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Association between proximity to industrial chemical installations and cancer mortality in Spain

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ABSTRACT

It is likely that pollution from chemical facilities will affect the health of any exposed population; however, the majority of scientific evidence available has focused on occupational exposure rather than environmental. Consequently, this study assessed whether there could have been an excess of cancer-related mortality associated with environmental exposure to pollution from chemical installations – for populations residing in municipalities in the vicinity of chemical industries. To this end, we designed an ecological study which assessed municipal mortality due to 32 types of cancer in the period from 1999 to 2008. The exposure to pollution was estimated using distance from the facilities to the centroid of the municipality as a proxy for exposure. In order to assess any increased cancer mortality risk in municipalities potentially exposed to chemical facilities pollution (situated at a distance of $\leq$5 km from a chemical installation), we employed Bayesian Hierarchical Poisson Regression Models. This included two Bayesian inference methods: Integrated Nested Laplace Approximations (INLA) and Markov Chain Monte Carlo (MCMC, for validation). The reference category consisted of municipalities beyond the 5 km limit. We found higher mortality risk (relative risk, RR; estimated by INLA, 95% credible interval, 95%CrI) for both sexes for colorectal (RR, 1.09; 95%CrI, 1.05–1.15), gallbladder (1.14; 1.03–1.27), and ovarian cancers (1.10; 1.02–1.20) associated with organic chemical installations. Notably, pleural cancer (2.27; 1.49–3.41) in both sexes was related to fertilizer facilities. Associations were found for women, specifically for ovarian (1.11; 1.01–1.22) and breast cancers (1.06; 1.00–1.13) in the proximity of explosives/pyrotechnics installations; increased breast cancer mortality risk (1.10; 1.03–1.18) was associated with proximity to inorganic chemical installations. The results suggest that environmental exposure to pollutants from some types of chemical facilities may be associated with increased mortality from several different types of cancer.

1. Introduction

According to data from the WHO's Global Health Observatory, non-communicable diseases (NCDs) are responsible for the majority of deaths worldwide, of which cancer is one of the leading

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causes (WHO, 2019). The etiology of many types of cancer is influenced by environmental- and lifestyle-related risk-factors (International Agency for Research on Cancer, 1991). Some studies have even estimated that high-income countries could avoid one-third to two-fifths of new cancer cases by eliminating or reducing exposure to environmental risk factors and/or improving lifestyle choices (Brown et al., 2018; Islami et al., 2018; Wilson et al., 2018).

One of these well-known environmental risk factors is exposure to airborne pollution, which can include numerous carcinogens, e.g. benzo[a]pyrene, benzene, and heavy metals (Boffetta and Nyberg, 2003). Some estimations claims that from 1 to 2% of lung cancer cases can be associated with the presence of such airborne compounds (Alberg and Samet, 2003). Other studies have found evidence of associations between various cancers and air pollution, for example bladder cancer (Loomis et al., 2013), lung cancer (Hamra, 2014) and post-menopausal breast cancer (Goldberg et al., 2017).

Millions of people are exposed to medium to high levels of air pollution, and – along with traffic –industrial activity is one of the principal non-natural sources (EEA, 2018); as a consequence, evaluating the possible adverse effects of industrial pollution has the potential to provide results of significant interest for public health policy.

Publicly held Pollutant Release and Transfers Registers (PRTRs) provide useful information about a broad variety of industrial activities pollutant releases into the environment (Wine et al., 2013). A number of studies have used data from these registries, several of which have found excess cancer risk in areas exposed to industrial pollution (Bulka et al., 2013; Cambra et al., 2013; Fernández-Navarro et al., 2017; 2018; Morton-Jones et al., 1999; Pascal et al., 2013). With specific regard to Spain, several studies have used PRTR data to evaluate potential associations between different industrial sectors and mortality from various forms of cancer (Fernández-Navarro et al., 2017). The results of these studies suggest that regions of Spain exposed to pollution from certain types of industrial facilities – also using proximity to the facilities as a proxy for exposure – have around 17% excess cancer mortality compared with those outside these areas. This excess mortality is concentrated in digestive and respiratory tract cancers; leukaemias; and prostate, breast, and ovarian cancers. A number of different industrial activities have been assessed by these studies, including the chemicals industry; however, the potential effects of the chemical sector have not been studied in depth, while the complexity and heterogeneity of this sector make such a study both necessary and useful.

In relation to the chemical industry, there are studies that have associated exposure to pollutants released by this sector with the following malignant tumors: stomach, breast, and lung cancers (Pasetto et al., 2012); bladder (Letašiová et al., 2012) (Brown et al., 2011), tracheal and bronchial cancers (Ruder and Yiin, 2011), non-Hodgkin's lymphomas and leukaemias (Ruder and Yiin, 2011); melanomas (Dika et al., 2010); brain (Gomes et al., 2011) and pleural cancers (López-Abente et al., 2012). However, as noted above, most of these studies focused on occupational exposure. Some studies have detected an excess of risk for workers involved in the rubber industry of developing specific cancers: bladder, lung, larynx, esophagus, stomach, colon, liver, pancreas, skin, prostate, kidney, brain, and thyroid cancer; leukaemias; malignant lymphomas; multiple myelomas (Kogevinas et al., 1998); tracheal and bronchial cancers, lymphosarcoma, reticulum sarcomas, and cancers of the overall lymphatic and hematopoietic systems (Lemen et al., 1990). Workers in the plastics industry have shown an excess of risk for breast cancer (DeMatteo et al., 2012). Biocides and organic chemicals industry workers have been associated with an excess of risk for pleural cancer (García-Pérez et al., 2016a), while workers involved in petrochemical industries have shown increased risk for malignant melanomas (Mehlman, 2006); leukaemias (Pan et al., 1994); brain cancers (Liu et al., 2008); liver cancers (Yang et al., 1997); and lung cancers (Iwatsubo et al., 2014).

A number of studies that used proximity to an industrial facility as a proxy for exposure to industrial pollution have used Bayesian hierarchical models with random effects; generally, these have been adjusted using integrated nested Laplace approximations (INLA) (Fernández-Navarro et al., 2012; López-Abente et al., 2012). The reason for this approach is that it allows researchers to obtain reliable results in a reasonable time and at much lower computational cost, when compared to the more traditional Markov Chain Monte Carlo (MCMC) method. Some studies suggest, however, that the two methods are largely equivalent when using Bayesian hierarchical models (Carroll et al., 2015; De Smedt et al., 2015), except for statistically rare diseases. To the best of our knowledge, no study has yet employed both approaches together to assess risk with spatial association models.

Given this paucity of analysis of environmental pollution in the vicinity of chemical installations, the aims of this study are (a) to assess the possible excess of risk of mortality due different types of cancer among populations in the vicinity of chemical installations in Spain, (b) to identify the potential risks associated with different types of chemical facilities and to validate the results using a variety of methodological approaches.

2. Material and methods

To achieve these objectives, we designed an ecological study in order to evaluate whether there was an excess of cancer mortality risk for 32 types of cancer in those municipalities potentially exposed to pollution from the chemical industry between 1999 and 2008. The analysis was conducted for the overall population and stratified by sex.

This study has been divided into two sections: (1) Characterization of the chemical industry in Spain, which assesses the emissions and the spatial distribution of industrial sites in this sector (2) Analysis of potential associations between chemical industry pollution and cancer mortality at municipal level.

2.1. Data sources

2.1.1. Chemical pollution exposure data

We obtained data about Spain's chemical industries from the Integrated Prevention and Pollution Control and Spanish Pollution Release and Transfer Register (PRTR-Spain) for the period 2007–2010 – provided by the Spanish Ministry of Agriculture, Food and the Environment. This database contains information about 6.850 industrial facilities, 538 of which are chemical facilities; the data provides details about geographical location, emissions, first year of operation, and "other". Some of this information has been validated by our group as part of previous studies (García-Pérez et al., 2015c).

In the case of pollution sources in Spain, the European Commission directives passed in 2002 afforded a new means of studying the consequences of industrial pollution: Integrated Pollution Prevention and Control (IPPC), governed both by Directive 96/61/CE (recently codified into Directive 2008/1/EC) and by Act 16/2002, which incorporates this Directive into the Spanish legal system, lays down that, to be able operate, industries covered by the regulation must obtain the Integrated Environmental Permit. This same enactment implemented the European Pollutant Release and Transfer Register (E-PRTR), which make it compulsory in 2007 to declare all pollutant emissions to air, water and soil, that exceed the designated thresholds. More details can be found in Fernández-Navarro et al. (2017).

The PRTR-Spain classifies chemical industries into six categories (see Supplementary Material Table 1): 1. Production of organic chemicals; 2. Production of inorganic chemicals; 3. Production of phosphorous-, nitrogen- or potassium-based fertilizers; 4. Production of plant protection products or biocides; 5. Production of pharmaceutical products; 6. Explosives/pyrotechnics production.

In this study, in order to take into account the induction period for cancer (at least ten years for the majority of solid tumors (UNSCEAR, 2006), we included only facilities which started activity before to 1993 (10 years before 2003, which correspond to the mid-year of the study period 1999–2008. However, for the study of leukemias, for which the induction period can be as little as 1 year (UNSCEAR, 2006) facilities which began their activities before 2002 (1 year before 2003, the mid-year of the study period 1999–2008) were also included. The date (year) of commencement of the respective industrial activities was provided by the industries themselves.

The use of the mid-year of the study period has already been used in other similar works of our group where mortality corresponds to a period of several years. In this design it is impossible to discriminate deaths every year, which would allow the induction periods to be calculated more precisely. So, it seems reasonable then in this study to assign a mid-point as a reference.

2.1.2. Population, mortality and sociodemographic data

We obtained municipal population data (n = 8073 Spanish towns), broken down by age-group and sex, from the Spanish Statistical Office (*Instituto Nacional de Estadística – INE*). Observed municipal mortality data – which corresponded to deaths as a result of 32 types of malignant tumors (see Supplementary Data Table 2) – were drawn from INE records for the period 1999–2008. We calculated expected cases by taking the rates for Spain as a whole for each tumour type, broken down by age-group into 5-year intervals (0–4, 5–9, …, 85 years and over), sex, and five year periods (1999–2003 and 2004–2008) and multiplying these by the person-years for each town, broken down by the same strata. Person-years for the two periods were calculated by multiplying the municipal population by the number of years in each (five). The figures corresponding to the midpoint of each period – i.e. 2001 and 2006 – were taken as an estimator for the population (Fernández-Navarro et al., 2012; García-Pérez et al., 2015c; Lopez-Abente et al., 2012).

We introduced socio-demographic indicators from the 1991 Spanish Census (INE) into our spatial models to control for potential confounding; these data were chosen for their availability at the municipal level and their ability to explain a number of geographical mortality patterns (Lopez-Abente et al., 2006). These variables were: municipal population size, categorized into three levels: 0–2000 inhabitants (rural areas), 2001 to 10,000 inhabitants (semi-urban), and >10,000 (urban areas); illiteracy rates; farmer rates; unemployment rates; average number of persons per household; and average income for each municipality.

2.2. Statistical analysis

First, we conducted a descriptive analysis to characterize pollution from the chemical industry; we then analyzed potential associations between cancer mortality and the pollution released by the industry.

2.2.1. Characterization of industrial pollution by the chemical sector

The descriptive analysis included the sum of the substance emissions classified as Group 1 carcinogens for humans by the International Agency for Research on Cancer (IARC) and released by chemical facilities during the study period (see Supplementary Material, Table 3). Subsequently, we plotted a map showing the locations of the chemical installations included in the analysis; this map includes information about chemical industry categories to assess the spatial distribution of this industrial sector in Spain.

2.2.2. Association between cancer mortality and chemical industry pollution

We carried out an exploratory study to assess if there could be an excess risk of cancer mortality in those municipalities potentially exposed to pollution from the chemical industry – as compared to those not in the vicinity of such industries. For this purpose, we created an "exposure to industrial pollution" variable based on the distance from a given municipal centroid to the industrial facilities identified. To determine the distance, we would use in this study, we conducted a "near *vs.* far" analysis at 15 different distances (from 1 to 15 km) stratified by sex. A similar approach has been used by other studies (Fernández-Navarro et al., 2012; García-Pérez et al., 2016b). This analysis showed that 5 km was the optimum distance, in terms of being able to both discern risk and provide a sufficient number of observed deaths – therefore providing enough statistical power to make the analysis meaningful (see Supplementary Material, Fig. 3). The 5 km limit coincides with that used by other authors (Fernández-Navarro et al., 2012; García-Pérez et al., 2013, 2015c). Once the distance was set at 5 km, municipalities could be classified as nearby to chemical facilities (exposed) or far from such industries (non-exposed). Two analyses were then carried out:

a) A "near *vs.* far" analysis to estimate Relative Risks (RRs) for towns situated at ≤5 km from any chemical industry site, where the variable "exposure" was coded as: 1) unexposed area ("far") consisting of municipalities which had no known industrial sites at within 5 km of their municipal centroid. This last category was considered as the reference group or unexposed towns (far) n; 2) intermediate area, consisting of towns lying at or within a distance of 5 km from any non-chemical industrial installations; and 3) exposed or proximal area, consisting of towns lying at or within a distance of 5 km from any chemical industry installation (Fig. 1, A).
b) A stratified "near *vs.* far" analysis, stratified by the different categories of industrial chemical production already mentioned. The exposure variable for each of chemical sector category was coded as a "dummy" with the following three levels: 1) Unexposed group ("far"): towns with no industry within 5 km of their municipal centroid; this is also the reference group); 2) Intermediate group: towns at a distance ≤ 5 km from any industrial facilities but not including chemical manufacturing; and 3) exposed group ("near"): 3) Exposure group: those towns with a municipal centroid at distance ≤ 5 km from one or more chemical installations belonging to one of the types of chemical facility already identified (organic, inorganic, fertilizer, biocide, pharmaceutical or explosives/pyrotechnics facility) (Fig. 1, B).

Relative Risks (RRs) for cancer mortality and their 95% credible intervals (95% CrIs) for the exposed versus the unexposed groups were estimated using Poisson regression models, specifically Besag, York and Molliè's (BYM) (Besag et al., 1991) Bayesian conditional autoregressive model with explanatory variables. This approach has been already used and described in detail by previous studies from our group (Fernandez et al., 2012; García-Pérez et al., 2015c, 2016b). Briefly, in this model, the contiguity criterion was adjacency

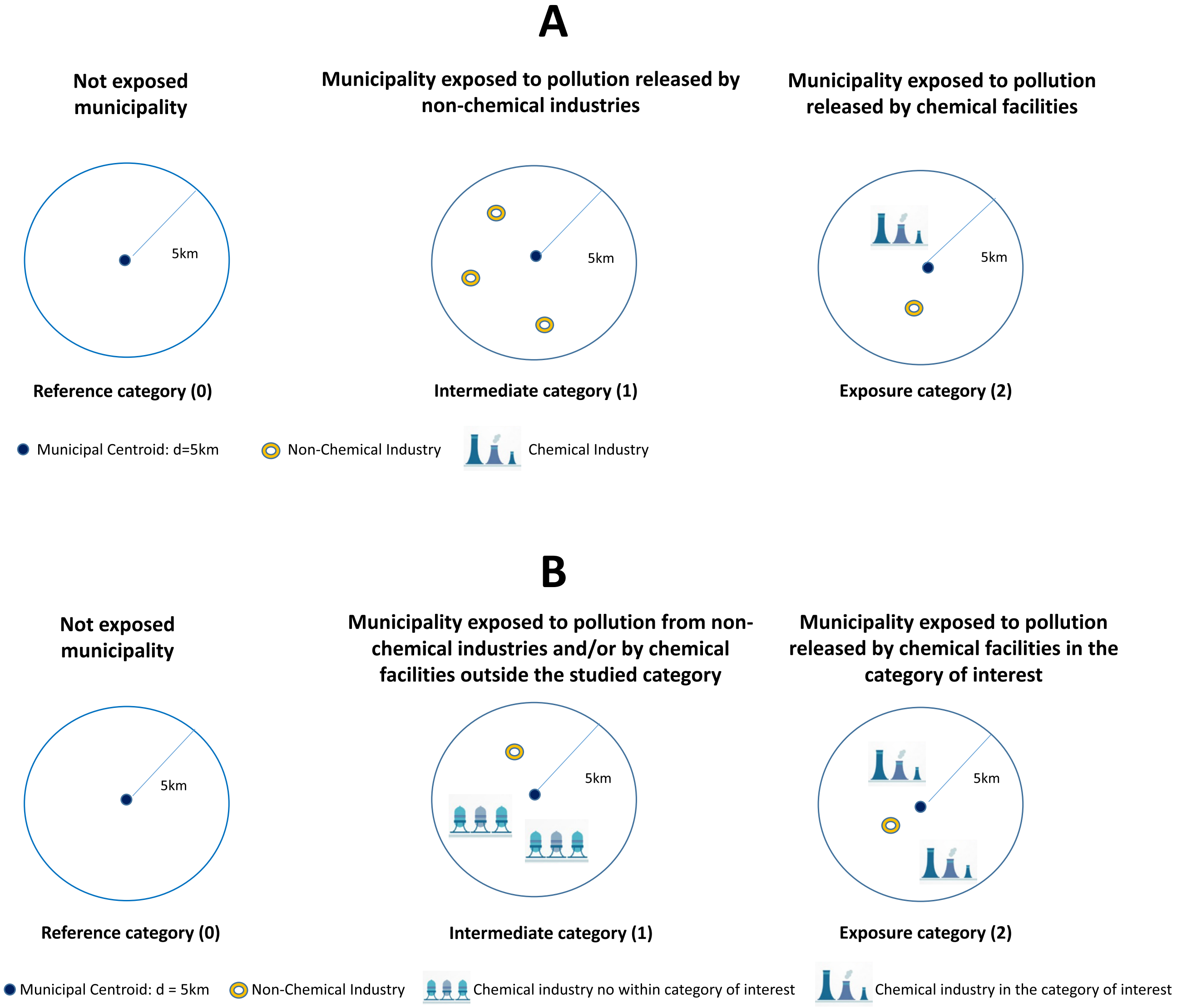

Fig. 1. Scheme followed for the definition of the exposure proxy at the municipal level according to distance to pollution source. A) Definition of the exposure to pollution released by any kind of chemical facility. B) Definition of the exposure to pollution released by a specific category of chemical facility.

to municipal boundaries; observed deaths were the dependent variable; and expected deaths the offset. All estimates were adjusted for the standardized socio-demographic indicators described above. Finally, INLAs were used as a Bayesian inference tool (Rue et al., 2009). To this end, we used the R-INLA package (Rue et al., 2016; Rue et al., 2009) with the option of “Simplified Laplace” estimation of the parameters; this package is available in the R Environment.

The results of these analyses showed evidence of increased risk in both men and women (suggesting an association with environmental exposure), so we performed the same analyses using Bayesian MCMC simulation methods (Gilks et al., 1995). In these cases, posterior distributions of the RRs were obtained using MCMC (Spiegelhalter et al., 2002). Convergence of the estimators was achieved before 400,000 iterations. We performed a “burn-in” of 100,000 iterations (iterations discarded to ensure convergence), as well as employing a thinning rate of 10. Finally, we only considered those results showing evidence an excess of risk in men and/or women using two Bayesian inference methodologies mentioned before (INLA and MCMC) for inclusion in the results and discussion sections. All analyses were performed with R software (Rue et al., 2009).

3. Results

3.1. Descriptive analysis of the chemical sector in Spain

Of the total number of chemical industry sites registered (n = 588), 77% (n = 457) had been in operation for over 10 years and 91% (n = 538) over a year. Of these, 60% were basic chemical transformation industries (organic and inorganic), 18% were explosives/pyrotechnics sites, 13% pharmaceutical products, 5% were fertilizer production sites, and 4% were phytosanitary and biocides industries (see Supplementary Material, Table 4).

Fig. 2 shows the geographical location of each chemical installation by industrial group. Significant levels of industrial density in the north, east, and south of the country can be seen; 73% of the chemical industries were concentrated in five autonomous communities: Catalonia, the Autonomous Community of Valencia, the Basque Country, the Autonomous Community of Aragón, and Andalusia (see Supplementary Material Fig. 1). Broken down by

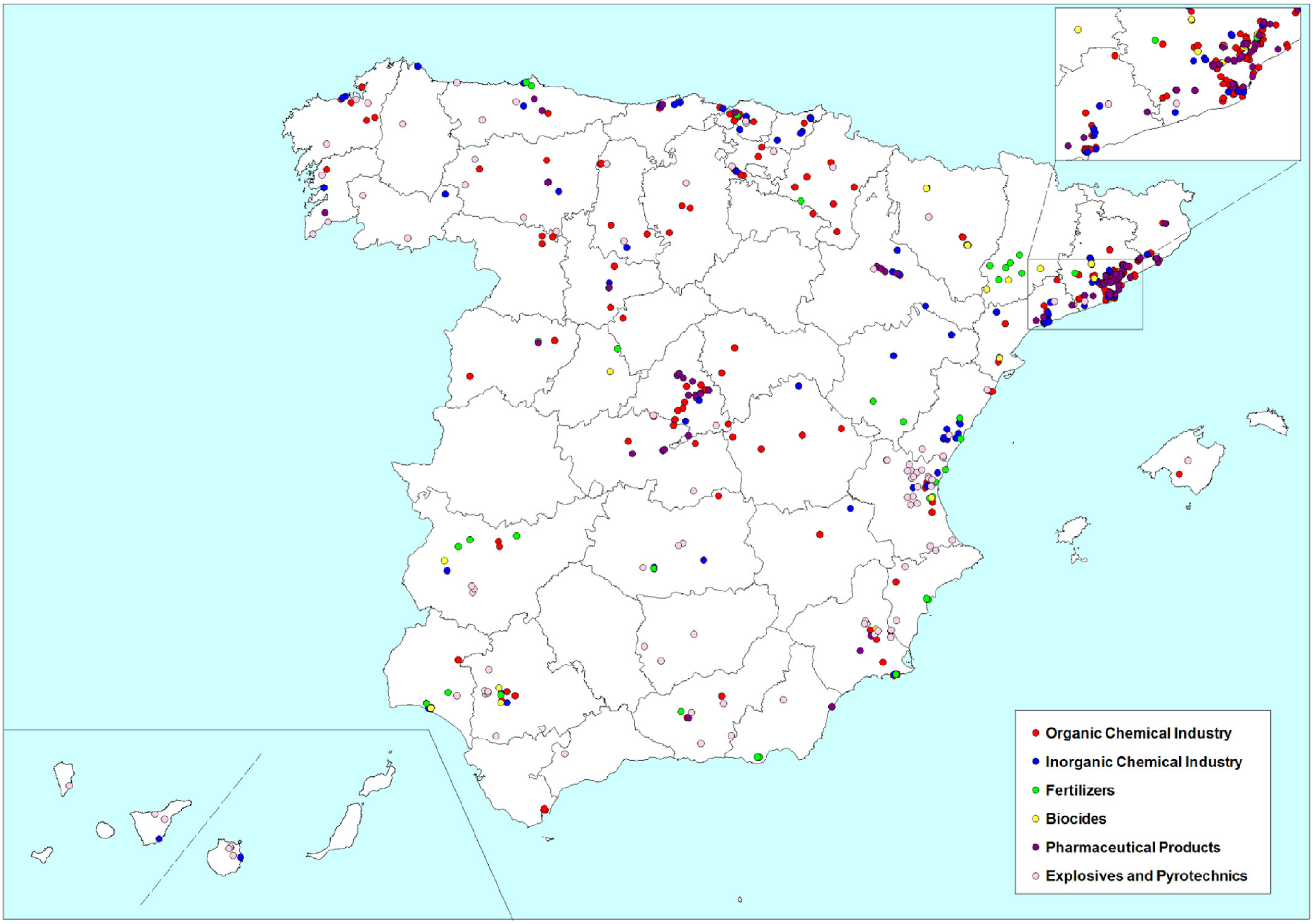

Fig. 2. Location of chemical facilities included in the study by category.

industrial group, we found that 70% of the general chemical industries (organic and inorganic) were located in the northeast of the Spain, 66% of the pharmaceutical industries in the east, and, finally, 70% of fertilizer industries and 50% of the explosives/pyrotechnics industries in the southeast of the country.

Table 1 shows that for the period 2007–2010, a total of 4768.42 tons of carcinogenic substances were released: 86% were released into the air; 8.5% to water indirectly; 5.5% to water directly; no emissions into the soil were recorded. By chemical industry categories, inorganic industries are made the greatest contribution to total emissions (42%), followed by organic (32%), fertilizers (18%) and pharmaceutical industries (4%) and explosives/pyrotechnic facilities (4%).

Focusing on exposure, there were 575 municipalities in Spain (7% of all municipalities) with at least one chemical facility at a distance of $\leq$5 km (213 were urban (37%), 184 were semi-urban (32%) and 178 were rurals (31%) (Table 5 in Supplementary Material). By chemical category 118 municipalities (1.5% of all municipalities) had at least one organic chemical industry installation in the municipality's vicinity, 79 (0.9%) had at least one inorganic industry, 33 (0.4%) had one or more industries producing fertilizers, 13 (0.2%) had at least one biocide industry, 32 (0.4%) had one or more pharmaceutical industry sites and 138 (1.7%) had at least one explosives/pyrotechnics industry installation, and finally 162 municipalities (2% of the total) had a combination of several types of chemical industry facilities (see Supplementary Material, Table 5).

Focusing on municipal areas studied, the mean area of the municipalities was 62.75 Km^2 (45.19 km^2 for rural municipalities, 96.34 km^2 for semi-urban municipalities and 145.04 km^2 for urban municipalities).

3.2. Associations between cancer mortality and chemical industry pollution

Table 2 shows the RRs and 95%Crl which registered statistically significant results for excess risk of cancer mortality for specific forms of cancer, in men and women and, for municipalities situated at $\leq$ 5 km from chemical installations, and by type of chemical group. These estimations were produced using spatial regression models.

Focusing first on statistically significant results using both Bayesian inference methodologies and for both, men and women, those municipalities situated next to (at $\leq$ 5 km) organic chemical installations had an excess of mortality risk for colorectal cancers (using INLA for both sexes = RR: 1.09; 95% Crl: 1.05–1.15), gallbladder (RR: 1.14; 95%Crl: 1.03–1.27), and ovarian cancers (RR: 1.10, 95%Crl: 1.02–1.20). Moreover, those towns situated at $\leq$ 5 km from explosives/pyrotechnics installations showed excess mortality risk for ovarian (INLA = RR: 1.11; 95%Crl: 1.01–1.21) and breast cancers (RR: 1.06; 95%Crl: 1–1.13). With regard to fertilizer industries, those municipalities situated $\leq$5 km from such facilities showed excess risk for pleural cancer mortality (INLA = RR: 2.27; 95%Crl: 1.49–3.41), which was the highest cancer mortality risk observed by the study. Finally, municipalities situated at $\leq$ 5 km from

Table 1
Chemical industries Group 1-IARC carcinogen emissions (kg) to air and water during the period 2007–2010. Carcinogens included in the discussion section are marked in bold.

Industrial category	Number of facilities	Carcinogen Issued	Air Emissions	Direct Water Emissions	Indirect Water Emissions	Soil Emissions
Production of Organic Chemicals	194	Arsenic and compounds, **Benzene**, **Cadmium** and compounds, **Chromium** and compounds, Ethylene oxide, Lindane, **Nickel** and compounds. Particulate matter (PM_{10}), PCDD & PCDF (dioxins & furans), Phosphorus total, Polychlorinated biphenyls (PCBs), **Polycyclic Aromatic Hydrocarbons (PAHs)**, Trichloroethylene, Vinyl Chloride	1275420	158044	91916	0
Production of Inorganic Chemicals	77	Arsenic and compounds, **Benzene**, **Cadmium** and compounds, **Chromium** and compounds, **Nickel** and compounds, Particulates matter (PM_{10}), PCDD & PCDF (dioxins & furans), Phosphorus total, Polychlorinated biphenyls,(PCBs), **Polycyclic Aromatic Hydrocarbons (PAHs)**, Trichloroethylene	1944983	18145	1206	0
Production of phosphorus-based nitrogen or potassium- based fertilizers	25	Arsenic and compounds, **Benzene**, **Cadmium** and compounds, **Chromium** and compounds, **Nickel** and compounds, Particulates matter (PM_{10}), PCDD & PCDF (dioxins & furans), Phosphorus total, **Polycyclic Aromatic Hydrocarbons (PAHs)**	864799	11252	1439	
Production of Plant protection products or Biocides	19	Chromium and compounds, **Nickel** and compounds, Particulates matter (PM_{10}), Phosphorus total	10092	0	1094	0
Producers of pharmaceutical products	61	Arsenic and compounds, **Benzene**, **Cadmium** and compounds, **Chromium** and compounds, **Nickel** and compounds, Particulates matter (PM_{10}), Phosphorus total, **Polycyclic Aromatic Hydrocarbons (PAHs)**, Trichloroethylene	56306	15950	108283	0
Manufacturers of explosives/ pyrotechnic products	81	Arsenic and compounds, **Benzene**, **Cadmium** and compounds, **Chromium** and compounds, Ethylene oxide, Lindane, **Nickel** and compounds. Particulates matter (PM_{10}), PCDDs & PCDFs (dioxins & furans), Phosphorus total, **Polychlorinated Aromatic Hydrocarbons (PAHs)**, Trichloroethylene, Vinyl Chloride	4487	61	204944	0

inorganic chemical installations showed excess risk for breast cancer (using INLA = RR: 1.10; 95%Crl: 1.03–1.18).

There are some statistically significant associations (RRs and 95%Crls) identified using INLA that were not found using MCMC: a) Organic chemical facilities were associated with excess stomach cancer risk in both men (RR: 1.18; 95%Crl: 1.08–1.28) and women (RR: 1.07; 95%Crl: 0.97–1.17) b) pharmaceutical installations with kidney cancer in men (RR: 1.19; 95%Crl: 1.00–1.40) and women (RR: 1.21; 95%Crl: 0.97–1.48); and with ovarian cancer (RR:1.12; 95%Crl: 0.98–1.28). However, the risks obtained by using INLA and MCMC were very similar, which gives greater credence to the environmental hypothesis; this hypothesis states that the presence of a chemical industry installation near to a municipality will imply an excess of mortality risk related to the tumors mentioned above. The results of the full analyses using INLA are shown in Table 6 of the Supplementary Material. In this table the significant and the marginal associations (those with a value of 0.99 in the lower limit of the 95% credible interval) are marked in bold. Moreover, there are some statistically significant associations (RRs and 95%Crls) only in men (see Table 7 of the Supplementary Material) in digestive tumors (stomach, gallbladder, pancreas, bladder…), respiratory cancers (lung, pleura), blood cancers (Hodgkin's Lymphoma, leukaemia,…) and others (skin, other central nervous system,…). And there are some statistically significant associations (RRs and 95%Crls) only in women (see Table 8 of the Supplementary Material) where it is worth noting the association between the fertilizer industries and bones cancer, melanoma and kidney cancer with inorganic industries and brain cancer and organic industries.

4. Discussion

Our results suggest that there is an excess risk of cancer mortality for some specific cancers for people living in municipalities near to of certain types of chemical installations in Spain. The majority of these installations are located in the north, east, and south of the country, and two-thirds of the total carcinogenic emissions released into the air by the sector come from organic and inorganic chemical facilities. The results by chemical category showed an increase in risk for colorectal and gallbladder cancer mortality for both men and women; and for ovarian cancer mortality in the vicinity of organic chemical installations; an excess of ovarian and breast cancer mortality in the vicinity of explosives/pyrotechnics installations; an excess of pleural cancer mortality in the vicinity of fertilizer industries; and an excess of breast cancer mortality in women in the vicinity of inorganic chemical installations.

There were other associations which are only significant using Laplace approximation: organic chemical facilities and stomach cancer; pharmaceutical installations and kidney and ovarian cancers. There were also other significant results for only men or women. These specific results have not been discussed in this article because they have not been (re)validated with the MCMC Bayesian approach, or because they may point to a possible occupational exposure instead of an environmental one.

With regard to proximity to organic chemical facilities, as noted above, there was evidence of excess risk for colorectal and gallbladder cancer mortality in both men and women, and for ovarian cancer mortality. Most evidence about the association between colorectal cancer mortality and exposure to pollution released by organic chemical facilities has come from occupational studies. For example, higher mortality for rectal cancer among workers of a petrochemical research facility has been found, but plastic and rubber production industries showed only statistically borderline results (Oddone et al., 2014). There are also longitudinal and case-control studies which have found evidence of association between exposure to chemical compounds such as nickel (Lightfoot et al., 2017), benzene (Goldberg et al., 2001), polycyclic aromatic hydrocarbons (Lynge et al., 1997) and toluene (López-Abente et al., 2012) and colorectal cancer in chemical industry workers. On the other hand, there are also ecological studies which suggest that environmental exposure to industrial emissions could be associated with colorectal cancer (Lopez-Abente et al., 2012, 2006). Specifically for the organic chemical industry, one study found no evidence of associations in Spain (Lopez-Abente et al., 2012). In this study, the exposure was estimated in a very similar way to the present study; however, there were some differences: the data

Table 2
Relative risks (RRs) and 95% credible intervals (95%CrI) for excess mortality from colorectal, gallbladder, pleural, ovarian and breast cancers in municipalities situated at ≤5 km from chemical installations using spatial regression models, by chemical industry category group and by the two Bayesian inference methods employed, Integrated Nested Laplace Approximations (INLA) and Markov Chain Monte Carlo Method (MCMC).

	Chemical Industry Categories		BOTH					MEN					WOMEN				
				INLA		MCMC			INLA		MCMC			INLA		MCMC	
		N[a]	Obs[b]	RR	95%Crl	RR	95%Crl	Obs[b]	RR	95%Crl	RR	95%Crl	Obs[b]	RR	95%Crl	RR	95% Crl
Colorectal	**All**	575	125797	1.08	1.04–1.11	1.05	1.02–1.08	71811	1.09	1.05–1.13	1.06	1.03–1.10	53986	1.06	1.03–1.10	1.05	1.01–1.09
	Organics	118	17640	1.09	1.05–1.15	1.06	1.02–1.11	9871	1.11	1.05–1.18	1.07	1.02–1.13	7769	1.08	1.02–1.14	1.05	1.00–1.12
	Inorganics	79	5098	1.08	1.02–1.14	1.06	1.00–1.12	2892	1.06	0.99–1.13	1.03	0.96–1.10	2206	1.12	1.05–1.20	1.10	1.02–1.17
	Fertilizers	33	1978	1.08	0.99–1.18	1.06	0.98–1.15	1122	1.13	1.02–1.25	1.10	1.00–1.21	856	1.04	0.94–1.15	1.02	0.93–1.13
	Biocides	13	337	0.98	0.86–1.13	0.96	0.84–1.10	199	1.03	0.86–1.21	0.99	0.84–1.18	138	0.94	0.78–1.13	0.91	0.76–1.10
	Pharmaceuticals	32	2285	1.06	0.98–1.15	1.03	0.96–1.11	1365	1.10	1.00–1.21	1.06	0.97–1.16	920	1.03	0.94–1.13	1.00	0.91–1.10
	Explosives/Pyrot	138	6326	1.05	1.00–1.10	1.05	1.01–1.11	3541	1.08	1.02–1.15	1.08	1.02–1.15	2785	1.04	0.98–1.10	1.03	0.97–1.10
Gallbladder	**All**	575	13170	1.10	1.02–1.18	1.08	1.01–1.17	4738	1.25	1.13–1.39	1.22	1.09–1.37	8432	1.02	0.94–1.11	1.01	0.93–1.11
	Organics	118	1816	1.14	1.03–1.27	1.11	1.00–1.24	629	1.20	1.03–1.40	1.16	1.00–1.35	1187	1.13	1.00–1.27	1.11	1.00–1.25
	Inorganics	79	448	0.98	0.86–1.13	0.97	0.84–1.11	168	1.12	0.92–1.37	1.08	0.89–1.33	280	0.89	0.75–1.05	0.88	0.75–1.04
	Fertilizers	33	199	1.12	0.92–1.36	1.09	0.91–1.32	81	1.38	1.05–1.81	1.35	1.04–1.76	118	0.98	0.77–1.23	0.96	0.76–1.21
	Biocides	13	35	1.08	0.74–1.54	1.05	0.73–1.52	11	1.02	0.53–1.81	0.95	0.50–1.78	24	1.09	0.69–1.66	1.06	0.68–1.66
	Pharmaceuticals	32	213	1.18	1.00–1.41	1.14	0.95–1.36	93	1.46	1.14–1.87	1.40	1.09–1.80	120	1.00	0.80–1.26	0.98	0.79–1.23
	Explosives/Pyrot	138	634	1.05	0.93–1.19	1.06	0.95–1.20	231	1.19	1.00–1.42	1.19	1.00–1.42	403	0.98	0.86–1.14	0.99	0.86–1.15
Pleura	**All**	575	2331	1.43	1.19–1.71	1.36	1.12–1.66	1648	1.49	1.21–1.85	1.40	1.11–1.78	683	1.31	1.00–1.73	1.34	0.99–1.84
	Organics	118	362	1.42	1.10–1.82	1.29	1.02–1.64	257	1.52	1.14–2.04	1.35	1.02–1.78	105	1.24	0.86–1.78	1.25	0.87–1.80
	Inorganics	79	130	1.59	1.18–2.13	1.49	1.13–1.99	97	1.56	1.10–2.20	1.47	1.05–2.06	33	1.38	0.87–2.17	1.39	0.89–2.20
	Fertilizers	33	64	2.27	1.49–3.41	2.16	1.46–3.19	48	2.45	1.51–3.94	2.28	1.45–3.60	16	1.95	1.04–3.53	1.92	1.04–3.59
	Biocides	13	4	0.77	0.25–2.01	0.66	0.22–2.02	3	0.85	0.23–2.52	0.68	0.18–2.50	1	0.61	0.06–3.40	0.36	0.03–4.73
	Pharmaceuticals	32	46	1.32	0.87–1.97	1.19	0.80–1.78	29	1.21	0.73–1.97	1.05	0.64–1.73	17	1.47	0.81–2.56	1.45	0.80–2.60
	Explosives/Pyrot.	138	111	1.05	0.75–1.44	1.12	0.83–1.52	77	1.10	0.75–1.59	1.16	0.81–1.67	34	1.18	0.73–1.86	1.21	0.77–1.92
Ovary	**All**	575											18830	1.10	1.04–1.16	1.09	1.04–1.16
	Organics	118											2659	1.10	1.02–1.20	1.10	1.02–1.20
	Inorganics	79											729	1.05	0.95–1.16	1.03	0.92–1.14
	Fertilizers	33											296	1.14	0.98–1.32	1.12	0.97–1.30
	Biocides	13											45	0,90	0.65–1.21	0.86	0.63–1.18
	Pharmaceuticals	32											349	1.12	1.00–1.28	1.09	0.96–1.26
	Explosives/Pyrot.	138											993	1.11	1.01–1.22	1.10	1.01–1.21
Breast	**All**	575											58325	1.02	1.00–1.06	1.02	1.00–1.06
	Organics	118											8238	0.97	0.91–1.02	0.97	0.92–1.03
	Inorganics	79											2560	1.10	1.03–1.18	1.09	1.03–1.17
	Fertilizers	33											899	1.04	0.93–1.15	1.04	0.94–1.15
	Biocides	13											171	0.91	0.77–1.09	0.91	0.76–1.09
	Pharmaceuticals	32											1031	1.00	0.92–1.10	1.00	0.92–1.10
	Explosives/Pyrot.	138											3114	1.06	1.00–1.13	1.06	1.00–1.13

[a] N = Number of towns situated ≤5 km from at least one chemical industry.
[b] Obs = Observed deaths.

used was for 1997–2006 and the distance selected was 2 km instead of 5 km. If we look at the RRs across a number of distances (see Supplementary Material, Fig. 3), the risk observed for colorectal cancer within a 2 km radius is similar to that previously reported by Lopez-Abente et al. (Lopez-Abente et al., 2012). Therefore, had a greater distance been selected by those researchers, similar RRs to the present study might have been detected.

Another noteworthy result, is the significant excess of gallbladder cancer mortality risk associated with proximity to organic chemical installations. There is evidence of associations between exposure to some of the pollutants released (methylene chloride, heavy metals like cadmium, chromium, nickel, cooper, and lead) by this kind of facility and gallbladder cancer (García-Pérez et al., 2016a; Lignell et al., 2013; Shah et al., 2015). Furthermore, several attempts have been made to study the effects of environmental pollutants on this particular cancer (Pandey, 2006). However, as Pandey explained in his study there is as yet no robust data to support this hypothesis. Consequently, new studies are needed with greater capacities to make causal inferences.

For ovarian cancer in municipalities in the proximity of organic chemical installations or explosives/pyrotechnics installations, previous studies have associations between higher mortality risk from this type of cancer and residential proximity to these kinds of installations (García-Pérez et al., 2015b). Specifically in Spain, a study with a similar methodological approach found an excess of risk for ovarian cancer mortality in the vicinity (≤5 km) of organic chemical installations (RR: 1.08; 95%CrI: 1.01–1.16) which is quite similar to our own estimations (RR: 1.10; 95%CrI: 1.02–1.20) (García-Pérez et al., 2015b). However, the excesses of mortality reported by García-Pérez et al. with inorganic, fertilizer, and pharmaceutical installations were not fully confirmed by our study, although the RRs found in that study were quite similar to ours. The possible reasons for this could be related to the different periods of time used to assess mortality, the inclusion of new selection criteria for significant results (MCMC Bayesian confirmation) and the selection of the facilities included in the analysis in accordance with the induction period for solid tumors (see material and methods section).

Our results also show significant excess risk of pleural cancer mortality associated with proximity to fertilizer industries (RR: 1.43; 95%CrI: 1.19–1.71)). López-Abente et al. did not specifically study fertilizer industries but found statistically significant mortality risk for pleural cancer among both men and women associated with a number of industries; in particular, they indicated that the results suggested there was potential airborne environmental exposure in the proximity (2 km) of biocide and organic chemical facilities (López-Abente et al., 2012). These results have not been replicated in our study. This may be due to the different distance selected as a proxy for exposure, and the different criteria adopted to select significant results. To the best of our knowledge, no previous study has assessed the potential relationship between the fertilizer industry and pleural cancer, although there is some evidence for associations with leukaemia and lung cancers (Pesatori et al., 2003). Moreover, the risk of ecological fallacy for this result with pleural cancer appears to be very high; consequently, the result should be considered with great caution. This is because a) the main known risk factor for pleural cancer is asbestos exposure (not released or produced by fertilizer installations); b) the spatial distribution of the fertilizer industry is not homogeneous (Supplementary material, Fig. 2) and c) they are mostly located in the areas which have high pleural cancer mortality in Spain (López-Abente et al., 2006).

A significant excess of risk for breast cancer mortality was found associated with explosives/pyrotechnics facilities and inorganic chemical installations. Evidence of an association between exposure to industrial pollution and breast cancer is scarce. There are some studies that show weak associations, or associations which border on the limit of statistical significance, for breast cancer and proximity to some kinds of industrial installations (steel mills, pulp mills, petroleum refineries, thermal power plants, chemical industry installations) (García-Pérez et al., 2018, 2016b; Lewis-Michl et al., 1996; Pan et al., 2011) which only partially support our results. As a result, these excesses of risk identified should be interpreted with caution.

In our study, one aspect to be borne in mind is that we have shown and discussed in the main manuscript text the statistically significant excess risks in men and women, which might be indicative of a pathway of environmental exposure. However, some tumors of our study (e.g., stomach, pleura and gallbladder) the significant excess risks solely affected men or women, being indicative of a possible occupational-exposure pathway (assuming that worker's residence was homogenously distributed) or other synergic effects as for example the possible interaction between chemical industry exposure and consumption of meat in men (Aune et al., 2009; González et al., 2006; Linseisen et al., 2002; Sotos Prieto et al., 2011).

There are some relevant aspects for the interpretation of the results that are worth highlighting, some of them related to assumptions made in this work. First of all, we assumed that the whole municipal population was exposed to the same type and amount of pollutant substances. Nevertheless, the use of small areas as units reduces the risks of ecologic bias and misclassification stemming from these assumptions. Second, the statistical significance does not imply a causal relationship due to the study design. Third, the current industrial facilities are probably not comparable to the old ones at many levels. Thus, it is important to take into account the induction period of the exposure to the pollutants emitted by the facilities to ensure that they may have been involved in the generation of cancer. Years of activity, was used as a criterion for the inclusion of industries. And the exposure time is also very important to determine a causal effect. For this reason, the beginning years of the industrial facility activities were taken into account. On the other hand, the exposure dose (for example, the amount of emission released) has not been taken into account. And of course, the ecological fallacy is present in our study because there is not any information about individual exposure to possible agents that cause the diseases assessed.

This study has a number of limitations, some of which are related to the kind of study design that should be taken into account in the interpretation of the results. To highlight some key points, it is worth mentioning: a) the use of mortality rather than incidence (especially for the study of non-lethal tumors). b) The use of the distance to the pollution source as a proxy for exposure, which assumes an isotropic model (introducing a misclassification problem) in addition to the use of centroids as coordinates for pinpointing the entire population of a town. There are other methodologies for exposure evaluation based in dispersion models; however, we do not have the information needed for applying these models like meteorological data. c) A further possible bias lies in the use of centroids as coordinates for pinpointing the entire population of a town, when, in reality, the population may be fairly widely dispersed. d) We did not take into account the number of employees living near the industries since we did not have any information about this number. e) We did not assess the actual amount of emissions from a given facility. f) Many comparisons are made and the probability of false positives increases (positive relationships found that are really not). However, the number of statistically significant excess risks in the whole study is much higher than the number we would expect to find at random and although there are mathematical methods to control this problem of multiple comparisons, they have not been developed in the context of the Bayesian models performed. g) The risk selection criteria to detect association with environmental exposure (increased risk in both men and women) could be giving a partial picture of the real associations.

There were also some uncontrolled confounding variables that may have affected the results (tobacco consumption, solar UVB irradiance, and exposure to traffic are the most obvious). In that way, we have tried to assess the relevance of solar UVB irradiance, given the ease of incorporating a good proxy of it (latitude (Cardoso et al., 2017) and also altitude) in the models performed and that the main results point to cancers associated in the literature (Grant, 2007) with levels of Vitamin D that is influenced by environmental factors such as UVB radiation available. Specifically literature show that the cutaneous synthesis of vitamin D is influenced by UVB radiation available, which is a function of the solar zenith angle that varies with latitude (as latitude increase, potential to synthesize vitamin D decreases), season and time of day, as well as other individual factors such as age, skin pigmentation and sun exposure behaviours (Cardoso et al., 2017). Relative Risks (RRs) for cancer mortality and their 95% credible intervals (95% CrIs) for the exposed versus the unexposed groups were estimated using the same spatial regression models described before, also including the altitude (meters) and the latitude (decimal degrees) of the municipalities (see results in Table 9 of Supplementary Material). According with these new analyses, there is no great variation in risk estimators for the main results of the study. However, it should be noted that in general there is a decreasing in the relative risks of association between industry and cancer mortality, therefore, latitude seems to explain a part of the mortality of the cancers studied. Moreover, it should be also noted that there is about 3% variation in the relative risk of colorectal cancer mortality associated with the organic chemical industry (RR: 1.063; 95%CrI: 1.016–1.113, in both sexes) and the association between gallbladder and the organic chemical industry in women is not significant (RR: 1.095; 95%CrI: 0.967–1.240). All these findings are supported by a previous study, where the mortality rates of the cancers analyzed correlated with latitude.

But we must be careful to interpret what this means in terms of exposure. Although, as already explained, latitude is a good proxy for exposure to solar radiation and therefore can partly explain the levels of vitamin D in the population, in Spain, latitude is associated with diet patterns, and other behaviors that could contribute to explain the mortality rates.

All these limitations and others mentioned makes the statistical significance of any findings somewhat limited (Fernández-Navarro et al., 2017).

Despite all these limitations, care was taken with the study design to avoid confounding as much as realistically possible. As with previous studies of this type (Fernández-Navarro et al., 2017), we included only those facilities, which had been active since a specific year in order to take the induction periods of the cancers being studied into account. Evidently, we also included available confounders in the statistical models (municipal population size, illiteracy rates, farmer rates; unemployment rates, average number of persons per household and average income for each municipality) and assessed the RR at several distances – both of which should have limited the possibility of the results being due to random error. And it is important to stress that ecological studies using PRTRs are a useful tool, not only for proposing etiological hypotheses about the risk entailed in living close to industrial pollutant sources, but also for providing data to account for situations of higher mortality in specific areas.

5. Conclusion

The results suggest that environmental exposure to pollution released by some types of chemical facilities could be associated with increased cancer mortality risk. Of the associations found, the most plausible appears to be that observed between colorectal and ovarian cancers and the organic chemical industry, and breast cancer and the inorganic chemical industry. Other results, which suggest associations between gallbladder cancer and organic chemical installations or explosives/pyrotechnics installations, and pleural cancer and fertilizer industries, should be taken with more caution. In order to confirm these results, it would be of great interest to analyze cancer incidence, which was not included in this study, or carry out local studies where the individual information of people is collected (diet, occupational behaviors, etc.) or use other methodologies for exposure evaluation that include meteorological and orographic data.

Declaration of competing interest

The authors declare that they have no conflicts of interest. This article presents independent research. The views expressed are those of the authors and not necessarily those of the Carlos III Institute of Health.

CRediT authorship contribution statement

Ana Ayuso-Álvarez: Conceptualization, Formal analysis, Writing - original draft, Writing - review & editing. **Javier García-Pérez:** Visualization, Data curation, Writing - review & editing. **José-Matías Triviño-Juárez:** Writing - review & editing. **Unai Larrinaga-Torrontegui:** Writing - review & editing. **Mario González-Sánchez:** Data curation. **Rebeca Ramis:** Data curation, Writing - review & editing. **Elena Boldo:** Data curation, Writing - review & editing. **Gonzalo López-Abente:** Data curation, Writing - review & editing. **Iñaki Galán:** Conceptualization, Writing - review & editing. **Pablo Fernández-Navarro:** Conceptualization, Data curation, Formal analysis, Writing - original draft, Writing - review & editing.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envpol.2019.113869.

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