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. Lastly, we assessed the relationship between neuroblastoma and residential proximity to industries, according to specific industrial pollutants released by the facilities (72 independent models). To this end, we created an exposure variable for each model, analogous to the previous analysis.

Since 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.

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 398 cases and 2388 controls included in the analysis were depicted in Table 1. Distribution by sex was the same in both boys and girls, and Catalonia and Madrid Region were the autonomous regions with the highest proportion of cases and controls (44.2% and 35.4%, respectively).

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, industries, and towns with more than 75,000 inhabitants.

Estimated ORs of neuroblastoma associated with residential proximity to industrial and urban sites, using different industrial distances, are shown in Table 2. Excess risks of neuroblastoma, although non-statistically significant, were detected for all distances analyzed, in both industrial and urban areas, with ORs ranged between 1.24 (95%CI=0.82-1.88) (at 1.5 km) and 1.33 (95%CI=0.90-1.97) (at 2.5 km) in the case of industrial areas, and between 1.22 (95%CI=0.76-1.96) (at 2 km) and 1.83 (95%CI=0.78-4.33) (at 5 km) in the case of urban areas. For the intersection between industrial and urban areas, however, there was a statistically significant excess risk of neuroblastoma for industrial distances between 1 km (OR=2.52; 95%CI=1.20-5.30) and 2 km (OR=1.99; 95%CI=1.17-3.37), with this being higher than industrial area (only) and urban area (only) separately (synergic effect).

Figure 2 shows the most remarkable results for the analysis of proximity to industries by categories of industrial groups. Attention should be drawn to the statistically significant excess risks found for the following distances and industrial groups: 'Production and processing of metals' (OR=2.05; 95%CI=1.16-3.64 at 1.5 km), 'Surface treatment of metals' (OR=1.89; 95%CI=1.10-3.28 at 1 km, and OR=1.69; 95%CI=1.05-2.74 at 1.5 km), 'Mining industry'

(OR=5.82; 95%CI=1.04-32.43 at 1.5 km, OR=5.31; 95%CI=1.47-19.18 at 2 km, OR=4.67; 95%CI=1.70-12.81 at 2.5 km, OR=3.88; 95%CI=1.53-9.82 at 3 km, and OR=2.33; 95%CI=1.09-5.01 at 4 km), ‘Explosives and pyrotechnics’ (OR=4.04; 95%CI=1.31-12.42 at 4 km, and OR=2.86; 95%CI=1.04-7.84 at 5 km), and ‘Urban waste-water treatment plants’ (OR=2.14; 95%CI=1.08-4.27 at 1.5 km, and OR=1.60; 95%CI=1.05-2.43 at 5 km). It is also noteworthy to emphasize that there is a risk gradient effect (rise in OR with increasing proximity to industries of a specific sector) for ‘Mining industry’, where OR increases from 1.53 at 5 km to 6.89 at 1 km (p -trend=0.0259, data not shown).

Analysis of the previous figure was performed separately for each of the 25 categories of industrial groups (see Supplementary Data, Table S1).

Finally, the results for specific industrial pollutants (data not shown) displayed statistically significant excess risks of neuroblastoma in children living close to industrial facilities releasing benzo(b)fluoranthene (OR=2.20; 95%CI=1.05-4.62 at 3 km, OR=2.57; 95%CI=1.34-4.94 at 4 km, and OR=2.10; 95%CI=1.14-3.88 at 5 km), benzo(a)pyrene (OR=2.28; 95%CI=1.06-4.93 at 4 km), benzo(k)fluoranthene (OR=3.59; 95%CI=1.06-12.18 at 1.5 km), naphthalene (OR=1.61; 95%CI=1.02-2.54 at 4 km), lead and compounds (OR=1.72; 95%CI=1.07-2.76 at 1.5 km), toluene (OR=2.84; 95%CI=1.11-7.26 at 1 km), dichloromethane (OR=3.28; 95%CI=1.44-7.47 at 1 km), and tetrachloroethylene (OR=2.97; 95%CI=1.21-7.28 at 1 km).

4. Discussion

In the present paper, we set out to examine the effects of exposure to industrial and urban pollution on neuroblastoma risk in Spain, taking into account different industrial groups. Our

analyses indicate an excess risk of neuroblastoma among children living near industrial and urban areas, separately, though estimates failed to attain statistical significance. However, a high excess risk for neuroblastoma was detected in children living in the intersection between industrial and urban areas, for industrial distances between 1 km and 2 km. Moreover, analyses by industrial group show an association between risk of neuroblastoma and proximity to mining industries and, to a lesser extent, metal industry (production and processing of metals, and surface treatment of metals and plastic), explosives and pyrotechnics, and urban waste-water treatment plants.

The study of childhood cancer in areas surrounding environmental pollution sources is beginning to assume growing importance (Boothe et al., 2014; Heck et al., 2013a; Kheifets et al., 2015; Shrestha et al., 2014; 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 pollution exposures and neuroblastoma are concerned, there are few studies focused on pollution released by industrial facilities, even though industrial plants are known to release carcinogens, such as benzene, metals, dioxins, and polycyclic aromatic hydrocarbons (PAHs), as well as endocrine disrupting chemicals (EDCs), substances that alter functions of the endocrine system and are related to neuroblastoma (Zhu et al., 2009; Zhu et al., 2010). Heck et al. (Heck et al., 2013a) examined maternal exposure to specific ambient air toxics in relation to childhood neuroblastoma, using different radii (5, 4, 3, and 2.5 km) around air pollution monitors located in industrial areas, heavily traffic highways, and in agriculturally intense rural regions in California (USA), and the results showed an increased risk of neuroblastoma in relation to higher maternal exposure to specific pollutants, such as carbon

tetrachloride (OR=2.65; 95%CI=1.07-6.53 at 5 km, and OR=7.87; 95%CI=1.37-45.34 at 2.5 km), hexavalent chromium (OR=1.32; 95%CI=1.00-1.74 at 5 km), and PAHs (OR=1.39; 95%CI=1.05-1.84 at 2.5km). In this sense, our analyses for specific industrial pollutants (data not shown) yielded similar results, although non-statistically significant, for PAHs (OR=1.41; 95%CI=0.85-2.25 at 2.5 km), and chromium and compounds (OR=1.31; 95%CI=0.88-1.95 at 5 km). On the other hand, Thompson et al. (Thompson et al., 2008) did not find increased risk for neuroblastoma in children close to hazardous air pollutant release facilities in Texas (USA), including petroleum refineries and related industries, chemical industries, and plastics production. Our results for these industrial sectors also showed no statistically significant excess risks (see Supplementary Data, Table S1).

With regard to the industrial groups with statistically significant ORs in our study, one of the most noteworthy results is the high excess risk found in the proximity of mining industries. These installations release carcinogenic substances to the environment (metals, PAHs, particulate matter, and asbestos) and generate great amounts of toxic waste (mineral-based non-chlorinated engine, gear and lubricating oils, solvents, oil filters, and lead batteries) (Fernandez-Navarro et al., 2012; Spanish Ministry of Economy and Competitiveness, 2016). In this sense, Zota et al. (Zota et al., 2011) suggested that nearby outdoor sources of metal contaminants from mine waste may migrate indoors. Some authors have found excess risks of some types of cancer in adult populations near mines (Fernandez-Navarro et al., 2012; Mueller et al., 2015), and it is known that children exposed to metals in mining sites might be more susceptible to DNA damage (Jasso-Pineda et al., 2012; Katic et al., 2010). Moreover, some studies have found high concentrations of metals in homes and fingernails of children living in mining communities (Wickre et al., 2004; Zota et al., 2011). In our study, additionally, we have detected a risk

gradient effect of neuroblastoma, from 5 km to 1 km around mines, which could be justified by the long residence time in the atmosphere of particulate matter emitted by these industries (Sanchez de la Campa et al., 2015), a mixture of pollutants recently identified as carcinogenic to humans (IARC, 2015). Lastly, populations living farther away from mining sites may also be exposed if secondary uses of mine waste occur in close proximity to homes (Zota et al., 2011).

In relation to other industrial groups, the metal industry (production and processing of metals, and surface treatment of metals and plastic) is the leading polluter of metals, polycyclic aromatic chemicals, and persistent organic pollutants in air and water, and the second-leading polluter of pesticides in water, substances which are known or suspected carcinogens. Moreover, these types of installations release manganese, an EDC which has been related to DNA damage in neuroblastoma cells (Di Lorenzo et al., 1996; Stephenson et al., 2013). In previous studies of our group, metal industries have been associated with other childhood tumors, as leukemia (Garcia-Perez et al., 2015b) or renal cancer (Garcia-Perez et al., 2016), and other authors have found increased risks of different types of childhood cancers in the environs of these industries (Knox and Gilman, 1997; Wulff et al., 1996).

Another industrial group with noteworthy results in our study is the referred to urban waste-water treatment plants, the leading polluter of pesticides in water, and the second-leading polluter of metals in air and water. Some authors have detected and quantified EDCs in the influents and effluents of these industries (Nelson et al., 2007), and several studies have found excess risks of ovarian (Garcia-Perez et al., 2015a) and respiratory cancers (Chellini et al., 2002) in the general population residing in the proximity of these plants. Moreover, a study revealed that the people living in the areas even more than 4 km away from a waste-water treatment plant were still potentially exposed to cancer risks exceeding the regulatory threshold limit (Yang et

al., 2014), a finding that could be related to the excess risk of neuroblastoma found by us at 5 km around these plants (OR=1.60; 95% CI=1.05-2.43).

Lastly, despite the fact that explosives and pyrotechnics industries release metals, particulate matter, and some volatile organic compounds, only an epidemiologic study on children living near these installations have been conducted: Kinlen (Kinlen, 2006) found excess risk of childhood leukemia around ordnance factories in England.

Insofar as environmental parental exposures and neuroblastoma are concerned, some papers have found associations between risk of neuroblastoma and certain parental occupations – in the service and retail industries, materials handling, farming, or employment in electric- and electronics-related occupations (Heck et al., 2009; Kerr et al., 2000; Olshan et al., 1999; Ross and Spector, 2006) –, whereas other studies have found associations with parental occupational exposures to specific pollutants, such as pesticides, hydrocarbons, and solvents (Daniels et al., 2001; De Roos et al., 2001; Parodi et al., 2014; Pearce et al., 2006; Petridou, 2001; Schuz et al., 2001).

In this paper, we have used several urban distances depending on the size of the municipality, as a proxy of residential traffic exposure to toxic substances, such as particulate matter. Our results show that children living near urban areas registered a non-statistically significant excess risk of neuroblastoma for all distances analyzed. Other studies, however, did not find any evidence of association between risk of neuroblastoma and traffic density within 500 m of the residence (Heck et al., 2013b) or residing in urban and metropolitan areas (Hsieh et al., 2009; Thompson et al., 2008).

One aspect addressed in the analyses is the problem of multiple comparisons (to find associations that are falsely positive by random chance). In Supplementary Data, Table S1, we

have provided adjusted p -values, though from an epidemiologic standpoint we have preferred to discuss the results in the light of a series of factors, namely, the magnitude of risk *per se*, the consistency of the associations observed, and biologic plausibility. Furthermore, we observed 12 positive associations for the analysis by category of industrial group shown in Supplementary Data, Table S1 and, for $\alpha=0.05$, we estimated that random chance would account for 4.2 positive associations (number of comparison \times percentage of statistically significant ORs >1 expected under the null hypothesis, i.e., 2.5%).

Aside from the limitations inherent to all case-control studies, in our case mention should also be made of the following: 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 – 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)); 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); and the non-inclusion of information about parental occupational exposures, and perinatal and reproductive factors, for their unavailability at an individual level.

It should be noted that we have the home address of the cases at the moment of diagnosis (i.e., residence at the time of incidence, because in neuroblastoma, 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 the children change their residence to a different province (National Statistics Institute, 2016). Therefore, we considered that the home address at diagnosis is the same as the home address at birth for the majority of the cases.

Yet another limitation is that, for the cases, we used the residential location at time of diagnosis to assess 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, and do not allow us to explore the effects of the latency period of neuroblastoma, thus inducing some degree of exposure misclassification (Ortega-Garcia et al., 2016; Vinceti et al., 2012).

Another 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 estimators of real risk greater than those found.

Finally, we have not considered the mother's residence during pregnancy (neither in cases nor in controls), which could be different from the child's last residence. Moreover, we have assumed in the analyses that children and mothers spend the majority of time at or near their residences, a fact that could introduce a bias in the allocation of exposure, since the mother can work during pregnancy or the child can be cared for outside the home.

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, which provides a description more exhaustive of neuroblastoma 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., 2015b).

5. Conclusions

The results suggest a possible increased risk of neuroblastoma among children living in the intersection between industrial and urban areas and, specifically, near mines, metal industries, explosives and pyrotechnics, and urban waste-water treatment plants. These findings support the need for more detailed exposure assessment and health risk analysis of certain toxic substances released by these types of industries.

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Figure legends

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

Figure 2: Odds ratios of neuroblastoma with statistically significant results for the analysis of proximity to industries by category of industrial group. Y-axis is plotted in logarithmic scale.

Table 2: Odds ratios of neuroblastoma 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
5 Km	Reference	225	40	-
	Industrial area - 5 km (only)	1567	262	1.30 (0.89-1.91)
	Urban area (only)	36	8	1.83 (0.78-4.33)
	Both ^c	560	88	1.41 (0.90-2.20)
4 Km	Reference	225	40	-
	Industrial area - 4 km (only)	1479	244	1.29 (0.88-1.90)
	Urban area (only)	143	25	1.46 (0.82-2.60)
	Both ^c	453	71	1.42 (0.90-2.25)
3 Km	Reference	225	40	-
	Industrial area - 3 km (only)	1327	215	1.28 (0.87-1.89)
	Urban area (only)	277	45	1.38 (0.84-2.27)
	Both ^c	319	51	1.48 (0.91-2.41)
2.5 Km	Reference	225	40	-
	Industrial area - 2.5 km (only)	1187	197	1.33 (0.90-1.97)
	Urban area (only)	350	54	1.32 (0.81-2.13)
	Both ^c	246	42	1.62 (0.98-2.69)
2 Km	Reference	225	40	-
	Industrial area - 2 km (only)	993	156	1.27 (0.85-1.90)
	Urban area (only)	420	60	1.22 (0.76-1.96)
	Both ^c	176	36	1.99 (1.17-3.37)
1.5 Km	Reference	225	40	-
	Industrial area - 1.5 km (only)	751	115	1.24 (0.82-1.88)
	Urban area (only)	484	72	1.29 (0.81-2.03)
	Both ^c	112	24	2.12 (1.18-3.83)
1 Km	Reference	225	40	-
	Industrial area - 1 km (only)	465	75	1.30 (0.83-2.01)
	Urban area (only)	551	84	1.35 (0.86-2.11)
	Both ^c	45	12	2.52 (1.20-5.30)

^aIndustrial distance referred to the industrial area (only) in the exposure category.

^bORs 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.

^cIntersection area between industrial area defined by the corresponding industrial distance and urban area (only).

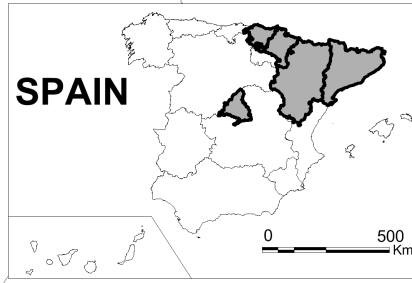
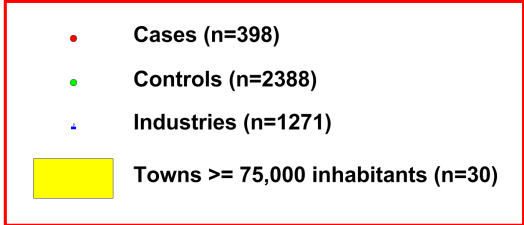
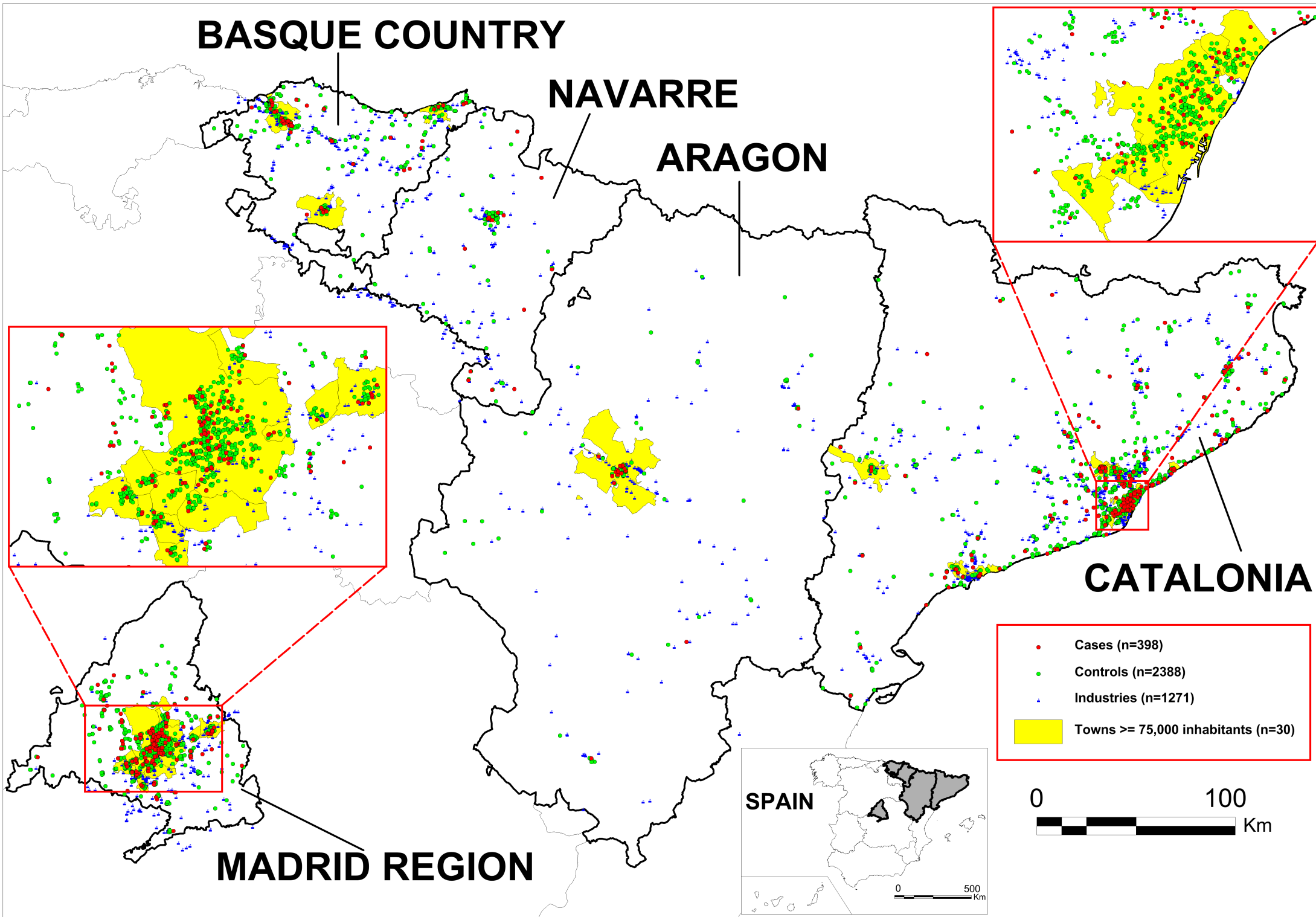
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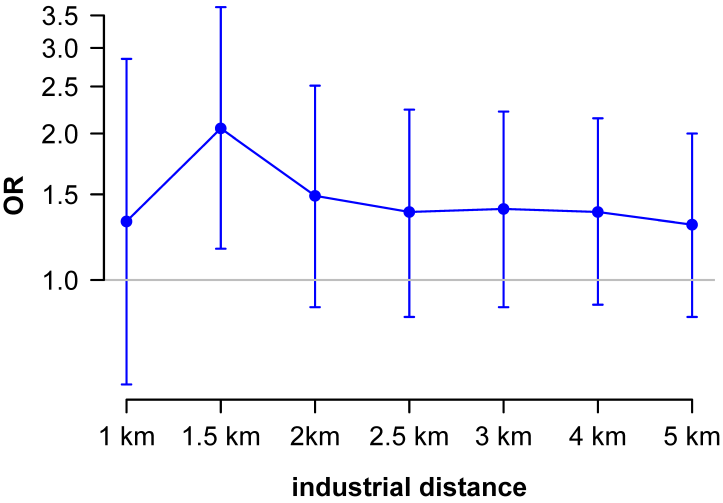
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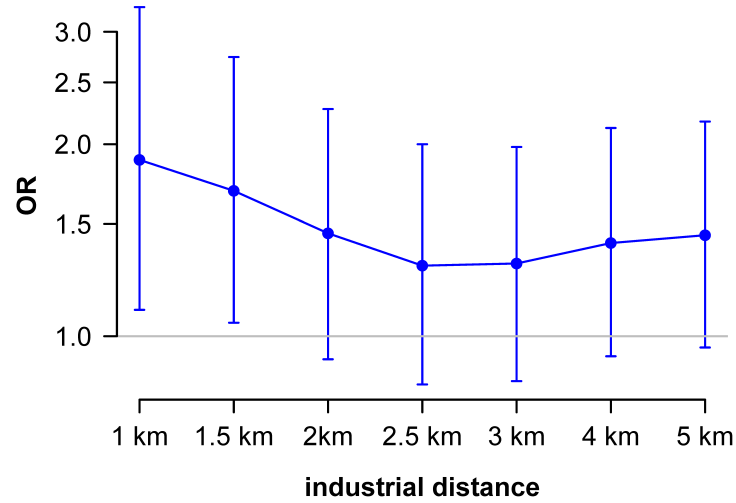
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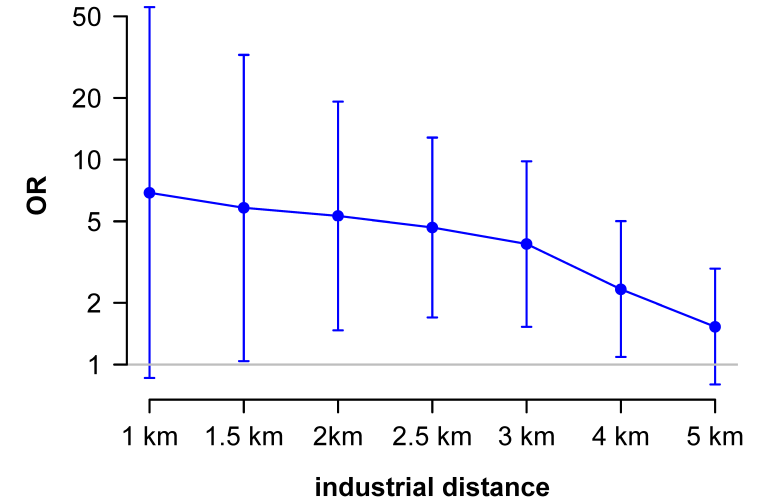
Production and processing of metals (n=119)



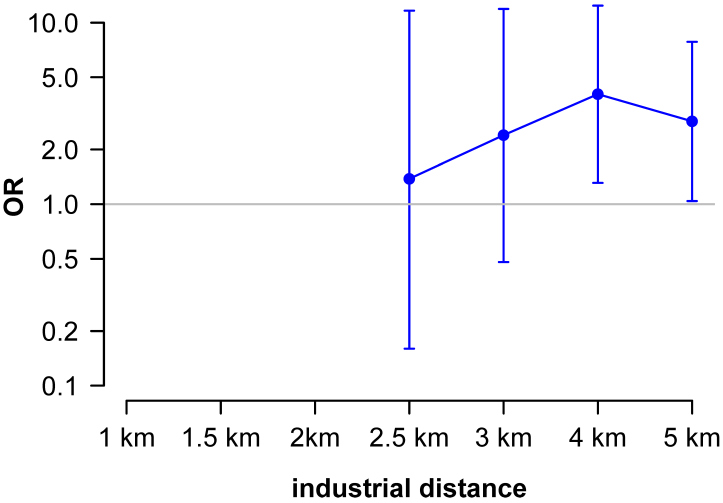
Surface treatment of metals and plastic (n=197)



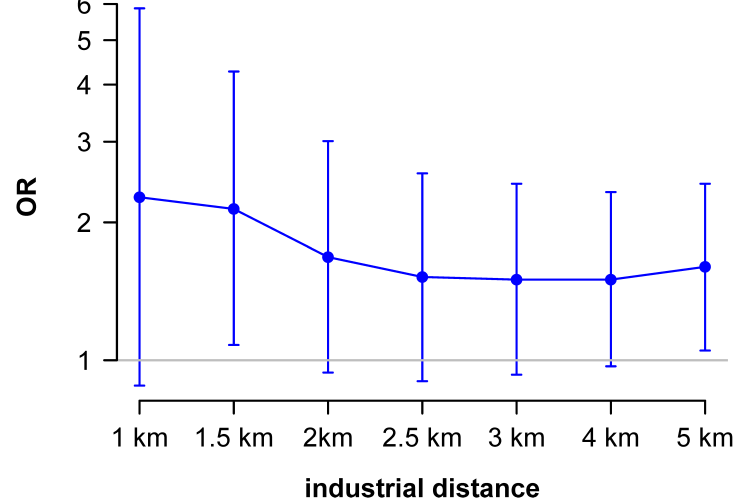
Mining industry (n=39)



Explosives and pyrotechnics (n=9)



Urban waste-water treatment plants (n=53)



Supplementary Material

Title of the manuscript: “Risk of neuroblastoma and residential proximity to industrial and urban sites: a case-control study”.

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

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

Supplementary Material, Table S1: Odds ratios of neuroblastoma by industrial distance and category of industrial group.

Industrial group (no. industries)	Individuals residing at ≤1 km						Individuals residing at ≤1.5 km						Individuals residing at ≤2 km						Individuals residing at ≤2.5 km					
	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	225	40	-	-	-	-	225	40	-	-	-	-	225	40	-	-	-	-	225	40	-	-	-	-
All sectors (1271)	465	75	1.30 (0.83-2.01)				751	115	1.24 (0.82-1.88)				993	156	1.27 (0.85-1.90)				1187	197	1.33 (0.90-1.97)			
Combustion installations (42)	12	32.15	(0.56-8.24)	0.265	0.827	1.000	37	5.107	(0.39-2.97)	0.896	0.999	1.000	86	10.097	(0.45-2.07)	0.929	0.984	1.000	121	15.104	(0.54-2.00)	0.914	0.984	1.000
Refineries and coke ovens (4)	0	0	-	-	-	-	3	0.0	(0-inf)	0.982	0.999	1.000	9	1.0.83	(0.10-7.10)	0.862	0.984	1.000	26	4.1.24	(0.40-3.85)	0.713	0.980	1.000
Production and processing of metals (119)	71	10.1.32	(0.61-2.85)	0.476	0.990	1.000	118	26.2.05	(1.16-3.64)	0.014	0.242	0.914	210	35.1.49	(0.88-2.51)	0.135	0.806	1.000	281	45.1.38	(0.84-2.24)	0.203	0.823	1.000
Galvanization (19)	13	2.1.28	(0.28-5.94)	0.751	0.990	1.000	42	5.1.00	(0.37-2.73)	0.999	0.999	1.000	67	8.0.99	(0.43-2.26)	0.984	0.984	1.000	102	12.0.99	(0.49-2.00)	0.967	0.984	1.000
Surface treatment of metals and plastic (197)	142	30.1.89	(1.10-3.28)	0.022	0.514	1.000	284	53.1.69	(1.05-2.74)	0.030	0.242	0.914	463	73.1.45	(0.92-2.27)	0.111	0.806	1.000	618	90.1.29	(0.84-2.00)	0.249	0.823	1.000
Mining industry (39)	2	2.6.89	(0.86-55.46)	0.070	0.699	1.000	3	3.5.82	(1.04-32.43)	0.045	0.268	1.000	6	5.5.31	(1.47-19.18)	0.011	0.259	0.978	11	84.6.7	(1.70-12.81)	0.003	0.067	0.254
Cement and lime (33)	7	2.1.62	(0.30-8.65)	0.572	0.990	1.000	12	5.2.45	(0.77-7.73)	0.127	0.509	1.000	32	6.1.35	(0.51-3.56)	0.540	0.953	1.000	60	12.1.46	(0.70-3.04)	0.309	0.823	1.000
Glass and mineral fibers (20)	20	4.1.87	(0.59-5.89)	0.287	0.827	1.000	38	7.1.68	(0.68-4.16)	0.260	0.650	1.000	70	10.1.30	(0.60-2.84)	0.503	0.953	1.000	120	15.1.15	(0.59-2.25)	0.675	0.980	1.000
Ceramic (86)	29	40.7.8	(0.25-2.43)	0.673	0.990	1.000	54	9.1.13	(0.51-2.54)	0.761	0.999	1.000	89	12.0.91	(0.45-1.85)	0.788	0.984	1.000	113	17.1.03	(0.55-1.93)	0.931	0.984	1.000
Organic chemical industry (106)	48	8.1.32	(0.57-3.08)	0.516	0.990	1.000	111	13.0.95	(0.48-1.89)	0.883	0.999	1.000	207	30.1.17	(0.69-2.00)	0.564	0.953	1.000	276	40.1.17	(0.71-1.92)	0.541	0.980	1.000
Inorganic chemical industry (46)	18	5.1.84	(0.62-5.43)	0.270	0.827	1.000	49	10.1.55	(0.71-3.41)	0.271	0.650	1.000	84	15.1.34	(0.69-2.61)	0.392	0.953	1.000	115	20.1.30	(0.71-2.38)	0.394	0.944	1.000
Fertilizers (10)	4	0.0	(0-inf)	0.979	0.990	1.000	12	0.0	(0-inf)	0.977	0.999	1.000	19	0.0	(0-inf)	0.980	0.984	1.000	25	1.0.30	(0.04-2.32)	0.246	0.823	1.000
Biocides (12)	10	0.0	(0-inf)	0.979	0.990	1.000	15	2.1.17	(0.25-5.48)	0.838	0.999	1.000	22	4.1.57	(0.50-4.93)	0.442	0.953	1.000	44	7.1.36	(0.56-3.32)	0.502	0.980	1.000
Pharmaceutical products (41)	43	9.1.80	(0.80-4.09)	0.157	0.772	1.000	91	16.1.50	(0.78-2.89)	0.222	0.650	1.000	144	24.1.50	(0.84-2.67)	0.168	0.806	1.000	197	33.1.48	(0.87-2.51)	0.147	0.823	1.000
Explosives and pyrotechnics (9)	3	0.0	(0-inf)	0.982	0.990	1.000	3	0.0	(0-inf)	0.982	0.999	1.000	5	0.0	(0-inf)	0.977	0.984	1.000	7	1.1.38	(0.16-11.65)	0.765	0.980	1.000
Hazardous waste (60)	37	10.2.4	(0.03-1.83)	0.168	0.772	1.000	60	1.0.14	(0.02-1.08)	0.060	0.287	1.000	111	9.0.72	(0.33-1.57)	0.411	0.953	1.000	180	19.0.89	(0.49-1.63)	0.707	0.980	1.000
Non-hazardous waste (86)	10	10.9.6	(0.12-7.79)	0.969	0.990	1.000	21	1.0.44	(0.06-3.41)	0.433	0.864	1.000	51	5.0.82	(0.30-2.23)	0.691	0.982	1.000	89	10.0.90	(0.42-1.92)	0.776	0.980	1.000
Disposal or recycling of animal waste (18)	9	10.9.9	(0.12-8.20)	0.990	0.990	1.000	25	3.1.11	(0.31-3.94)	0.872	0.999	1.000	42	6.1.32	(0.51-3.39)	0.566	0.953	1.000	80	11.1.33	(0.63-2.81)	0.454	0.980	1.000
Urban waste-water treatment plants (53)	23	7.2.27	(0.88-5.87)	0.091	0.699	1.000	57	15.2.14	(1.08-4.27)	0.030	0.242	0.914	120	24.1.68	(0.94-3.01)	0.079	0.806	1.000	183	30.1.52	(0.90-2.56)	0.120	0.823	1.000
Paper and wood production (63)	38	5.1.06	(0.38-2.93)	0.914	0.990	1.000	68	6.0.75	(0.30-1.89)	0.542	0.930	1.000	99	10.0.86	(0.40-1.83)	0.696	0.982	1.000	129	16.1.03	(0.54-1.97)	0.925	0.984	1.000
Pre-treatment or dyeing of textiles (9)	3	0.0	(0-inf)	0.983	0.990	1.000	4	1.2.32	(0.25-21.95)	0.462	0.864	1.000	9	3.2.47	(0.62-9.96)	0.202	0.809	1.000	16	4.1.93	(0.59-6.30)	0.274	0.823	1.000
Tanning of hides and skins (2)	8	0.0	(0-inf)	0.980	0.990	1.000	11	1.0.60	(0.07-5.00)	0.638	0.999	1.000	12	1.0.57	(0.07-4.66)	0.596	0.953	1.000	12	1.0.57	(0.07-4.66)	0.596	0.980	1.000
Food and beverage sector (145)	88	100.8.4	(0.42-1.89)	0.750	0.990	1.000	160	25.1.23	(0.70-2.16)	0.468	0.864	1.000	237	39.1.30	(0.79-2.14)	0.312	0.953	1.000	311	51.1.31	(0.81-2.09)	0.269	0.823	1.000
Surface treatment using organic solvents (50)	23	10.3.9	(0.05-2.97)	0.362	0.925	1.000	61	4.0.53	(0.18-1.57)	0.255	0.650	1.000	111	14.1.06	(0.54-2.08)	0.862	0.984	1.000	164	19.0.99	(0.54-1.82)	0.984	0.984	1.000
Production of electro-graphite (2)	0	0	-	-	-	-	0	0	-	-	-	-	0	0	-	-	-	-	0	0	-	-	-	-
Industrial group (no. industries)	Individuals residing at ≤3 km						Individuals residing at ≤4 km						Individuals residing at ≤5 km											
	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	225	40	-	-	-	-	225	40	-	-	-	-	225	40	-	-	-	-	225	40	-	-	-	-
All sectors (1271)	1327	215	1.28 (0.87-1.89)				1479	244	1.29 (0.88-1.90)				1567	262	1.30 (0.89-1.91)									
Combustion installations (42)	145	18.1.06	(0.57-1.97)	0.861	0.956	1.000	247	37.1.26	(0.75-2.10)	0.378	0.504	1.000	341	56.1.41	(0.88-2.26)	0.154	0.427	1.000						
Refineries and coke ovens (4)	32	8.2.00	(0.83-4.82)	0.120	0.603	1.000	40	9.1.89	(0.82-4.35)	0.133	0.407	1.000	53	12.1.86	(0.88-3.93)	0.104	0.427	1.000						
Production and processing of metals (119)	377	62.1.40	(0.88-2.22)	0.152	0.603	1.000	501	81.1.38	(0.89-2.15)	0.150	0.407	1.000	609	94.1.30	(0.84-2.00)	0.237	0.429	1.000						
Galvanization (19)	120	15.1.04	(0.54-2.01)	0.901	0.956	1.000	148	22.1.23	(0.68-2.20)	0.492	0.621	1.000	193	32.1.38	(0.81-2.34)	0.236	0.429	1.000						
Surface treatment of metals and plastic (197)	773	115.1.30	(0.85-1.98)	0.226	0.603	1.000	938	149.1.40	(0.93-2.12)	0.108	0.407	1.000	1025	166.1.44	(0.96-2.17)	0.081	0.427	1.000						
Mining industry (39)	15	9.3.88	(1.53-9.82)	0.004	0.101	0.382	35	12.2.33	(1.09-5.01)	0.030	0.362	1.000	74	17.1.53	(0.80-2.94)	0.196	0.429	1.000						
Cement and lime (33)	89	15.1.21	(0.62-2.35)	0.571	0.835	1.000	168	29.1.40	(0.81-2.40)	0.229	0.407	1.000	251	40.1.32	(0.80-2.17)	0.278	0.429	1.000						
Glass and mineral fibers (20)	172	180.9.7	(0.52-1.82)	0.933	0.956	1.000	249	28.1.02	(0.59-1.76)	0.951	0.951	1.000	323	35.0.97	(0.58-1.63)	0.910	0.948	1.000						
Ceramic (86)	136	190.9.8	(0.53-1.79)	0.936	0.956	1.000	200	26.0.91	(0.53-1.58)	0.740	0.807	1.000	257	34.0.95	(0.57-1.57)	0.828	0.941	1.000						
Organic chemical industry (106)	337	46.1.12	(0.69-1.80)	0.655	0.835	1.000	463	74.1.32	(0.85-2.06)	0.222	0.407	1.000	585	98.1.37	(0.89-2.09)	0.151	0.427	1.000						
Inorganic chemical industry (46)	141	27.1.42	(0.82-2.47)	0.216	0.603	1.000	204	34.1.26	(0.75-2.12)	0.375	0.504	1.000	277	45.1.27	(0.78-2.06)	0.343	0.452	1.000						
Fertilizers (10)	28	20.4.9	(0.11-2.19)	0.347	0.758	1.000	31	2.0.43	(0.10-1.91)	0.266	0.407	1.000	48	7.0.94	(0.39-2.27)	0.882	0.948	1.000						
Biocides (12)	55	11.1.62	(0.76-3.46)	0.210	0.603	1.000	84	15.1.49	(0.76-2.93)	0.243	0.407	1.000	113	19.1.42	(0.76-2.64)	0.271	0.429	1.000						
Pharmaceutical products (41)	246	43.1.56	(0.95-2.56)	0.083	0.603	1.000	360	61.1.49																

Food and beverage sector (145)	363	61	1.34 (0.85-2.11)	0.209	0.603	1.000	489	82	1.33 (0.86-2.05)	0.195	0.407	1.000	655	102	1.27 (0.83-1.93)	0.273	0.429	1.000
Surface treatment using organic solvents (50)	215	29	1.15 (0.67-1.97)	0.614	0.835	1.000	335	53	1.37 (0.85-2.20)	0.192	0.407	1.000	445	68	1.31 (0.84-2.06)	0.238	0.429	1.000
Production of electro-graphite (2)	0	0	-	-	-	-	0	0	-	-	-	-	4	0	0 (0-inf)	0.980	0.980	1.000

^aNumber of neuroblastoma cases.

^bNumber of controls.

^cORs 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.