HHS Public Access

Author manuscript

Environ Res. Author manuscript; available in PMC 2017 November 14.

Published in final edited form as:

Environ Res. 2017 July ; 156: 63–73. doi:10.1016/j.envres.2017.03.009.

Childhood cancer in small geographical areas and proximity to air-polluting industries

Juan A. Ortega-García[a,*], **Fernando A. López-Hernández**[b], **Alberto Cárceles-Álvarez**[a], **José L. Fuster-Soler**[c], **Diana I. Sotomayor**[a], and **Rebeca Ramis**[d,e]

[a]Pediatric Environmental Health Speciality Unit, Department of Paediatrics, Laboratory of Environment and Human Health (A5), Institute of Biomedical Research, IMIB-Arrixaca, Clinical University Hospital Virgen de la Arrixaca, University of Murcia, Murcia, Spain

[b]Departamento de Métodos Cuantitativos e Informáticos, Universidad Politécnica de Cartagena, Spain

[c]Oncology & Hematology Section, Pediatrics Department, Clinical University Hospital Virgen de la Arrixaca, Murcia, Spain

[d]Environmental Epidemiology and Cancer Unit, National Centre for Epidemiology, Instituto de Salud Carlos III - ISCIII, Madrid, Spain

[e]Consortium for Biomedical Research in Epidemiology & Public Health (CIBER en Epidemiología y Salud Pública-CIBERESP), Madrid, Spain

Abstract

Aim—Pediatric cancer has been associated with exposure to certain environmental carcinogens. The purpose of this work is to analyse the relationship between environmental pollution and pediatric cancer risk.

Method—We analysed all incidences of pediatric cancer (< 15) diagnosed in a Spanish region during the period 1998–2015. The place of residence of each patient and the exact geographical coordinates of main industrial facilities was codified in order to analyse the spatial distribution of cases of cancer in relation to industrial areas. Focal tests and focused Scan methodology were used for the identification of high-incidence-rate spatial clusters around the main industrial pollution foci.

Results—The crude rate for the period was 148.0 cases per 1,000,0000 children. The incidence of pediatric cancer increased significantly along the period of study. With respect to spatial distribution, results showed significant high incidence around some industrial pollution foci group and the Scan methodology identify spatial clustering. We observe a global major incidence of non Hodgkin lymphomas (NHL) considering all foci, and high incidence of Sympathetic Nervous System Tumour (SNST) around Energy and Electric and organic and inorganic chemical industries foci group. In the analysis foci to foci, the focused Scan test identifies several significant spatial

[*]Correspondence to: Pediatric Environmental Health Speciality Unit, Department of Paediatrics, Laboratory of Environment and Human Health (A5), Institute of Biomedical Research, IMIB Arrixaca Hospital Clinic University Virgin of Arrixaca, University of Murcia, Ctra. Madrid-Cartagena, s/n, 30120 El Palmar, Murcia, Spain. ortega@pehsu.org (J.A. Ortega-García).

clusters. Particularly, three significant clusters were identified: the first of SNST was around energy-generating chemical industries (2 cases versus the expected 0.26), another of NHL was around residue-valorisation plants (5 cases versus the expected 0.91) and finally one cluster of Hodgkin lymphoma around building materials (3 cases versus the expected 2.2)

Conclusion—Results suggest a possible association between proximity to certain industries and pediatric cancer risk. More evidences are necessary before establishing the relationship between industrial pollution and pediatric cancer incidence.

Keywords

Childhood cancer; Spatial analysis; Industrial pollution; Residential proximity; Urban pollution

1. Introduction

Pediatric Cancer (PC) was the leading cause of disease-related death in children under 15 in 2014 in Spain (INE, 2016). The most common tumours (age-adjusted rates per million for children aged 0–14) are leukaemia (Spain 47.0, Europe 44.0), central nervous system tumours (CNST) (Spain 33.2, Europe 29.9) and lymphoma (Spain 19.4, Europe 15.2) (Peris-Bonet et al., 2010; Stiller et al., 2006). The causes of PC are largely unknown, although in recent years an increase in incidence rates has been detected (Kaatsch, 2010; Ward et al., 2014). The reason for this increase is unknown, although it is believed that environmental changes are a contributing factor (Buka et al., 2007; Kaatsch, 2010).

Ambient air, especially in big cities and in the vicinity of industrial pollution foci, contains a wide variety of known human carcinogens, including polycyclic aromatic hydrocarbons, dioxins, arsenic, benzene, fine and ultrafine particles, asbestos and volatile organic compounds. In adults, it is estimated that 1–2% of cases of lung cancer can be associated with the presence of a high concentration of these compounds (Alberg and Samet, 2003). In Europe, national registers of polluting industries have increased awareness of the activities and emissions of the main foci of industrial pollution, which has facilitated the analysis of emissions and their effects. Several works have identified residential areas that are in the vicinity of industrial pollution foci as higher-risk cancer areas for adults (Bulka et al., 2013; Garcia-Perez et al., 2015a, 2015b; Morton-Jones et al., 1999; Ramis et al., 2009; Reynolds et al., 2003). Based on this empirical evidence, the World Health Organisation (WHO) has confirmed that air pollution is a human carcinogen, owing to the direct link between it and lung cancer (Loomis et al., 2013).

The presence of spatial clusters in pediatric cancer (PC) cases has been analysed in the search for etiological factors (Alexander et al., 1998; Demoury et al., 2012; McNally et al., 2009; Ramis et al., 2015). Observational studies that relate PC and air pollution are scarce (Garcia-Perez et al., 2016a; Reynolds et al., 2003), and in most cases focus on traffic density and the proximity of high-capacity roads; no consistent results on a global scale have been reached to date. Regarding industrial pollution, several works recently published in Spain argue for the relationship between exposure to industrial pollution and leukaemia, neuroblastoma, kidney and bone tumours in children aged 0–14 (Garcia-Perez et al., 2015b, 2016a, 2016b; García-Pérez et al., 2017). The low incidence of PC, the high degree of

uncertainty associated with the variables under consideration, and the formation of micro-clusters emphasise the need to carry out spatial epidemiological studies, which can then be used to analyse the incidence of cancer in small urban units (Ortega-García et al., 2016).

The target of this work is to undertake a preliminary analysis, based on empirical evidence, of the spatial distribution of PC around industrial facilities in a European region (Region of Murcia, Spain).

2. Methods

2.1. Study area and population

Census track (CT) represents the smallest territorial unit for which population data are available in Spain. The region of Murcia (RM) is a European Region (NUTS II in Eurostat terminology) located in southeastern of Spain and is divided in 2011 into 1220 CT. We consider this spatial unit as reference to evaluate risk and spatial clusters. A latitude and longitude coordinates (centroid) was assigned to each CT and the distance between two CT was defined as the distance between centroids.

Reference population (risk population) came from Spanish Census 2001 and 2011. The total population (< 15 years) was 207,822 in 2001 and 259,083 in 2011. We performed linear interpolation to estimate the population between the censuses. For each CT we used the population at the census times immediately preceding and immediately following. For times before the first census time, the population size is set equal to the population size at that first census time, and for times after the last census time, the population is set equal to the population size at that last census time.

2.2. Cases

The subjects of analysis were PC (< 15) cases diagnosed in the RM between January 1998 and December 2015 by the MACAPEMUR (Environment and Pediatric Cancer in the RM) project. MACAPEMUR is a project for the compilation of Pediatric Environmental History in newly diagnosed cancer patients since 1998 in the RM (Cárceles-Álvarez et al., 2015; Ferris Tortajada et al., 2004; Ortega-García et al., 2011). The single-province character of the RM and the centralized care reference units of Pediatric Oncohematology and the Pediatric Environmental Health Speciality Unit site at the Clinical University Hospital Virgen of Arrixaca facilitated the access to medical records. The hospital registry from the Clinical University Hospital Virgen of Arrixaca register 100% of the children diagnosed with cancer in the RM. The classification of the cases is done by checking the clinical-pathological diagnosis with the international classification of diseases for oncology (ICD-O-3) (IARC, 2011) and the International Classification of Childhood Cancer (ICCC-3) (Steliarova-Foucher et al., 2005) within 0–2 months after of diagnosis. Over 99% of the cases are morphologically verified. Annually, a medical doctor performs an additional check of all cases to verify the correct classification and elimination of double registrations.

In all cases, the families were contacted by phone or in person. Once the diagnosis is made, a face-to-face interview is carried out by one doctor trained in pediatric cancer, environmental health and risk communication, which collect information on addresses at

diagnosis; as well as another series of environmental data (Cárceles-Álvarez et al., 2015; Ferris Tortajada et al., 2004; Ortega-García et al., 2012). In this study, inclusion criteria comprised: children (< 15) diagnosed with cancer between 1998 and 2015 with an address in the RM corresponding to at-diagnosis residence. A total of 669 children were diagnosis with cancer during this period. Of these, we excluded 45 cases because they simply went to the RM in order to obtain a second opinion or complete the diagnostic and therapeutic process. Another 6 cases rejected to participate in the study. Finally, 624 cases were included in the study. Information on the residence at the time of diagnosis was then collected. These addresses were georeferenced and assigned a CT.

In order to reduce the border effects an exhaustive revision of hospital-based records of adjacent regions (Castilla-La Mancha and Comunidad Valenciana) was performed. This review did not provide new case studies.

The project was approved by the ethics research committee of Clinical University Hospital Virgen de la Arrixaca. Informed consent forms signed by all parents and children over 12 were collected.

2.3. Polluting industries

The identification of industrial pollution foci in the RM was carried out by studying the national emission and pollution register, which is maintained by the Spanish environment ministry (PRTR-Spain, http://www.prtr-es.es/). This register takes into consideration air pollution emitted by industrial facilities in the RM, and excludes the agricultural and animal-husbandry sectors. The geographical coordinates of industrial complexes were compiled using Google Maps and on-the-ground survey. Facilities located within 2 km of one another were grouped together in a single foci, which was, for analytical purposes, located in the geographic centroid. In total, the list includes 88 facilities, of which only 28 produce emissions; these were grouped in 12 foci. Fig. 1 illustrates the locations of these foci. Five types of industrial activity were defined (NACE Rev.2, http://ec.europa.eu/ eurostat/web/ nace-rev2) and foci were assigned accordingly: energy industries (2 foci); organic and inorganic chemical industries (5 foci); pharmaceutical industries (3 foci); building material industries (2 foci); industries concerned with the incineration or valorisation of dangerous waste (4 foci). Some foci were assigned more than one category because of the presence of industrial facilities of different kinds. Table 1 provides further details about the facilities that make up each industrial foci and the exposure of the population under 15 in 2011.

2.4. Statistical analysis

In first place, a descriptive analysis of the main diagnostic groups according to age group and sub-period was carried out, which involved the calculation of standardised incidence ratio (SIR) and its confidence intervals (CI) by cancer type and sub-periods. In second place, [1] we calculated several risk indicators (observed cases; expected cases and crude incidence rate; lowest number of observed cases which would be statistical significant at the one sided 5% type one level or less; exact value of the one sided type one error corresponding to this

[1]Thanks to anonymous referee for this suggestion.

limit; power of the test based on this limit of statistical significance under the alternative hypothesis of a doubling of the incidence rate) for an area delimited by a buffer of 4 km (window) around each foci groups (E, C, P, Ce, I) and all foci of industry activity (Ramis et al., 2011). Moreover, under the hypothesis of Poisson distribution of cases, we computed a test of equal incidence rates inside and outside of each window. Additionally, similar results for each foci. Lastly, we used the focused-local spatial scan statistic in order to identify cluster of high incidence around each foci. The Scan methodology (Kulldorff et al., 1997) has been developed for different types of processes and in this paper we used the focused version under the hypothesis of Poisson distribution. The basic idea of this simple yet powerful methodology is using circular moving windows centred in any foci of different size to "scan" a study area. For each window the number of events within the windows and the risk population is counted. The likelihood of the observed spatial distribution of events in compared to the likelihood of distribution under the null hypothesis of no clustering (e.g. the relative risk inside an outside of window is the same). For more details about this methodology an annexed section is include.

The scan procedure identifies the window where the likelihood ratio is maximum (Most Likelihood Cluster. MLC). Furthermore, it is possible to attach a probability value to the MLC in order to support inferential statements using permutation bootstrapping. The model outputs were the location and radius of clusters, the number of CT in the cluster, the population in the clusters, the number of observed and expected cases. In our case, the local-focused scan statistic is used to determine high-risk areas around a pre-determined set of points (pollutant sources).

The analysis was carried out to examine overall cancer incidence and also, with the most common tumours: leukaemia, lymphoma (HL: Hodgkin lymphoma and NHL: non Hodgkin lymphoma), CNST and SNST. Information on other types was also shown by completeness.

3. Results

Table 2 illustrates the distribution of CR/ASRw and SIR, divided by type of tumour and period and compared the results with other Spanish and European studies (Peris Bonet et al., 2015; Steliarova-Foucher et al., 2002). A CR of 148.0 cases per million children under age of 15 years was obtained. Leukaemia and CNST were the most common types. The number of cases of NHL and SNST diagnosed in the six-year period 2010–2015 is twice that observed in the first six-year period (1998–2003). A significant increase in the incidence of overall cancer and the subtypes of SNST, NHL and leukaemia may also be observed in 2010–2015.

In the population exposed less than 4 kms, the most relevant results (Table 3) shows an increase in the incidence of NHL around all foci group (p=0.07). A significant increase in the incidence of SNST related to energy industries (0.02) and the group other tumours with the building material industries. By foci to foci analysis (Table 4), we observe a significant increase of PC (all types) around Foci #4, due to the significant increase of SNST and others tumours. Additionally, we found around the foci #3 and #9 a significant increase and NHL and HL, respectively.

Table 5 shows the result of using the Scan test to look for high-incidence clusters around the 12 foci identified. Overall results for all types of tumours indicate significant values in only one cluster, near energy industries in Foci #4, where 8 cases within a radius of 3.39 km were noted; these results should be compared to the expected incidence, based on population, of 2.99 cases. Results per type of tumour for leukaemia, CNST and SNST did not result in the formation of significant clusters, in contrast with lymphomas. Five cases of NHL have been observed around Foci #3 (influence radius of 2.69 km). The population is 5218 and the number of expected cases was 0.91. Foci #3 is at the centre of a cluster of waste-valorisation industries. A cluster with three cases of Hodgkin lymphoma has been observed around foci #9. Results in others foci yielded p-values < 0.1: foci #4 in SNST, foci #2 and foci #10 in NHL.

4. Discussion

This study described the incidence of PC according to period and age in the RM and analysed the geographical pattern of the cases examining the relationship between these patterns and industrial pollution foci.

The results from the descriptive analysis show that the incidence of PC in the RM was similar to that in other European regions (Gatta et al., 2014; Peris-Bonet et al., 2015). The significant increase in PC, and specifically in leukaemia, lymphoma and neuroblastoma is a common trend that has been observed over the last decade (Kaatsch, 2010; Ward et al., 2014). Although a major effort is being made in recent years to reduce industrial emissions in Europe, some hazardous pollutants such as methane or benzopyrene continue to increase (European Environment Agency, 2016).

The results from the geographical analysis suggest some spatial clustering around certain industrial pollution foci. Globally, the results show a high incidence of NHL around the industrial facilities with some spatial clustering around certain industrial pollution foci. Also, the overall results (for all types of tumour) indicated a cluster around energy industries. Results for NHL revealed one cluster near waste-valorisation industries and HL close to building material industries.

Most publications on the relationship between PC and environmental pollution focus on leukaemia, CNST and all cancer types combined. In recent years, spatial epidemiological studies have linked PC with several environmental risk factors, including pesticides (McNally et al., 2014; Wheeler et al., 2011), or industrial pollutants (García Pérez et al., 2015b; García-Pérez et al., 2016a). However, we should not rule out the hypothesis infectious aetiology as more plausible (Kreis et al., 2016; McNally and Eden, 2004; Ortega-García et al., 2016). The evaluation of exposure is generally limited, and the majority of studies focus on the proximity of highways or on traffic density, and results are disparate. A European study observed an increase in the number of cases of leukaemia (Harrison et al., 1999), but numerous studies carried out in the USA (Alexander et al., 1998; Harrison et al., 1999; Puett et al., 2010; Reynolds et al., 2002; Selvin et al., 2004; Von Behren et al., 2008) and Denmark (Raaschou-Nielsen et al., 2001) led to different conclusions. Crosignani et al. (2004) estimated the relationship between traffic-related benzene emissions and the

incidence of pediatric leukaemia and observed that concentrations above 10 micrograms per cubic metre increased the risk by 3.91 (95% 1.36, 11.7). Concerning CNST, several previous studies have found spatial patterns. A British study showed evidence of overall spatio-temporal clustering among cases of primitive neuroectodermal tumours (McNally et al., 2012). Another British study found evidence of space-time clustering in cases of astrocytoma and ependymoma (McNally et al., 2002). In the literature, there are very few studies of cluster of cases of lymphomas in children. A British space-time clustering study found space-time clustering for HL and NHL (Goodman et al., 2014). Proximity to high-capacity thoroughfares has also been associated with the incidence of NHL among Danish children (Raaschou-Nielsen et al., 2001).

Concerning industrial foci, a higher incidence of leukaemia has been observed in the vicinity of petrol stations (Harrison et al., 1999; Steffen et al., 2004; Weng et al., 2009), repair workshops (Steffen et al., 2004), nuclear plants (Kaatsch et al., 2008; Spix et al., 2008), mineral-treatment plants, and galvanisation and metallurgical industries (Garcia-Perez et al., 2015b). A higher incidence of neuroblastoma has also been reported in areas in proximity to metal plants and mines (Garcia-Perez et al., 2016b). Moreover, it has been reported that proximity to industrial facilities, especially those dealing with metals and organic chemistry, increases the incidence of kidney tumours (Garcia-Perez et al., 2016a). A higher risk of CNST has been associated with intrauterine exposure to carcinogenic industrial substances, although no direct association between this and specific industrial foci has yet been established (McKean-Cowdin et al., 1998). A recent Spanish study detected a cluster of four cases of NHL within a radius of 643 m (Ramis et al., 2015).

The findings in our study showed a global higher incidence of NHL around foci of industrial pollution. The aetiology of most NHLs is unknown. Some analyses link the higher risk of NHL to exposure to chemicals, pesticides, organochlorines, alkylphenols and organic solvents (De Roos et al., 2010). A higher risk of NHL has also been related to proximity to paper industries (Ramis et al., 2009), rubber/plastic refineries, metallic-derivate industries (De Roos et al., 2010), benzene-emitting foci (Bulka et al., 2013) and cement kilns (Pronk et al., 2013). In certain professions, an increased risk of NHL has been noted: rubber-industry employees, vets, uranium miners, workers exposed to asbestos, timber-, metal- and textile-industry workers, farmers and cleaners (Baris and Zahm, 2000; t Mannetje et al., 2008).

Concerning our research, a higher overall risk of cancer is observed around Foci #4. The chemical/energy complex located on Foci #4 is related to the manufacture of bisphenol-A derived polycarbonate plastics and resins. This statistically significant result concerns all types of tumour combined, which limits the value of these results. However, it is important to highlight that reviewing MACAPEMUR database we found 4 out of the 8 cases observed are neuroectodermal or derived from the neural crest, and there are previous studies that have found associations between SNST and exposures to environmental toxicants such as bisphenol A, polycyclic aromatic hydrocarbons or carbon tetrachloride (Heck et al., 2013; Zheng et al., 2015). Muirhead et al. (2015) describe in their study that neuroblastic tumours occur in mini-epidemics where transient environmental exposures, such as infections or air pollution, are involved. These chemical products have motivated studies regarding child health effects, mainly birth outcomes and neurodevelopment but not cancer (Rochester,

2013). More research about exposure to bisphenol A and childhood health is needed to fill the gap in cancer aetiology.

In the proximity of Foci #3 (industries concerned incineration and valorisation of dangerous waste), there are more environmental hazards that could be associated with the high incidence of NHL, such as an urban area and the Foci #2. Also, it is very close an area of over 20 ha, in which thousands of tons of soil rich in heavy metals (lead, cadmium, arsenic) and phosphogypsum-derived radioactive elements (uranium, thorium, and polonium), sit in the open air.

In the case of Foci #9 (building material industries), 3 cases of HL have been observed. The presence of aggregated or clustered cases of LH is a known risk factor for this type of tumour. Some authors have proposed infectious aetiologies, such as EBV and herpesvirus (Cader et al., 2010; Linabery et al., 2014).

Finally, we must discuss the main limitations of this study. The approach used in the paper may have at least three important short-comings. Firstly, the low incidence of PC and the small size of the population of children studied hamper attempts to obtain consistent evidence, although the time-span of the project is relatively long (18 years), which makes the analysis more consistent. Additionally, two complementary methods have been used in the analysis, obtaining the same results. Secondly, the use of Focused Scan methodology, based on an isotropic model with circular windows, may lead to a false classification, as exposure depends on prevailing winds, topography and water pollution. This limits the possibility of attaining positive results, but does not invalidate the associations found. Thirdly, the non-inclusion of possible confounding factors, both indoor (professional-related exposure, lifestyle of the parents) and outdoor (non-atmospheric and non-identified pollution foci), can also lead to spurious results. Finally, another limitation is that the results of this study are based on the address at the time of diagnosis and do not allow us to explore the effects of the latency period of PC and the changes of residence between the pregnancy and the time of diagnosis, among other aspects.

All cases are being carefully monitored by project MACAPEMUR (Ortega-García et al., 2011) in the hope that the etiopathogenesis of these clusters can be clarified further (Ortega-Garcia et al., 2016; Ortega-García et al., 2012). This study is part of an ongoing research project that aims at improving the environmental health and quality of life of PC survivors in the RM. We expect to be able to offer more evidence in future works.

5. Conclusion

The results of this study suggest a possible association between proximity to certain industries and increased risk of PC. Globally, living in the vicinity of any industrial activity seem to increase the incidence of NHL. Furthermore, the energy/chemical industries seems to increase the overall risk of PC (taking all types of tumour into consideration), specifically neuroectodermics tumours. While residing near waste-valorisation industries and building material industries appear to increase the risk of NHL and HL, respectively. These results

stress the need to carry out detailed assessments on health hazards to children who have been exposed to industrial toxic emissions.

In the clusters detected, near foci #3, #4 and #9, a detailed integrative cancer risk-assessment, including an environmental clinical history of each case and the potentially relevant community-related data, may contribute to achieving two targets: improving our understanding of the etiopathogenesis behind these cases and to give the opportunities to improve public health decision making under complex problems.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors wish to express their gratitude to all the participants of the study. This work was supported by Mount Sinai International Exchange Program for Minority Students (grant MD001452) from the National Center on Minority Health and Health Disparities of the U.S. National Institutes of Health; and Prof. Fernando A. López, grateful for the financial support offered by the projects from Programa de Ayudas a Grupos de Excelencia de la Región de Murcia, Fundación Seneca (#19884-GERM-15) and Ministry of Economy and Competiveness (ECO2015-651758-P).

Appendix A. Supporting information

Supporting information associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.envres.2017.03.009.

References

Alberg AJ, Samet JM. Epidemiology of lung cancer. Chest. 2003; 123:21s–49s. [PubMed: 12527563]

Alexander FE, Boyle P, Carli PM, Coebergh JW, Draper GJ, Ekbom A, Levi F, McKinney PA, McWhirter W, Michaelis J, Peris-Bonet R, Petridou E, Pompe-Kirn V, Plisko I, Pukkala E, Rahu M, Storm H, Terracini B, Vatten L, Wray N. Spatial clustering of childhood leukaemia: summary results from the EUROCLUS project. Br J Cancer. 1998; 77:818–824. [PubMed: 9514064]

Baris D, Zahm SH. Epidemiology of lymphomas. Curr Opin Oncol. 2000; 12:383–394. [PubMed: 10975544]

Buka I, Koranteng S, Osornio Vargas AR. Trends in childhood cancer incidence: review of environmental linkages. Pediatr Clin N Am. 2007; 54:177–203.

Bulka C, Nastoupil LJ, McClellan W, Ambinder A, Phillips A, Ward K, Bayakly AR, Switchenko JM, Waller L, Flowers CR. Residence proximity to benzene release sites is associated with increased incidence of non-Hodgkin lymphoma. Cancer. 2013; 119:3309–3317. http://dx.doi.org/10.1002/cncr.28083. [PubMed: 23896932]

Cader FZ, Kearns P, Young L, Murray P, Vockerodt M. The contribution of the Epstein-Barr virus to the pathogenesis of childhood lymphomas. Cancer Treat Rev. 2010; 36:348–353. http://dx.doi.org/10.1016/j.ctrv.2010.02.011. [PubMed: 20193983]

Cárceles-Álvarez A, Ortega-García JA, Fuster-Soler JL, Rivera-Pagán GA, Bermúdez-Cortés M, Gomariz-Peñalver V, Monzó-Nuñez E, López-Hernández FA. Long-term follow up of childhood cancer survivors in the Murcia Region: preferences and attitudes of Primary Care professionals. An Pediatr. 2015; 83:264–271. http://dx.doi.org/10.1016/j.anpedi.2014.11.015.

Crosignani P, Tittarelli A, Borgini A, Codazzi T, Rovelli A, Porro E, Contiero P, Bianchi N, Tagliabue G, Fissi R, Rossitto F, Berrino F. Childhood leukemia and road traffic: a population-based case-control study. Int J Cancer. 2004; 108:596–599. [PubMed: 14696126]

De Roos AJ, Davis S, Colt JS, Blair A, Airola M, Severson RK, Cozen W, Cerhan JR, Hartge P, Nuckols JR, Ward MH. Residential proximity to industrial facilities and risk of non-Hodgkin lymphoma. Environ Res. 2010; 110:70–78. http://dx.doi.org/10.1016/j.envres.2009.09.011. [PubMed: 19840879]

Demoury C, Goujon-Bellec S, Guyot-Goubin A, Hemon D, Clavel J. Spatial variations of childhood acute leukaemia in France, 1990–2006: global spatial heterogeneity and cluster detection at 'living-zone' level. Eur J Cancer Prev. 2012; 21:367–374. http://dx.doi.org/10.1097/CEJ.0b013e32834e31d8. [PubMed: 22108445]

European Environment Agency. EEA Report No 28/2016. Luxembourg: 2016. Air Quality in Europe – 2016 report.

Ferris Tortajada J, Ortega-García JA, Marco Macián A, García Castell J. Environment and pediatric cáncer. An Pediatr. 2004; 61:42–50.

Garcia-Perez J, Lopez-Abente G, Castello A, Gonzalez-Sanchez M, Fernandez-Navarro P. Cancer mortality in towns in the vicinity of installations for the production of cement, lime, plaster, and magnesium oxide. Chemosphere. 2015a; 128:103–110. http://dx.doi.org/10.1016/j.chemosphere.2015.01.020. [PubMed: 25681568]

Garcia-Perez J, Lopez-Abente G, Gomez-Barroso D, Morales-Piga A, Romaguera EP, Tamayo I, Fernandez-Navarro P, Ramis R. Childhood leukemia and residential proximity to industrial and urban sites. Environ Res. 2015b; 140:542–553. http://dx.doi.org/10.1016/j.envres.2015.05.014. [PubMed: 26025512]

Garcia-Perez J, Morales-Piga A, Gomez J, Gomez-Barroso D, Tamayo-Uria I, Pardo Romaguera E, Fernandez-Navarro P, Lopez-Abente G, Ramis R. Association between residential proximity to environmental pollution sources and childhood renal tumors. Environ Res. 2016a; 147:405–414. http://dx.doi.org/10.1016/j.envres.2016.02.036. [PubMed: 26950029]

Garcia-Perez, J., Morales-Piga, A., Gomez-Barroso, D., Tamayo-Uria, I., Pardo Romaguera, E., Fernandez-Navarro, P., Lopez-Abente, G., Ramis, R. Risk of neuroblastoma and residential proximity to industrial and urban sites: a case-control study; Environ Int. 2016b. p. 92-93.p. 269-275.http://dx.doi.org/10.1016/j.envint.2016.04.023

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; 579:1333–1342. http://dx.doi.org/10.1016/j.scitotenv.2016.11.131. [PubMed: 27916304]

Gatta G, Botta L, Rossi S, Aareleid T, Bielska-Lasota M, Clavel J, Dimitrova N, Jakab Z, Kaatsch P, Lacour B, Mallone S, Marcos-Gragera R, Minicozzi P, Sánchez-Pérez MJ, Sant M, Santaquilani M, Stiller C, Tavilla A, Trama A, Visser O, Peris-Bonet R, EUROCARE Working Group. Childhood cancer survival in Europe 1999–2007: results of EUROCARE-5-a population-based study. Lancet Oncol. 2014; 15:35–47. http://dx.doi.org/10.1016/S1470-2045(13)70548-5. [PubMed: 24314616]

Goodman M, LaKind JS, Fagliano JA, Lash TL, Wiemels JL, Winn DM, Patel C, Van Eenwyk J, Kohler BA, Schisterman EF, Albert P, Mattison DR. Cancer cluster investigations: review of the past and proposals for the future. Int J Environ Res Public Health. 2014; 11:1479–1499. http://dx.doi.org/10.3390/ijerph110201479. [PubMed: 24477211]

Harrison RM, Leung PL, Somervaille L, Smith R, Gilman E. Analysis of incidence of childhood cancer in the West Midlands of the United Kingdom in relation to proximity to main roads and petrol stations. Occup Environ Med. 1999; 56:774–780. [PubMed: 10658564]

Heck JE, Park AS, Qiu J, Cockburn M, Ritz B. An exploratory study of ambient air toxics exposure in pregnancy and the risk of neuroblastoma in offspring. Environ Res. 2013; 127:1–6. http://dx.doi.org/10.1016/j.envres.2013.09.002. [PubMed: 24139061]

IARC. International Classification of Diseases for Oncology ICD-O-3. Lyon, France: 2011.

INE. Defunciones por causa de muerte. Madrid, Spain: 2016. Available at: ⟨http://www.ine.es/jaxiT3/Tabla.htm?T=7947⟩ (accessed on 12 December 2016)

Kaatsch P. Epidemiology of childhood cancer. Cancer Treat Rev. 2010; 36:277–285. http://dx.doi.org/10.1016/j.ctrv.2010.02.003. [PubMed: 20231056]

Kaatsch P, Spix C, Schulze-Rath R, Schmiedel S, Blettner M. Leukaemia in young children living in the vicinity of German nuclear power plants. Int J Cancer. 2008; 122:721–726. [PubMed: 18067131]

Kreis C, Grotzer M, Hengartner H, Spycher BD. Space-time clustering of childhood cancers in Switzerland: a nationwide study. Int J Cancer. 2016; 138:2127–2135. http://dx.doi.org/10.1002/ijc.29955. [PubMed: 26650335]

Kulldorff M, Feuer EJ, Miller BA, Freedman LS. Breast cancer clusters in the northeast United States: a geographic analysis. Am J Epidemiol. 1997; 146:161–170. [PubMed: 9230778]

Linabery AM, Erhardt EB, Fonstad RK, Ambinder RF, Bunin GR, Ross JA, Spector LG, Grufferman S. Infectious, autoimmune and allergic diseases and risk of Hodgkin lymphoma in children and adolescents: a Children's Oncology Group study. Int J Cancer. 2014; 135:1454–1469. http://dx.doi.org/10.1002/ijc.28785. [PubMed: 24523151]

Loomis D, Grosse Y, Lauby-Secretan B, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, Guha N, Baan R, Mattock H, Straif K. The carcinogenicity of outdoor air pollution. Lancet Oncol. 2013; 14:1262–1263. [PubMed: 25035875]

McKean-Cowdin R, Preston-Martin S, Pogoda JM, Holly EA, Mueller BA, Davis RL. Parental occupation and childhood brain tumors: astroglial and primitive neuroectodermal tumors. J Occup Environ Med. 1998; 40:332–340. [PubMed: 9571524]

McNally RJ, Eden TO. An infectious aetiology for childhood acute leukaemia: a review of the evidence. Br J Haematol. 2004; 127:243–263. [PubMed: 15491284]

McNally RJ, Cairns DP, Eden OB, Alexander FE, Taylor GM, Kelsey AM, Birch JM. An infectious aetiology for childhood brain tumours? Evidence from space-time clustering and seasonality analyses. Br J Cancer. 2002; 86:1070–1077. http://dx.doi.org/10.1038/sj.bjc.6600228. [PubMed: 11953851]

McNally RJ, Alexander FE, Vincent TJ, Murphy MF. Spatial clustering of childhood cancer in Great Britain during the period 1969–1993. Int J Cancer. 2009; 124:932–936. http://dx.doi.org/10.1002/ijc.23965. [PubMed: 19035447]

McNally RJ, James PW, Picton SV, McKinney PA, Laar M, van Feltbower RG. Space-time clustering of childhood central nervous system tumours in Yorkshire, UK. BMC Cancer. 2012; 12:13. http://dx.doi.org/10.1186/1471-2407-12-13. [PubMed: 22244018]

McNally RJ, Stiller C, Vincent TJ, Murphy MF. Cross-space-time clustering of childhood cancer in Great Britain: evidence for a common aetiology. Int J Cancer. 2014; 134:136–143. http://dx.doi.org/10.1002/ijc.28332. [PubMed: 23775892]

Morton-Jones T, Diggle P, Elliott P. Investigation of excess environmental risk around putative sources: stone's test with covariate adjustment. Stat Med. 1999; 18:189–197. [PubMed: 10028139]

Muirhead CR, Tweddle DA, Basta NO, McNally RJ. Temporal clustering of neuroblastic tumours in children and young adults from Northern England. Environ Health. 2015; 4 http://dx.doi.org/10.1186/s12940-015-0058-z.

Ortega-Garcia JA, López-Hernández FA, Carceles-Alvarez A, Santiago-Rodriguez EJ, Sanchez AC, Bermudez-Cortes M, Fuster-Soler JL. Analysis of small areas of pediatric cancer in the municipality of Murcia (Spain). An Pediatr. 2016; 84:154–162. http://dx.doi.org/10.1016/j.anpedi.2015.04.021.

Ortega-García JA, López-Hernández FA, Sobrino-Najul E, Febo I, Fuster-Soler JL. Environment and paediatric cancer in the Region of Murcia (Spain): integrating clinical and environmental history in a geographic information system. An Pediatr. 2011; 74:255–260. http://dx.doi.org/10.1016/j.anpedi.2010.11.005.

Ortega-García JA, Soldin OP, López-Hernández FA, Trasande L, Ferris-Tortajada J. Congenital fibrosarcoma and history of prenatal exposure to petroleum derivatives. Pediatrics. 2012; 130:e1019–e1025. http://dx.doi.org/10.1542/peds.2011-1307. [PubMed: 22945410]

Peris Bonet, R., Felipe García, S., Valero Poveda, S., Pardo Romaguera, E. Registro Español de Tumores Infantiles (RETI-SEHOP). Valencia, Spain: 2015. Cáncer infantil en España. Estadísticas 1980–2014.

Peris-Bonet R, Felipe García S, Martínez Ruiz N, Pardo Romaguera E, Valero Poveda S. Childhood cancer incidence and survival in Spain. Ann Oncol. 2010; 21(Suppl 3) http://dx.doi.org/10.1093/annonc/mdq092.

Pronk A, Nuckols JR, De Roos AJ, Airola M, Colt JS, Cerhan JR, Morton L, Cozen W, Severson R, Blair A, Cleverly D, Ward MH. Residential proximity to industrial combustion facilities and risk of non-Hodgkin lymphoma: a case-control study. Environ Health. 2013; 12:20. http://dx.doi.org/10.1186/1476-069X-12-20. [PubMed: 23433489]

Puett R, Lawson A, Clark A, Hebert J, Kulldorff M. Power evaluation of focused cluster tests. Environ Ecol Stat. 2010; 17:303–316. [PubMed: 24872726]

Raaschou-Nielsen O, Hertel O, Thomsen BL, Olsen JH. Air pollution from traffic at the residence of children with cancer. Am J Epidemiol. 2001; 153:433–443. [PubMed: 11226975]

Ramis R, Vidal E, Garcia-Perez J, Lope V, Aragones N, Perez-Gomez B, Pollan M, Lopez-Abente G. Study of non-Hodgkin's lymphoma mortality associated with industrial pollution in Spain, using Poisson models. BMC Public Health. 2009; 9:26. http://dx.doi.org/10.1186/1471-2458-9-26. [PubMed: 19159450]

Ramis R, Diggle P, Cambra K, López-Abente G. Prostate cancer and industrial pollution risk around putative focus in a multi-source scenario. Environ Int. 2011; 37:577–585. http://dx.doi.org/10.1016/j.envint.2010.12.001. [PubMed: 21216467]

Ramis R, Gomez-Barroso D, Tamayo I, Garcia-Perez J, Morales A, Pardo Romaguera E, Lopez-Abente G. Spatial analysis of childhood cancer: a case/control study. PLoS One. 2015; 10:e0127273. http://dx.doi.org/10.1371/journal.pone.0127273. [PubMed: 25992892]

Reynolds P, Von Behren J, Gunier RB, Goldberg DE, Hertz A, Smith D. Traffic patterns and childhood cancer incidence rates in California, United States. Cancer Causes Control. 2002; 13:665–673. [PubMed: 12296514]

Reynolds P, Von Behren J, Gunier RB, Goldberg DE, Hertz A, Smith DF. Childhood cancer incidence rates and hazardous air pollutants in California: an exploratory analysis. Environ Health Perspect. 2003; 111:663–668. [PubMed: 12676632]

Rochester JR. Bisphenol A and human health: a review of the literature. Reprod Toxicol. 2013; 42:132–155. http://dx.doi.org/10.1016/j.reprotox.2013.08.008. [PubMed: 23994667]

Selvin S, Ragland KE, Chien EYL, Buffler PA. Spatial analysis of childhood leukemia in a case/control study. Int J Hyg Environ Health. 2004; 207:555–562. http://dx.doi.org/10.1078/1438-4639-00327. [PubMed: 15729836]

Spix C, Schmiedel S, Kaatsch P, Schulze-Rath R, Blettner M. Case-control study on childhood cancer in the vicinity of nuclear power plants in Germany 1980– 2003. Eur J Cancer. 2008; 44:275–284. [PubMed: 18082395]

Steffen C, Auclerc MF, Auvrignon A, Baruchel A, Kebaili K, Lambilliotte A, Leverger G, Sommelet D, Vilmer E, Hemon D, Clavel J. Acute childhood leukaemia and environmental exposure to potential sources of benzene and other hydrocarbons; a case-control study. Occup Environ Med. 2004; 61:773–778. [PubMed: 15317919]

Steliarova-Foucher, E., Berrino, F., Coebergh, JW., Kaatsch, P., Lacour, B., Michaelis, J., Mitton, N., Stiller, CA., Parkin, DM. European Network of Cancer Registries. International Agency for Research on Cancer; Lyon, France: 2002. ACCISpass1.01, Software for Analysis and Presentation of Data on Incidence and Survival of Children and Adolescents in Europe.

Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P. International classification of childhood cancer. (Third Edition)Cancer. 2005; 103:1457–1467. http://dx.doi.org/10.1002/cncr.20910. [PubMed: 15712273]

Stiller CA, Marcos-Gragera R, Ardanaz E, Pannelli F, Almar Marques E, Canada Martinez A, Steliarova-Foucher E. Geographical patterns of childhood cancer incidence in Europe, 1988–1997. Report from the automated Childhood Cancer Information System project. Eur J Cancer. 2006; 42:1952–1960. [PubMed: 16919763]

't Mannetje A, Dryson E, Walls C, McLean D, McKenzie F, Maule M, Cheng S, Cunningham C, Kromhout H, Boffetta P, Blair A, Pearce N. High risk occupations for non-Hodgkin's lymphoma in New Zealand: case-control study. Occup Environ Med. 2008; 65:354–363. [PubMed: 18032530]

Von Behren J, Reynolds P, Gunier RB, Rull RP, Hertz A, Urayama KY, Kronish D, Buffler PA. Residential traffic density and childhood leukemia risk. Cancer Epidemiol Biomark Prev. 2008; 17:2298–2301. http://dx.doi.org/10.1158/1055-9965.

Ward E, DeSantis C, Robbins A, Kohler B, Jemal A. Childhood and adolescent cancer statistics, 2014. CA Cancer J Clin. 2014; 64:83–103. http://dx.doi.org/10.3322/caac.21219. [PubMed: 24488779]

Weng HH, Tsai SS, Chiu HF, Wu TN, Yang CY. Childhood leukemia and traffic air pollution in Taiwan: petrol station density as an indicator. J Toxicol Environ Health A. 2009; 72:83–87. http://dx.doi.org/10.1080/15287390802477338. [PubMed: 19034797]

Wheeler DC, De Roos AJ, Cerhan JR, Morton LM, Severson R, Cozen W, Ward MH. Spatial-temporal analysis of non-Hodgkin lymphoma in the NCI-SEER NHL case-control study. Environ Health. 2011; 10:63. http://dx.doi.org/10.1186/1476-069X-10-63. [PubMed: 21718483]

Zheng JC, Qi SQ, Yang L, Ma YY, Dong KR, Zhu HT, Yang SB, Xu T, Zheng S, Xiao XM. Effects of bisphenol A on decreasing the percentage and promoting the growth of stem cell-like cells from SK-N-SH human neuroblastoma cells. Genet Mol Res. 2015; 14:2986–2993. [PubMed: 25966062]

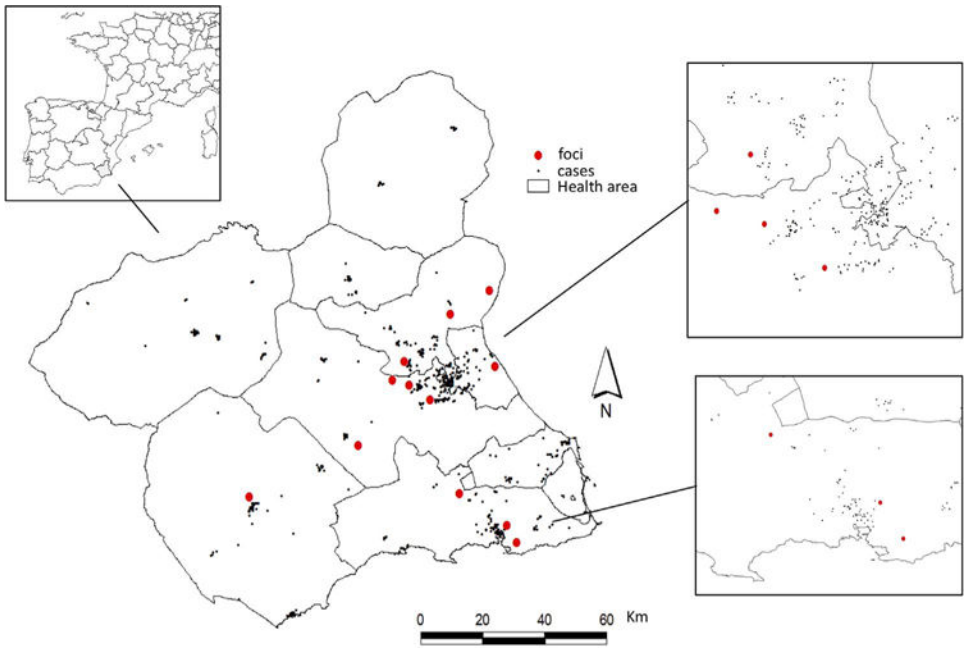

Fig. 1.
Cases and foci of air-polluting industries in RM (urban areas Murcia y Cartagena).

Table 1

List of industrial associated with each focus, industrial activity and population (< 15 years) exposed.

	Industrial activity[a]						Population under 15 in 2011			
Foci	**E**	**C**	**P**	**Ce**	**I**	**E-PRTR[b] (NACE Rev.2[c])**	**1 km**	**3 km**	**5 km**	**10 km**
Foci #1	–	x	–	–	–	6550 (20.53)	0	6173	17732	38426
Foci #2	x	x	–	–	x	722 (20.59); 1529 (19.20); 3442 (38.22); 3557 (20.59); 3589 (35.16); 3896 (20.14); 4791 (20.13); 5771 (52.10); 6515 (35.19); 6644 (35.16); 7733 (20.59); 7720 (20.14)	0	1326	2461	17245
Foci #3	–	–	–	–	x	3825 (38.22); 6251 (30.22); 7412 (81.22)	0	6608	23118	28846
Foci #4	x	x	–	–	–	1752 (20.16); 3965 (35.16)	0	355	1927	2416
Foci #5	–	x	–	–	–	6263 (20.41)	0	4734	9847	20367
Foci #6	–	–	x	–	–	4940 (21.10); 3490 (21.10)	320	2365	4653	7930
Foci #7	–	–	–	–	x	7750 (39.00)	0	831	1629	2488
Foci #8	–	–	–	x	–	9001 (23.51)	0	110	624	729
Foci #9	–	–	–	x	–	1574 (23.51)	0	7750	11541	12192
Foci #10	–	x	x	–	–	1702 (20.59); 1717 (21.10)	426	6162	11406	17874
Foci #11	–	–	–	–	x	3190 (38.21)	0	414	682	5607
Foci #12	–	–	x	–	–	6596 (21.10)	0	0	3061	4021

[a] E= energy industries; C= organic and inorganic chemical industries; P= pharmaceutical industries; Ce= building material industries; I= industries concerned with the incineration or valorisation of dangerous waste.

[b] European Pollutant Release and Transfer Register. (http://prtr.ec.europa.eu/)

[c] In brackets economic activity code.

Table 2

Distribution of diagnosed cases. CR and SIR by type and period.

		Cases by period								SIR (CI 95%) by type and period in the RM		
		98–03	04–09	10–15	All	%	CR[a]/ASRw MACAPEMUR	Spain (00–13)	Europe (88–97)	98–03	04–09	10–15
Leukaemia		44	55	72	171	27.4	40.5/41.2	46.1/47.0	41.7/44.1	0.91 (0.66–1.22)	1.14 (0.86–1.42)	**1.47 (1.15–1.85)**
	ALL	34	43	56	133		31.5/34.5	36.0/36.8	33.8/35.9	0.90 (0.62–1.26)	1.14 (0.87–1.47)	**1.48 (1.17–1.85)**
	AML	9	12	11	32		7.6/7.8	8.3/8.3	6.2/6.4	0.98 (0.45–1.86)	1.31 (0.75–2.12)	1.20 (0.67–1.98)
	Others	1	–	5	6		1.4/1.5	1.9/1.9		0.68 (0.01–3.79)	–	2.72 (0.93–6.24)
Lymphomas		19	11	35	65	10.4	15.4/16.1	19.6/19.2	15.9/15.2	1.01 (0.61–1.58)	0.59 (0.29–1.05)	**1.76 (1.12–1.93)**
	HL	8	4	10	22		5.2/5.2	7.2/6.9	6.3/5.8	1.22 (0.52–2.40)	0.61 (0.16–1.56)	1.52 (0.73–2.80)
	NHL	11	7	25	43		10.2/11.0	12.4/12.4	9.6/9.3	0.90 (0.45–1.61)	0.57 (0.23–1.18)	**1.88 (1.19–2.82)**
CNST		43	47	56	146	23.4	34.6/35.6	34.2/34.5	29.4/29.9	1.03 (0.74–1.38)	1.12 (0.82–1.49)	1.31 (0.99–1.71)
SNST		14	15	31	60	9.6	14.2/14.5	13.1/13.8	9.4/10.9	0.83 (0.46–1.40)	0.89 (0.50–1.47)	**1.85 (1.25–2.62)**
Others		52	62	68	182	29.2	43.2/43.8	40.8/41.3		–	–	–
Total		172	190	262	624	100	148.0/151.6	153.9/155.8	133.7/138.5	0.97 (0.83–1.12)	1.06 (0.92–1.23)	**1.44 (1.27–1.63)**
CR[a]		138.4	133.9	168.4	148.0							

[a]CR = Crude rate 1000000 under 15; ASRw =age-world-standardized incidence rate; SIR = standardized incidence ratio; IC = confidence interval. ALL = acute lymphoblastic leukemias; AML = acute myeloblastic leukemias; HL = Hodking lymphomas; NHL = non Hodking lymphomas; CNST = central nervous system tumours; SNST = sympathetic nervous system tumours. Spanish data obtained from Peris Bonet el al. (2015). European data obtained from Steliarova-Foucher et al. (2002).

Table 3

List of industrial activity and population (< 15 years) exposed less than 4 km.

Foci Group	Population (< 15) in 2011 around focus		L	HL	NHL	CNST	SNST	Other	All
All	62473	Observed (Expected)	29 (35.87)	5 (4.61)	13 (8.58)	30 (30.53)	13 (12.71)	36 (37.94)	126 (130.24)
		SIR	0.81	1.08	1.52	0.98	1.02	0.95	0.97
		CI 95% (SIR)	(0.54,1.16)	(0.35,2.53)	(0.81,2.59)	(0.66,1.40)	(0.54,1.75)	(0.66,1.31)	(0.81,1.15)
		p-value[a]	0.91	0.50	0.07	0.57	0.50	0.64	0.65
		CI 95% ratio λ_y/λ_x	(0.536,+∞)	(0.39,+∞)	(0.933,+∞)	(0.679,+∞)	(0.578,+∞)	(0.679,+∞)	(0.813,+∞)
		Lowest (p-value)	46 (0.03)	9 (0.02)	14 (0.03)	40 (0.03)	19 (0.03)	48 (0.03)	147 (0.05)
		Power	0.999	0.442	0.732	0.997	0.883	1.000	1.000
E	4388	Observed (Expected)	1 (1.68)	1 (0.21)	0 (0.38)	1 (1.41)	3 (0.61)	3 (1.75)	9 (6.04)
		SIR[c]	0.6	4.82	–	0.71	4.95	1.71	1.49
		CI[d] 95% (SIR)	(0.02,3.33)	(0.12,26.84)	–	(0.02,3.95)	(1.02,14.48)	(0.35,5.00)	(0.68,2.83)
		p-value[a]	0.80	0.19	–	0.75	0.02	0.24	0.14
		CI[b] 95% ratio λ_y/λ_x	(0.031,+∞)	(0.242,+∞)	–	(0.037,+∞)	(1.445,+∞)	(0.477,+∞)	(0.796,+∞)
		Lowest (p-value)[e]	5 (0.02)	2 (0.01)	3 (0.00)	5 (0.01)	3 (0.02)	5 (0.03)	11 (0.03)
		Power	0.124	0.009	0.008	0.067	0.036	0.142	0.548
C	31967	Observed (Expected)	9 (12.77)	2 (1.62)	5 (3.02)	10 (10.83)	8 (4.55)	18 (13.47)	52 (46.26)
		SIR	0.70	1.23	1.66	0.92	1.76	1.34	1.12
		CI 95% (SIR)	(0.32,1.34)	(0.15,4.45)	(0.54,3.87)	(0.44,1.70)	(0.76,3.46)	(0.79,2.11)	(0.84,1.47)
		p-value[a]	0.89	0.49	0.18	0.64	0.07	0.11	0.19
		CI 95% ratio λ_y/λ_x	(0.358,+∞)	(0.208,+∞)	(0.647,+∞)	(0.491,+∞)	(0.911,+∞)	(0.881,+∞)	(0.889,+∞)
		Lowest (p-value)	19 (0.04)	5 (0.02)	7 (0.03)	17 (0.04)	9 (0.03)	20 (0.04)	58 (0.04)
		Power	0.887	0.110	0.262	0.813	0.426	0.897	1.000
P	14467	Observed (Expected)	12 (9.69)	2 (1.24)	3 (2.32)	9 (8.24)	2 (3.43)	8 (10.24)	36 (35.16)
		SIR	1.24	1.61	1.30	1.09	0.58	0.78	1.02
		CI 95% (SIR)	(0.64,2.16)	(0.19,5.80)	(0.27,3.78)	(0.50,2.07)	(0.07,2.11)	(0.34,1.54)	(0.72,1.42)
		p-value[a]	0.25	0.35	0.41	0.43	0.86	0.80	0.45

Foci Group	Population (< 15) in 2011 around focus		L	HL	NHL	CNST	SNST	Other	All
		CI 95% ratio λ_y/λ_x	(0.715,+∞)	(0.277,+∞)	(0.344,+∞)	(0.563,+∞)	(0.1,+∞)	(0.382,+∞)	(0.759,+∞)
		Lowest (p-value)	16 (0.03)	4 (0.03)	6 (0.02)	14 (0.03)	8 (0.02)	16 (0.04)	46 (0.03)
			0.736	0.106	0.187	0.676	0.253	0.808	0.999
Ce	12165	Observed (Expected)	3 (7.24)	3 (0.92)	0 (1.72)	8 (6.13)	3 (2.57)	13 (7.59)	30 (26.17)
		SIR	0.41	3.27	–	1.3	1.17	1.71	1.15
		CI 95% (SIR)	(0.09,1.21)	(0.67,9.56)	–	(0.56,2.57)	(0.24,3.41)	(0.91,2.93)	(0.77,1.64)
		p-value[a]	0.97	0.06	–	0.26	0.46	0.03	0.22
		CI 95% ratio λ_y/λ_x	(0.111,+∞)	(0.908,+∞)	–	(0.652,+∞)	(0.319,+∞)	(1.039,+∞)	(0.834,+∞)
		Lowest (p-value)	13 (0.02)	4 (0.01)	5 (0.02)	11 (0.04)	6 (0.04)	13 (0.03)	35 (0.04)
		Power	0.585	0.039	0.135	0.568	0.259	0.654	0.993
I	9847	Observed (Expected)	8 (15.05)	1 (1.95)	6 (3.63)	11 (12.85)	4 (5.31)	11 (15.97)	41 (54.76)
		SIR	0.53	0.51	1.65	0.86	0.75	0.69	0.75
		CI 95% (SIR)	(0.23,1.05)	(0.01,2.85)	(0.61,3.60)	(0.43,1.53)	(0.21,1.93)	(0.34,1.23)	(0.54,1.02)
		p-value[a]	0.98	0.87	0.15	0.74	0.79	0.92	0.98
		CI 95% ratio λ_y/λ_x	(0.249,+∞)	(0.024,+∞)	(0.722,+∞)	(0.463,+∞)	(0.243,+∞)	(0.371,+∞)	(0.549,+∞)
		Lowest (p-value)	22 (0.04)	5 (0.04)	8 (0.02)	20 (0.03)	10 (0.03)	23 (0.04)	68 (0.03)
		Power	0.922	0.199	0.305	0.848	0.494	0.938	1.000

Abbreviations: L = leukaemia; HL = Hodking lymphomas; NHL = non Hodking lymphomas; CNST = central nervous system tumours. SNST = sympathetic nervous system tumours.

[§]E= energy industries; C= organic and inorganic chemical industries; P= pharmaceutical industries; Ce= building material industries; I= industries concerned with the incineration or valorisation of dangerous waste.

[a]p-value (H_0: $\lambda_y/\lambda_x \leq 1$; H_A: $\lambda_y/\lambda_x > 1$). Assume that $Y \sim Poisson(n\lambda_y)$ and $X \sim Poisson(m\lambda_x)$. n=total population around (< 4 km) Foci; m=total population outside (≥4 km) Foci. Y = Cases around (< 4 km) Foci; X = Cases outside (≥4 km) Foci influence.

[b]Exact confidence interval α=0.05 to the ratio λ_y/λ_x.

[c]SIR=Standardize Incidence Ratio by age group with respect to Murcia Region.

[d]Exact Confidence Interval α=0.05.

[e]Lowest number of observed cases which would be statistical significant at the one sided 5% type one level or less test using this test. In brackets: Exact value of the one sided type one error corresponding to this limit.

Table 4

List of industrial associated with each focus, industrial activity and population (< 15 years) exposed less than 4 km.

Foci	*Number Facilities*	Types of Emission[§]	Population (< 15) around focus 2011		L	HL	NHL	CNST	SNST	Others	All
Foci #1	1	C	17732	Observed (Expected)	5 (7.27)	1 (0.93)	2 (1.74)	7 (6.19)	5 (2.58)	10 (7.68)	30 (26.39)
				SIR[c](CI[d] 95%)	0.69 (0.22,1.60)	1.07(0.03,5.97)	1.15 (0.14,4.16)	1.13(0.45,2.33)	1.94 (0.63,4.52)	1.30 (0.62,2.39)	1.14 (0.77,1.62)
				p-value[a]	0.85	0.61	0.52	0.42	0.11	0.23	0.25
				CI[b] 95% ratio λ_y/λ_x	(0.26,+∞)	(0.05,+∞)	(0.19,+∞)	(0.52,+∞)	(0.77,+∞)	(0.71,+∞)	(0.82,+∞)
				Lowest (p-value)[e]	13 (0.03)	4 (0.01)	5 (0.02)	11 (0.04)	6 (0.04)	13 (0.04)	36 (0.03)
				Power	0.592	0.041	0.140	0.581	0.262	0.670	0.992
Foci #2	12	E; C; I	2461	Observed (Expected)	0 (0.90)	0 (0.11)	0 (0.21)	0 (0.76)	1 (0.32)	0 (0.95)	1 (3.25)
				SIR (CI[d] 95%)	–	–	–	–	3.12 (0.08,17.40)	–	0.31 (0.01,1.71)
				p-value[a]	–	–	–	–	0.26	–	0.96
				CI 95% ratio λ_y/λ_x	–	–	–	–	(0.16,+∞)	–	(0.01,+∞)
				Lowest (p-value)	4 (0.01)	2 (0.00)	2 (0.01)	3 (0.04)	2 (0.03)	4 (0.01)	7 (0.04)
				Power	0.036	0.002	0.009	0.068	0.027	0.044	0.327
Foci #3	3	I	23118	Observed (Expected)	7 (13.07)	1 (1.70)	5 (2.06)	10 (11.16)	3 (4.61)	9 (13.87)	35 (47.57)
				SIR (CI[d] 95%)	0.54 (0.22,1.10)	0.59 (0.01,3.28)	2.43 (0.79,5.68)	0.90 (0.43,1.65)	0.65 (0.13,1.90)	0.65 (0.30,1.23)	0.74 (0.51,1.02)
				p-value[a]	0.98	0.82	0.05	0.68	0.85	0.93	0.98
				CI 95% ratio λ_y/λ_x	(0.23,+∞)	(0.02,+∞)	(0.98,+∞)	(0.47,+∞)	(0.16,+∞)	(0.32,+∞)	(0.52,+∞)
				Lowest (p-value)	20 (0.03)	5 (0.02)	6 (0.01)	18 (0.03)	9 (0.04)	21 (0.03)	60 (0.03)
				Power	0.867	0.129	0.124	0.787	0.442	0.885	1.000
Foci #4	2	E; C	1927	Observed (Expected)	1 (0.78)	1 (0.09)	0 (0.17)	1 (0.65)	2 (0.29)	3 (0.81)	8 (2.79)
				SIR (CI[d] 95%)	1.28 (0.03,7.15)	10.7 (0.27,59.60)	–	1.54 (0.04,8.59)	7.01 (0.85,25.33)	3.72 (0.77,10.86)	2.87(1.24,5.66)
				p-value[a]	0.52	0.09	–	0.46	0.02	0.04	0.00
				CI 95% ratio λ_y/λ_x	(0.06,+∞)	(0.53,+∞)	–	(0.08,+∞)	(1.3,+∞)	(1.05,+∞)	(1.48,+∞)
				Lowest (p-value)	3 (0.03)	2 (0.00)	2 (0.01)	3 (0.02)	2 (0.02)	3 (0.04)	7 (0.02)
				Power	0.073	0.001	0.005	0.043	0.021	0.082	0.198

Foci	*Number Facilities*	Types of Emission[§]	Population (< 15) around focus 2011		L	HL	NHL	CNST	SNST	Others	All
Foci #5	1	C	9847	Observed (Expected)	3 (3.82)	0 (0.48)	3 (0.89)	2 (3.24)	0 (1.37)	5 (4.03)	13 (13.84)
				SIR (CI[d] 95%)	0.78 (0.16,2.29)	–	3.35 (0.69,9.80)	0.62 (0.07,2.23)	–	1.24 (0.40,2.89)	0.94 (0.50,1.61)
				p-value[a]	0.72	–	0.06	0.83	–	0.36	0.61
				CI 95% ratio λ_y/λ_x	(0.21,+∞)	–	(0.91,+∞)	(0.10,+∞)	–	(0.49,+∞)	(0.55,+∞)
				Lowest (p-value)	8 (0.03)	3 (0.01)	4 (0.01)	7 (0.04)	4 (0.04)	8 (0.04)	21 (0.03)
				Power	0.357	0.017	0.035	0.324	0.143	0.416	0.880
Foci #6	2	P	4653	Observed (Expected)	3 (2.56)	0 (0.33)	0 (0.61)	3 (2.18)	0 (0.91)	1 (2.71)	7 (9.30)
				SIR (CI[d] 95%)	1.17 (0.24,3.43)	–	–	1.38 (0.28,4.02)	–	0.37 (0.01,2.06)	0.75 (0.30,1.55)
				p-value[a]	0.47	–	–	0.37	–	0.93	0.81
				CI 95% ratio λ_y/λ_x	(0.31,+∞)	–	–	(0.37,+∞)	–	(0.01,+∞)	(0.35,+∞)
				Lowest (p-value)	6 (0.04)	2 (0.04)	3 (0.02)	6 (0.02)	4 (0.01)	7 (0.01)	15 (0.04)
					0.256	0.029	0.036	0.151	0.038	0.181	0.758
Foci #7	1	I	1629	Observed (Expected)	1 (1.06)	0 (0.14)	0 (0.26)	1 (0.90)	0 (0.37)	2 (1.12)	4 (3.85)
				SIR (CI[d] 95%)	0.95 (0.02,5.27)	–	–	1.11 (0.03,6.16)	–	1.79 (0.22,6.46)	1.04 (0.28,2.66)
				p-value[a]	0.65	–	–	0.59	–	0.30	0.53
				CI 95% ratio λ_y/λ_x	(0.04,+∞)	–	–	(0.05,+∞)	–	(0.31,+∞)	(0.35,+∞)
				Lowest (p-value)	4 (0.02)	2 (0.00)	2 (0.02)	4 (0.01)	3 (0.00)	4 (0.02)	8 (0.04)
					0.064	0.003	0.016	0.036	0.007	0.077	0.366
Foci#8	1	Ce	624	Observed (Expected)	0 (0.38)	0 (0.05)	0 (0.09)	0 (0.32)	0 (0.13)	0 (0.40)	0 (1.38)
				SIR (CI[d] 95%)	–	–	–	–	–	–	–
				CI 95% (SIR)	–	–	–	–	–	–	–
				p-value[a]	–	–	–	–	–	–	–
				CI 95% ratio λ_y/λ_x	–	–	–	–	–	–	–
				Lowest (p-value)	3 (0.00)	1 (0.04)	2 (0.00)	2 (0.04)	2 (0.00)	3 (0.00)	5 (0.01)
				Power	0.008	0.005	0.001	0.027	0.002	0.009	0.062
Foci#9	1	Ce	11541	Observed (Expected)	3 (6.86)	3 (0.87)	0 (1.62)	8 (5.81)	3 (2.44)	13 (7.20)	30 (24.79)

Foci	*Number Facilities*	Types of Emission[§]	Population (< 15) around focus 2011		L	HL	NHL	CNST	SNST	Others	All
				SIR (CI[d] 95%)	0.44 (0.09,1.28)	3.46 (0.71,10.10)	–	1.38 (0.59,2.71)	1.23 (0.25,3.59)	1.81 (0.96,3.09)	1.21 (0.82,1.73)
				p-value[a]	0.96	0.05	–	0.22	0.42	0.02	0.15
				CI 95% ratio λ_y/λ_x	(0.11,+∞)	(0.96,+∞)	–	(0.69,+∞)	(0.33,+∞)	(1.09,+∞)	(0.88,+∞)
				Lowest (p-value)	12 (0.04)	4 (0.01)	5 (0.02)	11 (0.03)	6 (0.03)	13 (0.02)	34 (0.03)
				Power	0.613	0.032	0.110	0.494	0.220	0.577	0.987
Foci#10	2	C; P	11406	Observed (Expected)	8 (6.16)	2 (0.80)	3 (1.49)	5 (5.26)	2 (2.17)	7 (6.52)	27 (22.41)
				SIR (CI[d] 95%)	1.3 (0.56,2.56)	2.5 (0.30,9.04)	2.01 (0.41,5.87)	0.95 (0.31,2.22)	0.92 (0.11,3.33)	1.07 (0.43,2.21)	1.2 (0.79,1.75)
				p-value[a]	0.27	0.18	0.18	0.60	0.64	0.47	0.18
				CI 95% ratio λ_y/λ_x	(0.64,+∞)	(0.44,+∞)	(0.54,+∞)	(0.36,+∞)	(0.15,+∞)	(0.50,+∞)	(0.85,+∞)
				Lowest (p-value)	11 (0.04)	3 (0.04)	5 (0.01)	10 (0.03)	6 (0.02)	12 (0.03)	31 (0.04)
				Power	0.574	0.079	0.082	0.482	0.149	0.541	0.981
Foci#11	1	I	682	Observed (Expected)	0 (0.27)	0 (0.04)	1 (0.07)	0 (0.23)	0 (0.09)	0 (0.29)	1 (0.97)
				SIR(CI[d] 95%)	–	–	15.33 (0.39,85.43)	–	–	–	1.03 (0.03,5.72)
				p-value[a]	–	–	0.06	–	–	–	0.62
				CI 95% ratio λ_y/λ_x	–	–	(0.783,+∞)	–	–	–	(0.05,+∞)
				Lowest (p-value)	2 (0.031)	1 (0.03)	2 (0.00)	2 (0.02)	2 (0.00)	2 (0.03)	4 (0.01)
				Power	0.018	0.003	0.000	0.012	0.001	0.021	0.047
Foci#12	1	P	3061	Observed (Expected)	1 (0.96)	0 (0.12)	0 (0.21)	1 (0.80)	0 (0.35)	0 (1.00)	2 (3.45)
				SIR(CI[d] 95%)	1.04 (0.03,5.78)	–	–	–	–	–	0.58 (0.07,2.09)
				p-value[a]	0.60	–	–	–	–	–	0.84
				CI 95% ratio λ_y/λ_x	(0.05,+∞)	–	–	–	–	–	(0.10,+∞)
				Lowest (p-value)	4 (0.01)	2 (0.00)	2 (0.02)	3 (0.04)	2 (0.04)	4 (0.01)	8 (0.02)
				Power	0.046	0.002	0.009	0.079	0.034	0.053	0.258

Abbreviations: L = leukaemia; HL = Hodking lymphomas; NHL = non Hodking lymphomas; CNST = central nervous system tumours. SNST = sympathetic nervous system tumours.

[a] p-value[a] (H_0: $\lambda_y/\lambda_x \leq 1$; H_A: $\lambda_y/\lambda_x > 1$). Assume that $Y \sim Poisson(n\lambda_y)$ and $X \sim Poisson(m\lambda_x)$. n=total population around (< 4 km) Foci; m=total population outside (≥4 km) Foci. Y = Cases around (< 4 km) Foci; X = Cases outside (≥4 km) Foci influence.

[b] Exact confidence interval α=0.05 to the ratio λ_y/λ_x.

Environ Res. Author manuscript; available in PMC 2017 November 14.

[c] SIR=Standardize Incidence Ratio by age group with respect to Murcia Region.

[d] Exact Confidence Interval α=0.05.

[e] Lowest number of observed cases which would be statistical significant at the one sided 5% type one level or less test using this test. In brackets: Exact value of the one sided type one error corresponding to this limit.

[§] E= energy industries; C= organic and inorganic chemical industries; P= pharmaceutical industries; Ce= building material industries; I= industries concemed with the incineration or valorisation of dangerous waste.

Table 5

Focused space Scan test results by tumour type and type of industry.

		Energy	Chemical	Pharmaceutical	Building material	Dangerous waste	All foci
All	#CT en MLC	**4**	4	5	25	6	4
	Foci	**Foci #4**	Foci #4	Foci #10	Foci #9	Foci #3	Foci #4
	Population	**1017**	1017	5993	6093	1786	1017
	Km	**3.39**	3.62	2.75	2.23	2.00	3.39
	Number of cases	**8**	8	25	22	5	8
	Expected cases	**2.99**	2.68	15.77	16.03	4.7	2.68
	Annual cases/10^6	**43.7**	43.7	23.2	20.1	15.6	43.7
	p-value	**0.02** **	0.13	0.21	0.26	0.99	0.27
Leukaemia	# CT en MLC	7	25	15	–	–	15
	Foci	Foci #4	Foci #10	Foci #12	–	–	Foci #12
	Population	1750	5993	2807	–	–	2807
	Km	4.80	2.75	4.74	–	–	4.74
	Number of cases	2	7	6	–	–	6
	Expected cases	1.27	4.34	2.03	–	–	2.03
	Annual cases/10^6	6.3	6.5	11.9	–	–	11.9
	p-value	0.58	0.88	0.15	–	–	0.45
CNST	#CT en MLC	–	17	22	8	62	17
	Foci	–	Foci #1	Foci #10	Foci #9	Foci #3	Foci#1
	Population	–	3418	5487	1725	10458	3418
	Km	–	2.04	2.65	2.30	3.20	2.04
	Number of cases	–	5	5	3	8	5
	Expected cases	–	2.11	3.39	1.07	6.46	2.11
	Annual cases/10^6	–	8.1	5.1	2.86	4.3	8.1
	p-value	–	0.62	0.79	0.25	0.82	0.84
SNST	#CT en MLC	**4**	58	37	24	9	4
	Foci	**Foci #4**	Foci #1	Foci #10	Foci #9	Foci #2	Foci #4
	Population	**1017**	12453	8991	6093	2019	1017
	Km	**3.39**	4.44	4.27	2.99	4.73	3.39

		Energy	Chemical	Pharmaceutical	Building material	Dangerous waste	All foci
	Number of cases	**2**	7	3	3	2	2
	Expected cases	**0.26**	3.18	2.20	1.56	0.52	0.26
	Annual cases/10^6	**10.9**	3.1	1.9	2.7	5.5	10.9
	p-value	**0.06** *	0.41	0.74	0.30	0.43	0.46
NHL	#CT en MLC	**12**	**4**	15	–	**24**	**26**
	Foci	**Foci #2**	**Foci #10**	Foci #10	–	**Foci #3**	**Foci #3**
	Population	**2447**	**775**	3838	–	**5218**	**5218**
	Km	**5.00**	**1.16**	2.36	–	**2.69**	**2.69**
	Number of cases	**2**	**2**	3	–	**5**	**5**
	Expected cases	**0.43**	**0.14**	0.67	–	**0.91**	**0.91**
	Annual cases/10^6	**4.5**	**14.3**	4.3	–	**5.3**	**5.3**
	p-value	**0.09** *	**0.08** *	0.151	–	**0.01** **	**0.06** *
HL	#CT en MLC	–	13	13	**18**	80	32
	Foci	–	Foci #10	Foci #10	**Foci #9**	Foci #3	Foci #9
	Population	–	3462	3462	**7493**	20640	7493
	Km	–	2.26	2.26	**2.67**	4.35	3.37
	Number of cases	–	2	2	**3**	2	3
	Expected cases	–	0.32	0.32	**0.70**	1.93	0.7
	Annual cases/10^6	–	3.2	3.2	**2.2**	0.5	2.2
	p-value	–	0.26	0.127	**0.04** **	0.612	0.360

CT = Census track; MLC =Most Likelihood Cluster; Population = Population (< 15) inside of MLC; Km = radius of MLC around foci; Number of cases= Number of cases inside of cluster; Expected cases= Expected cases inside of cluster.

Abbreviations: L = leukaemia; HL = Hodking lymphomas; NHL = non Hodking lymphomas; CNST = central nervous system tumours. SNST = sympathetic nervous system tumours

** p-value < 0.05.

* p-value < 0.1.