RISK OF BONE TUMORS IN CHILDREN AND RESIDENTIAL PROXIMITY TO INDUSTRIAL AND URBAN AREAS: NEW FINDINGS FROM A CASE-CONTROL STUDY

García-Pérez J, Morales-Piga A, Gómez-Barroso D, Tamayo-Uria I, Pardo Romaguera E, López-Abente G, Ramis R. Risk of bone tumors in children and residential proximity to industrial and urban areas: New findings from a case-control study. Sci Total Environ. 2017 Feb 1;579:1333-1342. doi: 10.1016/j.scitotenv.2016.11.131. PMID: 27916304.

Risk of bone tumors in children and residential proximity to industrial and urban areas: new findings from a case-control study

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Abbreviations:

RETI-SEHOP: Spanish Registry of Childhood Tumors

NSI: National Statistics Institute

E-PRTR: European Pollutant Release and Transfer Register

ORs: Odds ratios

95%CIs: 95% confidence intervals

POPs: Persistent organic pollutants

PACs: Polycyclic aromatic chemicals

Non-HPCs: Non-halogenated phenolic chemicals

PAHs: Polycyclic aromatic hydrocarbons

Abstract

Few epidemiologic studies have explored risk factors for bone tumors in children, and the role of environmental factors needs to be analyzed. Our objective was to ascertain the association between residential proximity to industrial plants and urban areas and risk of bone tumors in children, taking into account industrial groups and toxic pollutants released. **A** population-based case-control study of childhood bone cancer in Spain was carried out, covering 114 incident cases obtained from the Spanish Registry of Childhood Tumors (between 1996 and 2011), and 684 controls individually matched by sex, year of birth, and autonomous region of residence. Distances from the subject's residences to the 1271 industries and the 30 urban areas (towns) with ≥75,000 inhabitants located in the study area were computed. Unconditional logistic regression models were fitted to estimate odds ratios (ORs) and 95% confidence intervals (95%CIs) for categories of distance (from 1 km to 3 km) to industrial and urban areas, with adjustment for matching variables and sociodemographic indicators. Excess risk (OR; 95%CI) of bone tumors in children was detected for children close to industrial facilities as a whole (2.33; 1.17-4.63 at 3 km) –particularly surface treatment of metals (OR=2.50; 95%CI=1.13-5.56 at 2 km), production and processing of metals (OR=3.30; 95%CI=1.41-7.77 at 2.5 km), urban waste-water treatment plants (OR=4.41; 95%CI=1.62-11.98 at 2 km), hazardous waste (OR=4.63; 95%CI=1.37-15.61 at 2 km), disposal or recycling of animal waste (OR=4.73; 95%CI=1.40-15.97 at 2 km), cement and lime (OR=3.89; 95%CI=1.19-12.77 at 2.5 km), and combustion installations (OR=3.85; 95%CI=1.39-10.66 at 3 km)–, and urban areas (4.43; 1.80-10.92). These findings support the need for more detailed exposure assessment of certain toxics released by these facilities.

Key Words: childhood cancer; bone cancer; case-control study; industrial pollution; urban area; residential proximity

1. Introduction

Bone cancers in children account for approximately 4-6% of cancer cases among children <15 years of age (Larranaga et al., 2016; Ward et al., 2014), where Ewing tumor and osteosarcomas are the two main histologic types.

Little is known about the etiology of malignant bone tumors in children. Some evidence points to a genetic predisposition for Ewing tumor (Delattre et al., 1994; Linet et al., 2003; Ross and Spector, 2006), and a meta-analysis found some evidence of an association of this tumor with hernias (Valery et al., 2005). On the other hand, the incidence of osteosarcoma is increased among children with the hereditary form of retinoblastoma and Li-Fraumeni syndrome, as well as other genetic syndromes, but these conditions account for a few cases (Ross and Spector, 2006; Ward et al., 2014). Other risk factors, such as reproductive, perinatal, social, developmental, and dietary factors, have been explored with inconsistent findings, suggesting a probable role of gene-environment interactions in the etiology of bone tumors in children (Eyre et al., 2009; Ottaviani and Jaffe, 2009).

Insofar as environmental pollution exposures and bone tumors are concerned, there are few papers focused on pollution released by industrial plants or urban areas (Bovill et al., 1975; Pan et al., 1994). The diverse histologic types, clinical behaviors, and low numbers of cases limit the research in these rare cancers in children, and, therefore, epidemiologic science research is needed to ascertain whether residential proximity to environmental exposures might have an influence on the frequency of these tumors.

The present paper assessed the possible association between residential proximity to industrial facilities and urban areas, –including different industrial groups, groups of carcinogenic and other toxic pollutants, and specific substances–, and risk of bone tumors in children, in the

context of the biggest population-based case-control study of incident childhood cancer carried out in Spain (Garcia-Perez et al., 2016b; Ramis et al., 2015).

2. Materials and methods

2.1 Study area and subjects

A population-based case-control study of bone tumors in children (0-14 years) was carried out. Incident cases were obtained from the Spanish Registry of Childhood Tumors (RETI-SEHOP) for Autonomous Regions with a coverage of 100%: Catalonia, the Basque Country, Aragon, and Navarre (period 1996-2011), and Autonomous Region of Madrid (period 2000-2011). These cases corresponded to diseases coded as malignant bone tumors (code VIII of the International Classification of Diseases for Oncology, 3rd revision) (Steliarova-Foucher et al., 2005). Six controls per case were selected, according to a simple random sampling from among all live births included in the Birth Registry of the Spanish National Statistics Institute (NSI) between 1996 and 2011, individually matched to cases by sex, year of birth, and autonomous region of residence.

2.2 Residential locations

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

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

2.3 Industrial facility and urban locations

We used industrial information about industries governed by the Integrated Pollution Prevention and Control Directive and facilities included in the European Pollutant Release and Transfer Register (E-PRTR), provided by the Spanish Ministry for Agriculture, Food & Environment in 2009. This industrial database included information, previously validated, about the geographic position and pollution emissions of the 1271 facilities located in the study area that reported their releases to air and water. These industries were classified into one of the 25 categories of industrial groups listed in Table 1. Additionally, Supplementary Data, Figure S1 shows the distribution of the years of commencement of operations of the facilities studied, by industrial group. The mean year of commencement of operations for industries as a whole was 1974.

Finally, we considered as urban areas the 30 municipalities ≥75,000 inhabitants ("big cities" according the Spanish Act 57/2003) included in the 2001 census, and located in the study area.

2.4 Exposure coding and statistical analysis

For each individual, the following distances were calculated: a) industrial distance: the shortest distance between the individual's residence and any of the 1271 industrial installations; and b) urban distance: the shortest distance between the individual'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., 2016a), five types of statistical analysis, including mixed multiple unconditional logistic

regression models, were performed to estimate odds ratios (ORs) and 95% confidence intervals (95%CIs):

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

$$Y\ is\ the\ case - control\ statuts\ (1 = case, 0 = control),\ i = 1, \dots, 798\ children$$

All models included: matching factors (year of birth ($year_i$), sex (sex_i), and autonomous region of residence (r_i)); other potential confounders provided by the 2001 census at a census tract level (percentage of illiteracy (ill_i), percentage of unemployed ($unem_i$), and socioeconomic status (SES_i)); and percentage of total crop surface in a 1-km buffer around each subject's last residence (GCI_i) as a measure of exposure to pesticides (Gomez-Barroso et al., 2016). The exposure variable, the matching factors $year_i$ and sex_i, and potential confounding factors were fixed-effects in the models, whereas r_i was a random effect.

1) Analysis 1 (relationship between bone tumors in children and proximity to industrial installations and urban areas as a whole). Taking into account several industrial distances 'D' (3, 2.5, 2, 1.5, and 1 km), each subject was classified into one of the following 4 categories of the exposure variable ($ExpoVariable$) for each distance 'D' (5 independent models): a) residence in the *"industrial area (only)"*, if it resides at ≤'D' km from any industrial facility; b) residence in the *"urban area (only)"*, taking the zones defined by urban distances according to the spatial characteristics and size of the municipalities in Spain; c) residence in the intersection between industrial and urban areas (*"both"*); and, d) residence within the *"reference area"*: zones with children having no industries within 3 km of their residences and far from urban zones.
2) Analysis 2 (relationship between bone tumors in children and proximity to facilities by category of industrial groups). Taking into account the 25 categories of industrial groups

defined in Table 1, we created an exposure variable ($ExpoVariable$) for each distance 'D' (25 independent models), 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 >3 km from any industry and far from urban areas.

3) Analysis 3 (relationship between bone tumors in children and residential proximity to industries releasing groups of carcinogens according to the International Agency for Research on Cancer, and other toxic substances). To this end, an exposure variable ($ExpoVariable$) for each distance 'D' (12 independent models) was created, 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.
4) Analysis 4 (relationship between bone tumors in children and residential proximity to industries by specific industrial pollutants released by the facilities). To this end, an exposure variable ($ExpoVariable$) for each distance 'D' (72 independent models) was created, where each subject was categorized as resident near industries releasing the specific "*industrial pollutant"* or resident in the "*reference area"*, analogous to the previous analyses.
5) Analysis 5 (assessment of the existence of radial effects near industries). To this end, we perform an analysis to analyze the risk gradient in the proximity of industrial installations, described in Supplementary Data, Appendix A.

Additionally, with the aim of introducing robustness in our analysis and controlling potential biases, two sensitivity analyses were performed for the analyses 1-4: a) a first sensitivity analysis with only individuals of the autonomous regions with the highest proportion of cases and controls; and, b) a second sensitivity analysis including only cases with the same address at the time of birth and at the moment of diagnosis. For this purpose, a matching strategy to find children with the addresses on the Birth Registry of the NSI matched to the addresses on RETI-SEHOP was used.

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).

3. Results

3.1 Characteristics of the study population

The final study population comprised 114 cases and 684 controls. The main characteristics of subjects included in the analyses were depicted in Table 2. Catalonia and Madrid Region were the autonomous regions with the highest proportion of individuals (48.3 and 29.8%, respectively), so these two regions were used in the first sensitivity analysis above mentioned. Histologically, Ewing tumor was the main type of bone cancer in children (63.1% of cases).

3.2 Results of the analysis 1

Estimated ORs of childhood cancers associated with residential proximity to industrial and urban areas, using several industrial distances, are shown in Table 3. Children close to industrial areas (only) registered excess risks of bone cancer for all industrial distances analyzed in the analysis with all individuals, statistically significant in the case of 3 km (OR=2.33; 95%CI=1.17-4.63) and 2.5 km (OR=2.19; 95%CI=1.10-4.39). However, when the two sensitivity analyses were applied, the statistical significance disappeared, and all risk estimates decreased for all distances analyzed. On the other hand, children living near urban areas (only) registered high and statistically significant excess risks for all industrial distances in the case of the analysis with all individuals –with ORs ranged between 4.01 (95%CI=1.77-9.06) (at 1 km) and 4.43 (95%CI=1.80-10.92) (at 3 km)– and the sensitivity analysis with only individuals of Catalonia and Madrid Region –with ORs ranged between 2.77 (95%CI=1.19-6.44) (at 1 km) and 3.24 (95%CI=1.29-8.10) (at 3 km)–. The second sensitivity analysis registered non-statistically significant excess risks of bone tumors near urban areas (only). Lastly, for the intersection area between industrial and urban zones, there were statistically significant excess risks of bone tumors for all industrial distances (with the exception of 1.5 km) in the analysis with all individuals, ranged from 3 km (OR=3.66; 95%CI=1.53-8.75) to 1 km (OR=4.39; 95%CI=1.19-16.23). However, only the second sensitivity analysis showed statistically significant excess risks in the case of 2.5 km (OR=4.10; 95%CI=1.07-15.68) and 2 km (OR=5.89; 95%CI=1.51-22.98).

3.3 Results of the analysis 2

The most noteworthy results for the analysis of proximity to facilities by categories of industrial groups are shown in Figure 1. Attention should be drawn to the increased risks found for the following industrial groups and distances: ‘Surface treatment of metals and plastic’ at 2

km (OR=2.50; 95%CI=1.13-5.56 in the analysis with all individuals, and OR=3.43; 95%CI=1.06-11.12 in the second sensitivity analysis); 'Production and processing of metals' at 2.5 km (OR=3.30; 95%CI=1.41-7.77 in the analysis with all individuals, and OR=3.58; 95%CI=1.03-12.40 in the second sensitivity analysis); 'Urban waste-water treatment plants' at 2 km (OR=4.41; 95%CI=1.62-11.98 in the analysis with all individuals, and OR=3.51; 95%CI=1.26-9.82 in the first sensitivity analysis); 'Hazardous waste' at 2 km (OR=4.63; 95%CI=1.37-15.61 in the analysis with all individuals, and OR=3.93; 95%CI=1.13-13.90 in the first sensitivity analysis); 'Disposal or recycling of animal waste' at 2 km (OR=4.73; 95%CI=1.40-15.97 in the analysis with all individuals, and OR=3.97; 95%CI=1.13-13.90 in the first sensitivity analysis); 'Cement and lime' at 2.5 km (OR=3.89; 95%CI=1.19-12.77 in the analysis with all individuals, and OR=3.45; 95%CI=1.01-11.73 in the first sensitivity analysis), and 'Combustion installations' at 3 km (OR=3.85; 95%CI=1.39-10.66 in the analysis with all individuals, and OR=3.69; 95%CI=1.22-11.18 in the first sensitivity analysis).

Detailed information on emission amounts by groups of substances released by the industrial groups analyzed is provided in Table 1.

3.4 Results of the analysis 3

In relation to the analysis of proximity to facilities by categories of groups of carcinogens and other toxic pollutants released by the facilities, the results showed statistically significant excess risks in children living near industries releasing carcinogens to humans (data not shown), for industrial distances of 2 km (OR=2.09; 95%CI=1.01-4.33), 2.5 km (OR=2.28; 95%CI=1.13-4.62), and 3 km (OR=2.25; 95%CI=1.12-4.52). The two sensitivity analyses also showed excess risks, although non-statistically significant. The most remarkable results of bone tumors in

children by reference to groups of other toxic chemical substances released by facilities are shown in Figure 2. The results showed high and statistically significant excess risks in children living close to industrial facilities releasing: 'Pesticides' at 2 k, 2.5, and 3km; 'Persistent organic pollutants' (POPs) at 2, 2.5, and 3 km; 'Polycyclic aromatic chemicals' (PACs) at 2 km; and, 'Non-halogenated phenolic chemicals' (non-HPCs) at 2 km.

3.5 Results of the analysis 4

The most remarkable ORs of bone tumors in children living near industries releasing specific substances are shown in Figure 3. Attention should be drawn to the significant excess risks found in the analysis and confirmed by the two sensitivity analyses, for the following pollutants and distances: 'Dioxins+furans' at 2 and 2.5 km; 'Polycyclic aromatic hydrocarbons' (PAHs) at 2 km; 'Benzene' at 3 km; '1-2-dichloroethane' at 2.5 and 3 km; and, 'Simazine' at 3 km.

3.6 Results of the analysis 5

Finally, the risk gradient analysis showed in Supplementary Data, Table S1 detected positive radial effects (rise in OR with increasing proximity to facilities of a specific sector) for 'Urban waste-water treatment plants' (OR=1.72, *p*-trend=0.029), 'Surface treatment using organic solvents' (OR=1.92, *p*-trend=0.034), 'Disposal or recycling of animal waste' (OR=2.11, *p*-trend=0.057), and 'Cement and lime' (OR=2.19, *p*-trend=0.065).

4. Discussion

4.1 Summary

To our knowledge, this is the first study that analyzes the risk of bone tumors in children in the vicinity of environmental pollution sources, as industrial installations and urban areas, according to different industrial groups, groups of carcinogens and other toxic pollutants, and specific industrial pollutants. Our results could suggest a possible association between residential proximity to certain industries –especially between 2 and 3 km– and urban sites and risk of bone tumors in children. However, the two sensitivity analyses –carried out with the aim of introducing robustness in our initial analyses– restricted the statistical significance to the following industrial groups and toxic substances: metal industry (surface treatment of metals and plastic, and production and processing of metals), waste management industries (urban and waste-water treatment plants, hazardous waste, and disposal or recycling of animal waste), cement and lime industries, and energy sector (combustion installations); and facilities releasing pesticides, POPs, PACs, and Non-HPCs.

In the case of industrial areas, the ORs decrease gradually when the industrial distances decrease for all analyses, with the loss of the statistical significance in the analysis with all individuals. This is probably due to the fact that the proportion of cases vs. controls decreases when the industrial distance decreases. However, in the case of urban areas, the ORs are statistically significant for all distances analyzed, in the analyses with all individual and the sensitivity analysis with only individuals of Catalonia and Madrid Region. This association is more robust, probably due to the fact that the proportion of cases vs. controls is more or less constant when the industrial distance decreases.

4.2 Results in relation to other studies

Insofar as environmental pollution exposures and bone tumors in children are concerned, there are few papers focused on pollution released by industries or urban areas. A Taiwanese study found a higher mortality of bone cancer in children aged 0-19 years in the petrochemical industrial districts than in the reference areas (Pan et al., 1994). In our study, the organic chemical industry showed statistically significant excess risks of bone cancer at 2.5 km (OR=3.07; 95%CI=1.23-7.62) and 3 km (OR=2.92; 95%CI=1.21-7.03) (data not shown).

In relation to urban pollution, two ecological analyses suggested a higher incidence of bone tumors in urban areas (Bovill et al., 1975; Larsson and Lorentzon, 1974), whereas another study showed upward trends in childhood bone cancer in males in urban Shanghai (China) (Bao et al., 2010), a finding that concurs with our results found in children living near urban sites. However, other authors showed no excess risks of malignant bone tumors in the urban counties of Texas (US) (Thompson et al., 2008). Traffic exhaust is a major cause of children's exposure to air toxics, including PAHs, metals, and particulate material (Belpomme et al., 2007; Garcia-Algar et al., 2015), and several studies have found associations between some childhood tumors and air pollutants (Filippini et al., 2015; Raaschou-Nielsen and Reynolds, 2006). In our study, we have found high and robust excess risks of bone tumors in children living in urban areas, especially in the two regions with the biggest number of big cities with high levels of traffic exposure (Madrid Region and Catalonia). It is possible that exposure to PAHs and metals released from motor vehicle exhaust relates to these high increased risks. Moreover, some authors have reported higher levels of DNA adducts in children living in urban areas compared to referents living in rural areas (Neri et al., 2006b).

With regard to proximity to other pollution sources, such as crop fields as a proxy of exposure to pesticides, a previous paper of our group found an association between proximity to

cultivated land and bone cancer in children (Gomez-Barroso et al., 2016), although another study of childhood cancer in Texas (US) did not confirm any association between risk of bone cancer in children and proximity of birth residence to agricultural use land (Carozza et al., 2009).

In relation to the industrial groups with statistically significant ORs of our study, the metal sector (surface treatment of metals and plastic, and production/processing of metals) releases known or suspected carcinogens (metals, dioxins, PAHs, and solvents), generate great amounts of toxic waste (gear and lubricating oils, mineral-based non-chlorinated engine, oil filters, solvents, and lead batteries), and their effluents are genotoxic: they induce mutations, cytogenetic damage, and DNA damage in the repair process (Houk, 1992; Katic et al., 2010). This group is the leading polluter of metals, PACs, and POPs in air and water, and the second-leading polluter of pesticides in water (see Table 1), substances which are known or suspected carcinogens. In this sense, a Swedish study about cancer incidence for children born in a smelting community found 13 childhood cancers vs. 6.7 cases expected in the neighborhood of the smelter (Wulff et al., 1996). On the other hand, some authors have found radioactive elements in the production processes and effluents of the metal industry (Bahari et al., 2007; Sofilic et al., 2006). Radiation is a mutagen, carcinogen, and an initiator as well as a promoter of cancer. Moreover, exposure to ionizing radiation is a recognized cause of bone cancer in the general population (Clapp et al., 2005), and the findings of an American study showed that bone cancer occurred more frequently among children of fathers in all facilities with moderate potential ionizing radiation exposure (Hicks et al., 1984). This fact could be related to the high excess risks found by us in the environs of this type of installations. In this case, exposure to radioactive materials from these industries, such as radium and strontium, can cause bone cancer because these minerals build up in bones (American Cancer Society, 2016; IARC, 2001; IARC, 2012).

Another important result of our study is the increased risk of bone cancer found in children living near urban waste-water treatment plants (OR=4.41 at 2 km), as well as a risk gradient (*p*-trend=0.0289). This industrial group was the leading polluter of pesticides in water, and the second-leading polluter of metals in air and water (see Table 1). Furthermore, high residual concentrations of radionuclides were identified in material derived from these installations (Kleinschmidt and Akber, 2008). In this sense, some studies have found that people living near these installations or exposed to soil treated with waste-water/sewage treatment plant sludge were potentially exposed to cancer risks (Eschenroeder et al., 1986; Yang et al., 2014).

With regard to hazardous waste, our results showed statistically significant increased risks at 2 km. In a previous ecological study about cancer mortality in the vicinity of this type of installations, we found excess risks for bone cancer in the general population near four specific installations (Garcia-Perez et al., 2013), three of them located in the present study (two incinerators in Catalonia, and one installation for the regeneration of spent baths in the Basque Country). These installations generate recognized and suspected carcinogen substances, such as arsenic, dioxins, benzene, chromium, PAHs, lead, cadmium, tetrachloroethylene, nickel, hexachlorobenzene, and naphthalene (European Commission, 2006), and their effluents represent a serious environmental problem, as they are a type of waste that contains fluorides, nitrates, heavy metals, and acids (Singhal et al., 2006; Vijay and Sihorwala, 2003). In this sense, some authors have explored childhood cancer incidence (White and Aldrich, 1999) and chromosomal anomalies in offspring (Brender et al., 2008) near hazardous waste sites, and did not find any association. However, a Chinese study found that childhood lead exposure affected both physical development and increased bone resorption of children of an electronic waste processing area (Yang et al., 2013). On the other hand, treatment of wastes gives rise to exposure to radioactive

materials among workers at these plants and populations in their environs (Donzella et al., 2007; Lubenau and Yusko, 1998; Parmaksiz et al., 2015; Vearrier et al., 2009).

The cement industry has been identified as one of the main sources of hazardous air pollutants' emissions, including, dioxins, metals, PAHs, benzene, particulate material, and polychlorinated biphenyls (European Commission, 2010; Schuhmacher et al., 2004; Sidhu et al., 2001). Some experiments in laboratory with animals exposed to dust cement showed that the chemical components of the cement dust particles inhaled by animals are accumulated in their bones (Meo, 2004; Reichrtova, 1986). Moreover, some authors have found radiation hazards in the cement industry (Aslam et al., 2012; El Bahi, 2004; El Taher et al., 2010), which could be related to the increased risk of bone cancer found in our study.

The energy sector (combustion installations) release carcinogens into the environment (metals, dioxins, PAHs, and benzene), and this industrial group was the second-leading polluter of PACs and POPs in air and water (see Table 1). In addition, emissions from coal-fired installations contain radioactive elements, principally thorium and uranium, as well as by-products deriving from the disintegration of these isotopes, such as radon, radium, bismuth, polonium, and lead (Gabbard, 1993; Samet and Cohen, 2006), a finding that could be related to the excess risk of bone cancer found by us in the proximity of these facilities.

With regard to specific pollutants, the studies existing in the literature focused on parental exposure to pesticides and Ewing sarcoma: whereas some papers have found increased risks of this tumor for children whose fathers had occupational exposure to fertilizers, pesticides, or herbicides (Holly et al., 1992; Valery et al., 2002; Vinson et al., 2011; Zahm and Ward, 1998), other studies did not find evidence of risk of Ewing tumor and parental exposure to pesticides (Belpomme et al., 2007; Flower et al., 2004; Moore et al., 2005; Pearce et al., 2006). In our study,

statistically significant excess risks for children close to industries releasing pesticides were found for all distances analyzed. In this case, exposure to the parents can lead to effects in the child in several potential ways: parental exposures prior to pregnancy could result in transmissible genetic effects that could cause childhood bone cancer; maternal exposures during pregnancy could result in *in utero* exposure to the developing infant; and maternal exposures prenatally or during the neonatal period could result in transmission of exposures in breast milk, affecting to the child's bones (Moya et al., 2004; Peters and Preston-Martin, 1984). In relation to other specific pollutants, some authors have provided molecular and genetic evidence of links between exposure to PAHs and increased fetal susceptibility. Moreover, prenatal exposure to PAHs affects epigenetic patterning by altering DNA methylation, and this has been shown to play a role in cancer (Perera, 2011; Perera et al., 1999). Insofar as exposure to metals are concerned, lead is a heavy metal that bioaccumulates in bone, more in children's bones doubling between infancy and the late ten years (Bearer, 1995). In our study, statistically significant excess risks were found for children close to industries releasing PAHs and lead at 2 km.

Lastly, children interact with the physical environment differently than adults, and are uniquely susceptible to environmental pollutants. Routes of absorption, distribution, metabolism, and target organ toxicities vary as children grow and develop (Falck et al., 2015; Neri et al., 2006a).

4.3 Limitations and strengths

Similarly to other case-control studies, our study has some limitations: the small sample size; the low statistical power in the case of the two sensitivity analyses carried out; the use of distances to the pollution sources, according to an isotropic model, as a proxy of exposure,

something that could introduce a problem of misclassification, since real exposure is dependent on prevailing winds or geographic landforms; and the non-inclusion of information about parental occupational exposures for their unavailability at an individual level. Moreover, we could not include possible confounders that might be associated with the distance (sociodemographic variables or life-style-related factors), for their unavailability at an individual level. However, 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).

On the other hand, we had the home address of the mother at birth for the controls, and the home address of the cases at the time of diagnosis. This difference could introduce some bias in the analyses. To control this bias, a sensitivity analysis including only cases with the same address at birth and at the moment of diagnosis was carried out. This reduces partially the problem of misclassification in the exposure due to the residential mobility of children, although it is possible that some controls had migrated after birth.

Although in Spain, there is a low rate of local migration between provinces (only around 1% of the children change their residence to another province (National Statistics Institute, 2016)), an important limitation is the possible residential mobility of individuals within the same province, something that could affect the accuracy of the exposure assessment. In this sense, we have no data on migration within each province. This fact would amount to a non-differential bias which would limit the capacity to find positive findings.

Another aspect is that the identification of the critical time window of exposure in children is problematic. The evidence for exposures occurring during the preconceptional period that have an association with bone tumors in children is equivocal. Moreover, the list of

environmental exposures that occur during the perinatal/postnatal period with potential to increase the risk of childhood cancer is lengthening, but the evidence available to date is inconsistent or inconclusive (Anderson et al., 2000).

Strengths of the study include the completeness of the several methodological approaches used in the statistical analyses, and the robustness provided for the two sensitivity analyses carried out. The sensitivity analysis with only individuals of Catalonia and Madrid Region was justified because almost all cases of the reference area are located in these two autonomous regions (11 of 12, see Table 3). Another advantage is the large control group (6 controls per case), which 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 zones). The matching strategy used accounts for the temporal and regional variation in the child population. Lastly, the stratification of the risk by industrial group and group of carcinogenic and toxic pollutants has provided a description more exhaustive of childhood cancer risk.

Lastly, the fact that potential risk factors in relation to risk of bone tumors in children have been explored with inconsistent findings (e.g.: dietary exposure) (Eyre et al., 2009) could reduce the impact of the aforementioned limitations.

4.4 Implications and future directions

The industrial registers, such as E-PRTR, afford a very useful tool for the monitoring and surveillance of possible effects of industrial pollution on the health of the children (Wine et al., 2014), such as bone tumors. In this sense, the main challenges and action points that the scientific community should take into account are: to assess robustness of current etiological hypotheses

regarding "suspected" environmental carcinogens and toxic substances; to improve the measurement of children population exposure to environmental pollution; to monitor exposure to proven environmental carcinogens; to carry out epidemiological surveillance of clusters of childhood cancers; to investigate interaction gen-environment; and to establish new biomarkers of exposure, effect, and susceptibility that can be infused into future studies of environmental factors in the childhood cancer etiology (Linet et al., 2003; Massey-Stokes and Lanning, 2002; Ramis et al., 2015; Ross and Spector, 2006; Terracini, 2002).

5. Conclusions

Our results could suggest a possible association between residential proximity to certain industrial and urban sites, specifically, plants involved in the metal industry, waste management, cement and lime, energy sector, and industries releasing pesticides, POPs, PACs, and Non-HPCs, and risk of bone tumors in children.

These findings support the need for more detailed exposure assessment and health risk analysis of certain substances released by these types of industries.

Acknowledgments:

This study was funded by Spain's Health Research Fund (*Fondo de Investigación Sanitaria* - FIS 12/01416) and Scientific Foundation of the Spanish Association Against Cancer (*Fundación Científica de la Asociación Española Contra el Cáncer (AECC)* – EVP-1178/14).

References

American Cancer Society. Bone cancer; 2016. Available: http://www.cancer.org/cancer/bonecancer/detailedguide/bone-cancer-risk-factors [accessed 3 November 2016].

Anderson LM, Diwan BA, Fear NT, Roman E. Critical windows of exposure for children's health: cancer in human epidemiological studies and neoplasms in experimental animal models. Environ Health Perspect 2000;108 Suppl 3:573-594.

Aslam M, Gul R, Ara T, Hussain M. Assessment of radiological hazards of naturally occurring radioactive materials in cement industry. Radiat Prot Dosimetry 2012;151:483-488.

Bahari I, Mohsen N, Abdullah P. Radioactivity and radiological risk associated with effluent sediment containing technologically enhanced naturally occurring radioactive materials in amang (tin tailings) processing industry. J Environ Radioact 2007;95:161-170.

Bao PP, Zheng Y, Gu K, Wang CF, Wu CX, Jin F, et al. Trends in childhood cancer incidence and mortality in urban Shanghai, 1973-2005. Pediatr Blood Cancer 2010;54:1009-1013.

Bearer CF. How are children different from adults? Environ Health Perspect 1995;103 Suppl 6:7-12.

Belpomme D, Irigaray P, Hardell L, Clapp R, Montagnier L, Epstein S, et al. The multitude and diversity of environmental carcinogens. Environ Res 2007;105:414-429.

Bovill EG, Silva JF, Subramanian N. An epidemiologic study of osteogenic sarcoma in Malaysia. Incidence in urban as compared with rural environments and in each of three separate racial groups, 1969-1972. Clin Orthop Relat Res 1975;119-127.

Brender JD, Zhan FB, Langlois PH, Suarez L, Scheuerle A. Residential proximity to waste sites and industrial facilities and chromosomal anomalies in offspring. Int J Hyg Environ Health 2008;211:50-58.

Carozza SE, Li B, Wang Q, Horel S, Cooper S. Agricultural pesticides and risk of childhood cancers. Int J Hyg Environ Health 2009;212:186-195.

Clapp RW, Howe GK, Jacobs MM. Environmental and Occupational Causes of Cancer. A Review of Recent Scientific Literature. 2005;Lowell Center for Sustainable Production;

Delattre O, Zucman J, Melot T, Garau XS, Zucker JM, Lenoir GM, et al. The Ewing family of tumors--a subgroup of small-round-cell tumors defined by specific chimeric transcripts. N Engl J Med 1994;331:294-299.

Donzella A, Formisano P, Giroletti E, Zenoni A. Risk assessment for chemical pickling of metals contaminated by radioactive materials. Radiat Prot Dosimetry 2007;123:74-82.

El Bahi SM. Assessment of radioactivity and radon exhalation rate in Egyptian cement. Health Phys 2004;86:517-522.

El Taher A, Makhluf S, Nossair A, Abdel Halim AS. Assessment of natural radioactivity levels and radiation hazards due to cement industry. Appl Radiat Isot 2010;68:169-174.

Eschenroeder A, Jaeger RJ, Ospital JJ, Doyle CP. Health risk analysis of human exposures to soil amended with sewage sludge contaminated with polychlorinated dibenzodioxins and dibenzofurans. Vet Hum Toxicol 1986;28:435-442.

European Commission. Integrated Pollution Prevention and Control (IPPC). Reference Document on Best Available Techniques for the Waste Incineration; 2006. Available: http://www.prtr-es.es/data/images/BREF%20Incineraci%C3%B3n%20de%20Residuos-43EA4732C41F2B44.pdf [accessed 3 November 2016].

European Commission. Reference Document on Best Available Techniques in the Cement, Lime and Magnesium Oxide Maufacturing industries; 2010. Available: http://www.prtr-es.es/Data/images//BREF-cemento-revisado-aprobado-por-Comisi%C3%B3n-mayo-2010-.pdf [accessed 3 November 2016].

Eyre R, Feltbower RG, Mubwandarikwa E, Eden TO, McNally RJ. Epidemiology of bone tumours in children and young adults. Pediatr Blood Cancer 2009;53:941-952.

Falck AJ, Mooney S, Kapoor SS, White KM, Bearer C, El Metwally D. Developmental Exposure to Environmental Toxicants. Pediatr Clin North Am 2015;62:1173-1197.

Filippini T, Heck JE, Malagoli C, Giovane CD, Vinceti M. A review and meta-analysis of outdoor air pollution and risk of childhood leukemia. J Environ Sci Health C Environ Carcinog Ecotoxicol Rev 2015;33:33-66.

Flower KB, Hoppin JA, Lynch CF, Blair A, Knott C, Shore DL, et al. Cancer risk and parental pesticide application in children of Agricultural Health Study participants. Environ Health Perspect 2004;112:631-635.

Gabbard A. Coal Combustion: Nuclear Resource or Danger. ORNL Review 1993;26[3]

Garcia-Algar O, Canchucaja L, d'Orazzio V, Manich A, Joya X, Vall O. Different exposure of infants and adults to ultrafine particles in the urban area of Barcelona. Environ Monit Assess 2015;187:4196.

Garcia-Perez J, Fernandez-Navarro P, Castello A, Lopez-Cima MF, Ramis R, Boldo E, et al. Cancer mortality in towns in the vicinity of incinerators and installations for the recovery or disposal of hazardous waste. Environ Int 2013;51:31-44.

Garcia-Perez J, Morales-Piga A, Gomez J, Gomez-Barroso D, Tamayo-Uria I, Pardo RE, et al. Association between residential proximity to environmental pollution sources and childhood renal tumors. Environ Res 2016a;147:405-414.

Garcia-Perez J, Morales-Piga A, Gomez-Barroso D, Tamayo-Uria I, Pardo RE, Fernandez-Navarro P, et al. Risk of neuroblastoma and residential proximity to industrial and urban sites: A case-control study. Environ Int 2016b;92-93:269-275.

Gomez-Barroso D, Garcia-Perez J, Lopez-Abente G, Tamayo-Uria I, Morales-Piga A, Pardo RE, et al. Agricultural crop exposure and risk of childhood cancer: new findings from a case-control study in Spain. Int J Health Geogr 2016;15:18.

Hicks N, Zack M, Caldwell GG, Fernbach DJ, Falletta JM. Childhood cancer and occupational radiation exposure in parents. Cancer 1984;53:1637-1643.

Holly EA, Aston DA, Ahn DK, Kristiansen JJ. Ewing's bone sarcoma, paternal occupational exposure, and other factors. Am J Epidemiol 1992;135:122-129.

Houk VS. The genotoxicity of industrial wastes and effluents. Mutat Res 1992;277:91-138.

IARC. Monographs on the Evaluation of Carcinogenic Risks to Humans. Ionizong radiation, part 2: some internally deposited radionuclides. Volume 78; 2001. Available: http://monographs.iarc.fr/ENG/Monographs/vol78/mono78.pdf [accessed 3 November 2016].

IARC. Monographs on the Evaluation of Carcinogenic Risks to Humans. Radiation. Volume 100F; 2012. Available: http://monographs.iarc.fr/ENG/Monographs/vol100D/mono100D.pdf [accessed 3 November 2016].

Katic J, Fucic A, Gamulin M. Prenatal, early life, and childhood exposure to genotoxicants in the living environment. Arh Hig Rada Toksikol 2010;61:455-464.

Kleinschmidt R, Akber R. Naturally occurring radionuclides in materials derived from urban water treatment plants in southeast Queensland, Australia. J Environ Radioact 2008;99:607-620.

Larranaga N, Sanchez MJ, Ardanaz E, Felipe S, Marcos-Gragera R, Ramos M, et al. Incidence Patterns and Trends of non-Central Nervous System Solid Tumours in Children and Adolescents. A Collaborative Study of the Spanish Population Based Cancer Registries. J Cancer 2016;7:335-343.

Larsson SE, Lorentzon R. The incidence of malignant primary bone tumours in relation to age, sex and site. A study of osteogenic sarcoma, chondrosarcoma and Ewing's sarcoma diagnosed in Sweden from 1958 to 1968. J Bone Joint Surg Br 1974;56B:534-540.

Linet MS, Wacholder S, Zahm SH. Interpreting epidemiologic research: lessons from studies of childhood cancer. Pediatrics 2003;112:218-232.

Lubenau JO, Yusko JG. Radioactive materials in recycled metals--an update. Health Phys 1998;74:293-299.

Massey-Stokes M, Lanning B. Childhood cancer and environmental toxins: the debate continues. Fam Community Health 2002;24:27-38.

587 Meo SA. Health hazards of cement dust. Saudi Med J 2004;25:1153-1159.

588 Mezei G, Borugian MJ, Spinelli JJ, Wilkins R, Abanto Z, McBride ML. Socioeconomic status
589 and childhood solid tumor and lymphoma incidence in Canada. Am J Epidemiol 2006;164:170-
590 175.

591 Moore LE, Gold L, Stewart PA, Gridley G, Prince JR, Zahm SH. Parental occupational
592 exposures and Ewing's sarcoma. Int J Cancer 2005;114:472-478.

593 Moya J, Bearer CF, Etzel RA. Children's behavior and physiology and how it affects exposure to
594 environmental contaminants. Pediatrics 2004;113:996-1006.

595 National Statistics Institute. Deaths according to Cause of Death 2012 ; 2016. Available:
596 http://www.ine.es/jaxiPx/tabla.do?path=/t15/p417/a2012/l0/&file=01001.px&type=pcaxis&L=1
597 [accessed 3 November 2016].

598 Neri M, Bonassi S, Knudsen LE, Sram RJ, Holland N, Ugolini D, et al. Children's exposure to
599 environmental pollutants and biomarkers of genetic damage. I. Overview and critical issues.
600 Mutat Res 2006a;612:1-13.

601 Neri M, Ugolini D, Bonassi S, Fucic A, Holland N, Knudsen LE, et al. Children's exposure to
602 environmental pollutants and biomarkers of genetic damage. II. Results of a comprehensive
603 literature search and meta-analysis. Mutat Res 2006b;612:14-39.

604 Open Source Geospatial Foundation. QGIS; 2016. Available:
605 http://www.qgis.org/en/site/index.html [accessed 3 November 2016].

606 Ottaviani G, Jaffe N. The etiology of osteosarcoma. Cancer Treat Res 2009;152:15-32.

607 Pan BJ, Hong YJ, Chang GC, Wang MT, Cinkotai FF, Ko YC. Excess cancer mortality among
608 children and adolescents in residential districts polluted by petrochemical manufacturing plants in
609 Taiwan. J Toxicol Environ Health 1994;43:117-129.

610 Parmaksiz A, Agus Y, Bulgurlu F, Bulur E, Oncu T, Ozkok YO. Measurement of enhanced
611 radium isotopes in oil production wastes in Turkey. J Environ Radioact 2015;141:82-89.

612 Pearce MS, Hammal DM, Dorak MT, McNally RJ, Parker L. Paternal occupational exposure to
613 pesticides or herbicides as risk factors for cancer in children and young adults: a case-control
614 study from the North of England. Arch Environ Occup Health 2006;61:138-144.

615 Perera F. Molecular Epidemiology, prenatal exposure and prevention of cancer. Environ Health
616 2011;10 Suppl 1:S5.

617 Perera FP, Jedrychowski W, Rauh V, Whyatt RM. Molecular epidemiologic research on the
618 effects of environmental pollutants on the fetus. Environ Health Perspect 1999;107 Suppl 3:451-
619 460.

620 Peters JM, Preston-Martin S. Childhood tumors and parental occupational exposures. Teratog
621 Carcinog Mutagen 1984;4:137-148.

622 Raaschou-Nielsen O, Reynolds P. Air pollution and childhood cancer: a review of the
623 epidemiological literature. Int J Cancer 2006;118:2920-2929.

624 Ramis R, Gomez-Barroso D, Tamayo I, Garcia-Perez J, Morales A, Pardo RE, et al. Spatial
625 analysis of childhood cancer: a case/control study. PLoS One 2015;10:e0127273.

626 Reichrtova E. Biomonitoring of industrial dusts on animals. I. Bioaccumulation of dust
627 components. Acta Biol Hung 1986;37:7-12.

628 Ross JA, Spector LG. Cancers in children. In: Cancer epidemiology and prevention. Third
629 Edition (Schottenfeld D, Fraumeni Jr JF, eds). New York:Oxford University Press, 2006.1251-
630 1268.

631 Rothman KJ, Greenland S, Lash TL. Case-control studies. In: Modern Epidemiology, third
632 edition (Rothman KJ, Greenland S, Lash TL, eds). Philadelphia, PA:Lippincott, Williams &
633 Wilkins, 2008.

634 Samet JM, Cohen AJ. Air Pollution. In: Cancer Epidemiology and Prevention. Third Edition
635 (Schottenfeld D, Fraumeni Jr JF, eds). New York:Oxford University Press, 2006.355-381.

636 Schuhmacher M, Domingo JL, Garreta J. Pollutants emitted by a cement plant: health risks for
637 the population living in the neighborhood. Environ Res 2004;95:198-206.

638 Sidhu S, Kasti N, Edwards P, Dellinger B. Hazardous air pollutants formation from reactions of
639 raw meal organics in cement kilns. Chemosphere 2001;42:499-506.

640 Singhal A, Tewari VK, Prakash S. A study on sludge minimization during the treatment of
641 pickling effluent. J Environ Sci Eng 2006;48:109-112.

642 Sofilic T, Marjanovic T, Rastovcan-Mioc A. [Radioactivity monitoring of steel processing in
643 Croatian steel mills and foundries]. Arh Hig Rada Toksikol 2006;57:45-54.

644 Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P. International Classification of Childhood
645 Cancer, third edition. Cancer 2005;103:1457-1467.

646 Terracini B. Cancer. In: Children's health and environment: a review of evidence (Tamburlini G,
647 von Ehrestein OS, Bertollini R, eds). Copenhagen:European Environment Agency, 2002.69-98.

648 Thompson JA, Carozza SE, Zhu L. Geographic risk modeling of childhood cancer relative to
649 county-level crops, hazardous air pollutants and population density characteristics in Texas.
650 Environ Health 2008;7:45.

651 Valery PC, Holly EA, Sleigh AC, Williams G, Kreiger N, Bain C. Hernias and Ewing's sarcoma
652 family of tumours: a pooled analysis and meta-analysis. Lancet Oncol 2005;6:485-490.

Valery PC, McWhirter W, Sleigh A, Williams G, Bain C. Farm exposures, parental occupation, and risk of Ewing's sarcoma in Australia: a national case-control study. Cancer Causes Control 2002;13:263-270.

Vearrier D, Curtis JA, Greenberg MI. Technologically enhanced naturally occurring radioactive materials. Clin Toxicol (Phila) 2009;47:393-406.

Vijay R, Sihorwala TA. Identification and leaching characteristics of sludge generated from metal pickling and electroplating industries by Toxicity Characteristics Leaching Procedure (TCLP). Environ Monit Assess 2003;84:193-202.

Vinson F, Merhi M, Baldi I, Raynal H, Gamet-Payrastre L. Exposure to pesticides and risk of childhood cancer: a meta-analysis of recent epidemiological studies. Occup Environ Med 2011;68:694-702.

Ward E, DeSantis C, Robbins A, Kohler B, Jemal A. Childhood and adolescent cancer statistics, 2014. CA Cancer J Clin 2014;64:83-103.

White E, Aldrich TE. Geographic studies of pediatric cancer near hazardous waste sites. Arch Environ Health 1999;54:390-397.

Wine O, Hackett C, Campbell S, Cabrera-Rivera O, Buka I, Zaiane O, et al. Using pollutant release and transfer register data in human health research: a scoping review. Environmental Reviews 2014;22:51-65.

Wulff M, Hogberg U, Sandstrom A. Cancer incidence for children born in a smelting community. Acta Oncol 1996;35:179-183.

Yang H, Huo X, Yekeen TA, Zheng Q, Zheng M, Xu X. Effects of lead and cadmium exposure from electronic waste on child physical growth. Environ Sci Pollut Res Int 2013;20:4441-4447.

Yang J, Wang K, Zhao Q, Huang L, Yuan CS, Chen WH, et al. Underestimated public health risks caused by overestimated VOC removal in wastewater treatment processes. Environ Sci Process Impacts 2014;16:271-279.

Zahm SH, Ward MH. Pesticides and childhood cancer. Environ Health Perspect 1998;106 Suppl 3:893-908.

Figure legends

Figure 1: Odds ratios of bone tumors in children with statistically significant results and a number of cases ≥5 for the analysis of proximity to industries by category of industrial group. Red line: analysis with all individuals. Blue line: sensitivity analysis with only individuals of Catalonia and Madrid Region. Green line: Sensitivity analysis with only cases with addresses on the Birth Registry matched to RETI-SEHOP. Y-axis is plotted in logarithmic scale.

Figure 2: Odds ratios of bone tumors in children with statistically significant results and a number of cases ≥5 for the analysis of proximity to industries by groups of toxic substances. Red line: analysis with all individuals. Blue line: sensitivity analysis with only individuals of Catalonia and Madrid Region. Green line: Sensitivity analysis with only cases with addresses on the Birth Registry matched to RETI-SEHOP. Y-axis is plotted in logarithmic scale.

Figure 3: Odds ratios of bone tumors in children with statistically significant results and a number of cases ≥5 for the analysis of proximity to industries releasing specific pollutants. Red line: analysis with all individuals. Blue line: sensitivity analysis with only individuals of Catalonia and Madrid Region. Green line: Sensitivity analysis with only cases with addresses on the Birth Registry matched to RETI-SEHOP. Y-axis is plotted in logarithmic scale.

Table 1: Industrial groups and amounts (in kg) released by facilities in 2009, by groups of carcinogenic substances (IARC classification) and other groups of toxic substances.

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

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

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

Table 2: Characteristics of cases of bone tumors in children and controls.

	n (%)	
Characteristic	Cases (n=114)	Controls (n=684)
Sex		
Male	58 (50.9)	348 (50.9)
Female	56 (49.1)	336 (49.1)
Year of birth, mean (SD)	1999.5 (2.8)	1999.5 (2.8)
Autonomous region		
Catalonia	55 (48.3)	330 (48.3)
Madrid Region	34 (29.8)	204 (29.8)
Basque Country	8 (7.0)	48 (7.0)
Aragon	13 (11.4)	78 (11.4)
Navarre	4 (3.5)	24 (3.5)
Age at diagnosis (years), mean (SD)	8.5 (3.5)	
median (IQR)	9.0 (5.0)	
Unemployment, mean (SD)	11.1 (3.8)	10.9 (3.7)
Illiteracy, mean (SD)	9.7 (6.3)	9.7 (6.8)
Socioeconomic status, mean (SD)	1.1 (0.1)	1.1 (0.1)
Global crop index		
Reference: 0%	88 (77.2)	569 (83.2)
1st quartile (Q1): (0-2.87]	4 (3.5)	31 (4.5)
2nd quartile (Q2): (2.87-9.87]	4 (3.5)	28 (4.1)
3rd quartile (Q3): (9.87-22.28]	7 (6.1)	27 (4.0)
4th quartile (Q2): (22.28-100]	11 (9.7)	29 (4.2)
Histologic type		
Osteosarcomas	41 (36.0)	
Ewing tumor and related sarcomas of bone	72 (63.1)	
Other specified malignant bone tumors	1 (0.9)	

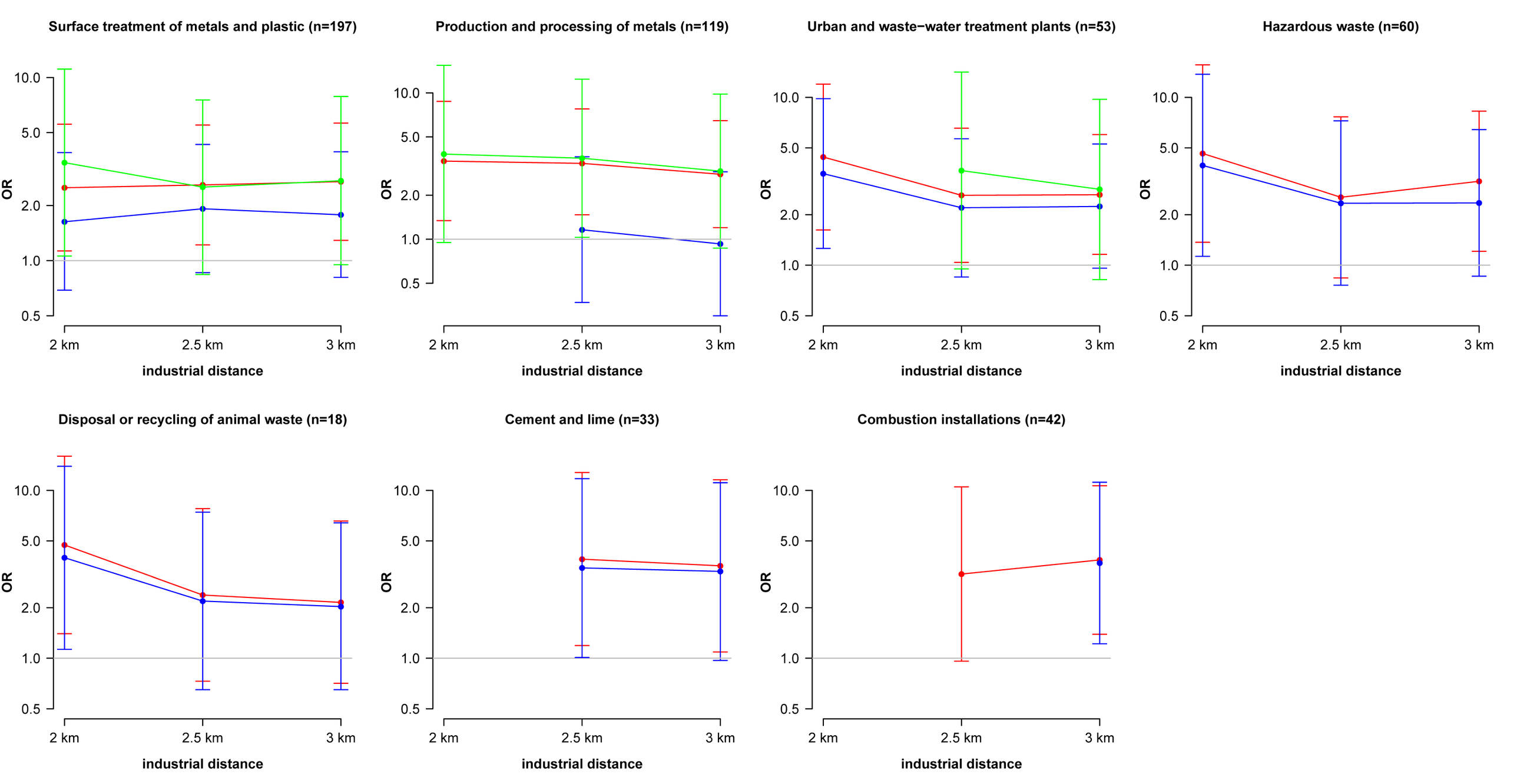
Table 3: Odds ratios of bone tumors in children by industrial distance and exposure category. Statistically significant results are in bold.

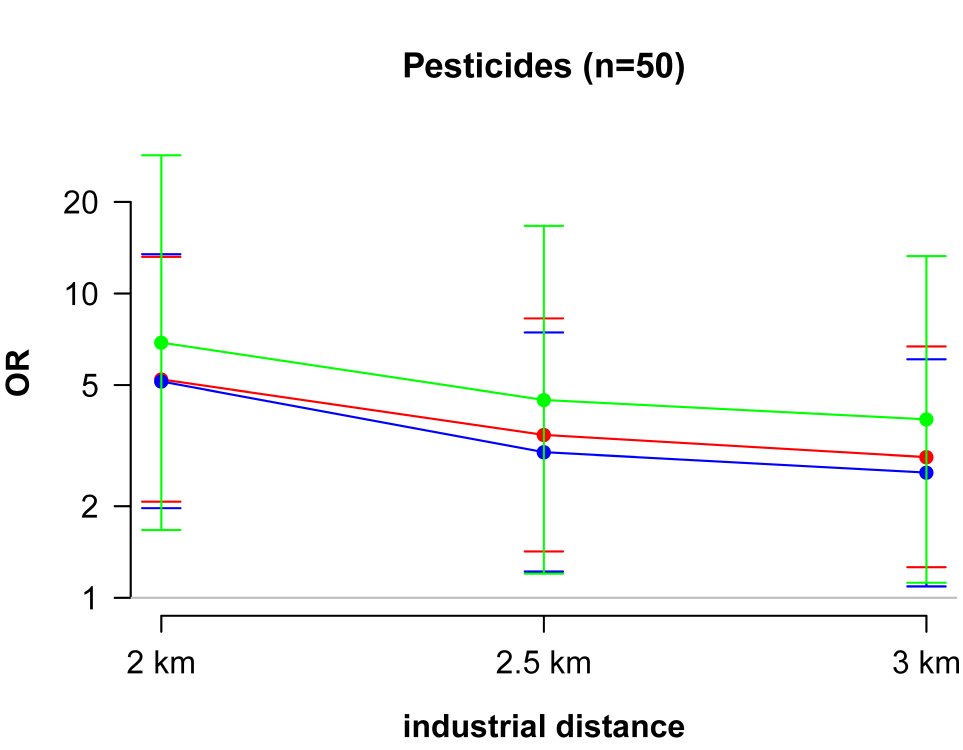
		Analysis with all individuals (114 cases / 684 controls)			Sensitivity analysis with only individuals of Catalonia and Madrid Region (89 cases / 534 controls)			Sensitivity analysis with only cases with addresses on the Birth Registry matched to RETI-SEHOP (48 cases / 288 controls)		
Industrial distance[a]	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]
3 Km										
	Reference	133	12	-	102	11	-	61	6	-
	Industrial area - 3 km (only)	400	67	**2.33 (1.17-4.63)**	292	47	1.61 (0.78-3.32)	161	28	1.96 (0.71-5.39)
	Urban area (only)	70	17	**4.43 (1.80-10.92)**	70	16	**3.24 (1.29-8.10)**	27	5	3.06 (0.73-12.91)
	Both[c]	81	18	3.66 (1.53-8.75)	70	15	2.50 (0.99-6.28)	39	9	3.17 (0.73-12.91)
2.5 Km										
	Reference	133	12	-	102	11	-	61	6	-
	Industrial area - 2.5 km (only)	368	58	**2.19 (1.10-4.39)**	271	40	1.47 (0.70-3.06)	150	26	1.93 (0.70-5.32)
	Urban area (only)	92	21	**4.08 (1.72-9.64)**	87	19	**2.99 (1.24-7.25)**	43	7	2.53 (0.67-9.50)
	Both[c]	59	14	**3.89 (1.55-9.76)**	53	12	2.55 (0.97-6.73)	23	7	**4.10 (1.07-15.68)**
2 Km										
	Reference	133	12	-	102	11	-	61	6	-
	Industrial area - 2 km (only)	310	44	1.97 (0.97-4.02)	235	31	1.31 (0.61-2.80)	126	20	1.77 (0.63-5.00)
	Urban area (only)	105	24	**4.02 (1.73-9.34)**	99	22	**2.90 (1.22-6.86)**	50	7	2.11 (0.57-7.84)
	Both[c]	46	11	**3.90 (1.48-10.29)**	41	9	2.39 (0.85-6.72)	16	7	**5.89 (1.51-22.98)**
1.5 Km										
	Reference	133	12	-	102	11	-	61	6	-
	Industrial area - 1.5 km (only)	231	31	1.87 (0.90-3.92)	171	21	1.22 (0.55-2.73)	96	15	1.73 (0.59-5.04)
	Urban area (only)	117	29	**4.42 (1.94-10.09)**	110	26	**3.12 (1.34-7.28)**	52	10	3.00 (0.86-10.49)
	Both[c]	34	6	2.82 (0.91-8.72)	30	5	1.74 (0.52-5.81)	14	4	3.75 (0.81-17.44)
1 Km										
	Reference	133	12	-	102	11	-	61	6	-
	Industrial area - 1 km (only)	119	14	1.62 (0.70-3.75)	88	8	0.83 (0.31-2.24)	52	6	1.26 (0.36-4.41)
	Urban area (only)	136	31	**4.01 (1.77-9.06)**	127	27	**2.77 (1.19-6.44)**	61	12	3.06 (0.90-10.45)
	Both[c]	15	4	**4.39 (1.19-16.23)**	13	4	3.56 (0.94-13.56)	5	2	5.54 (0.81-38.00)

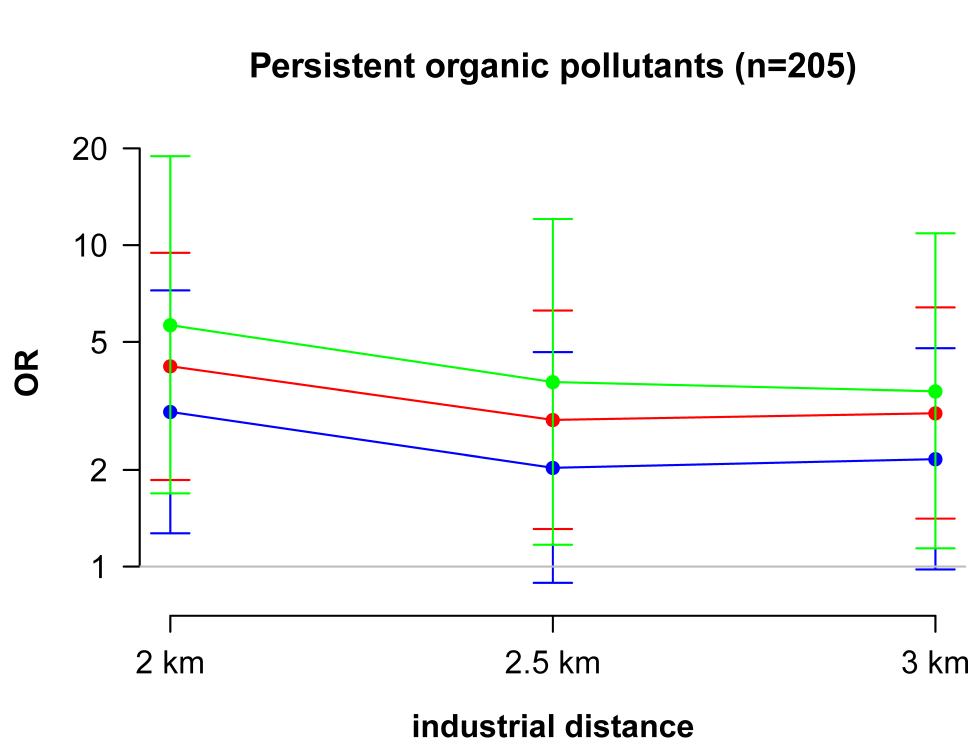
[a]Industrial distance referred to the industrial area (only) in the exposure category.

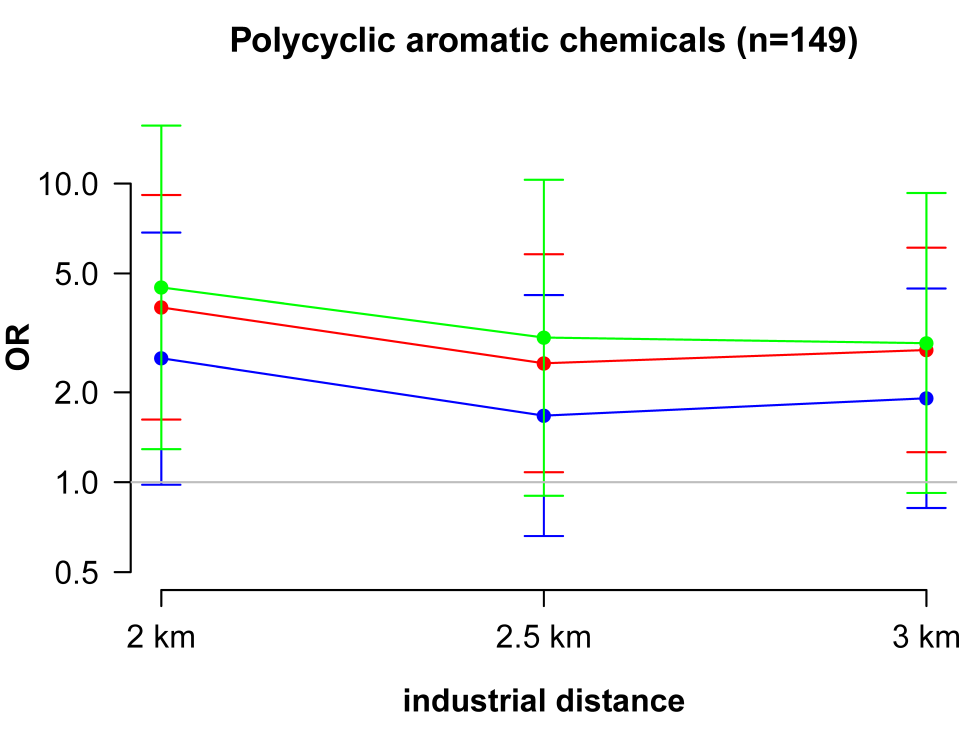
[b]ORs were estimated from various mixed multiple logistic regression models (an independent model for each of the categories of industrial distance), that included year of birth, sex, autonomous region of residence (as a random effect), percentage of illiteracy, percentage of unemployed, and socioeconomic status.

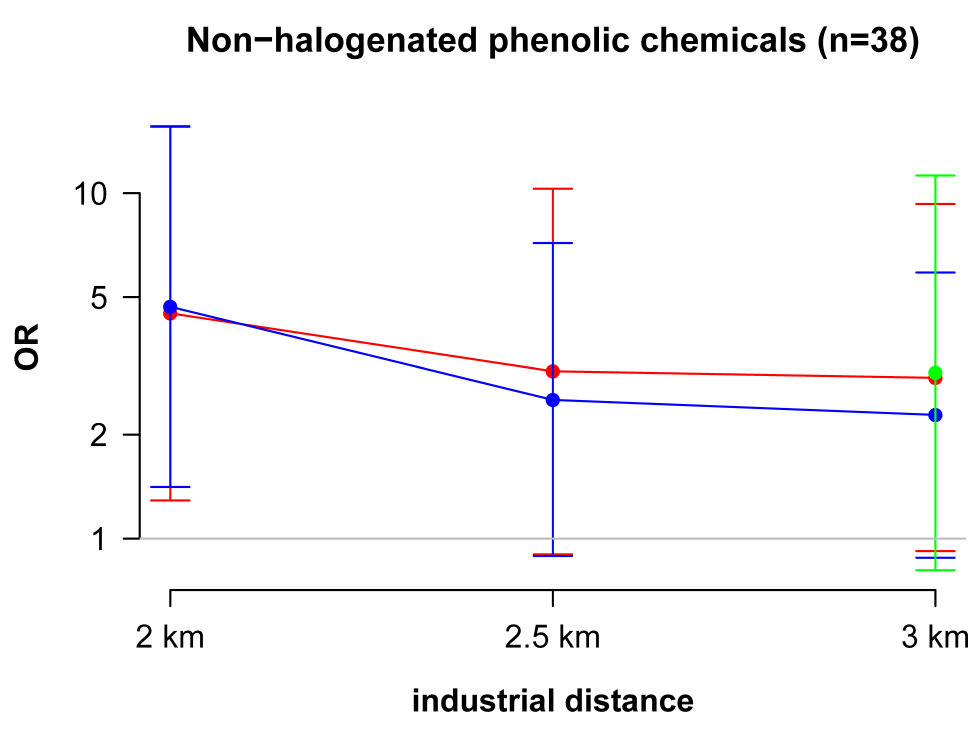
[c]Intersection area between industrial area defined by the corresponding industrial distance and urban area (only).

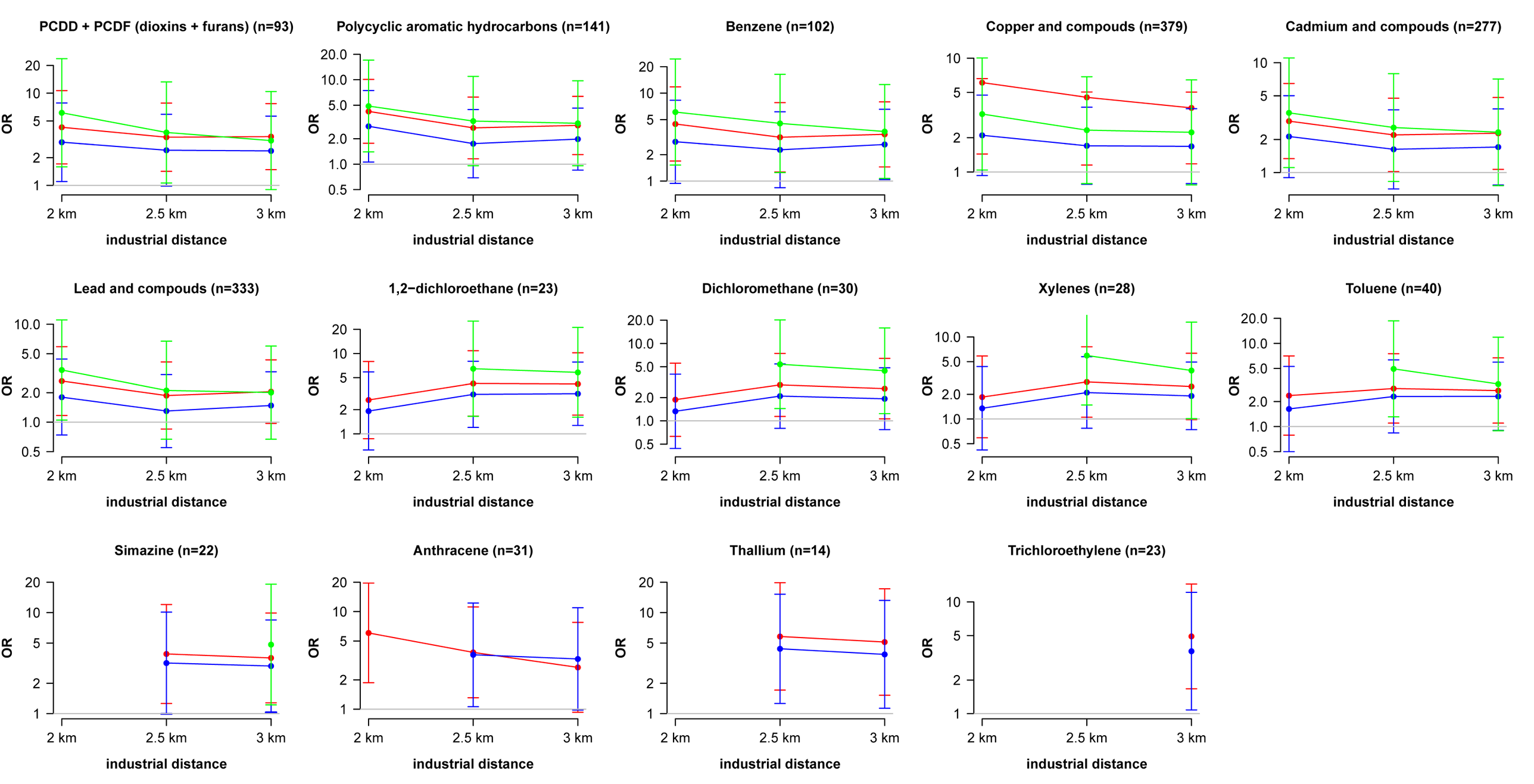

Surface treatment of metals and plastic (n=197)
Production and processing of metals (n=119)
Urban and waste−water treatment plants (n=53)
Hazardous waste (n=60)
Disposal or recycling of animal waste (n=18)
Cement and lime (n=33)
Combustion installations (n=42)
OR
10.0
5.0
2.0
1.0
0.5
2 km
2.5 km
3 km
industrial distance


Pesticides (n=50)
OR
20
10
5
2
1
2 km
2.5 km
3 km
industrial distance


Persistent organic pollutants (n=205)
OR
20
10
5
2
1
2 km
2.5 km
3 km
industrial distance


Polycyclic aromatic chemicals (n=149)
OR
10.0
5.0
2.0
1.0
0.5
2 km
2.5 km
3 km
industrial distance


Non−halogenated phenolic chemicals (n=38)
OR
10
5
2
1
2 km
2.5 km
3 km
industrial distance


PCDD + PCDF (dioxins + furans) (n=93)
Polycyclic aromatic hydrocarbons (n=141)
Benzene (n=102)
Copper and compouds (n=379)
Cadmium and compounds (n=277)
Lead and compouds (n=333)
1,2−dichloroethane (n=23)
Dichloromethane (n=30)
Xylenes (n=28)
Toluene (n=40)
Simazine (n=22)
Anthracene (n=31)
Thallium (n=14)
Trichloroethylene (n=23)
OR
2 km
2.5 km
3 km
industrial distance