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TITLE: Adverse birth outcomes in the vicinity of industrial installations in Spain 2004-2008.

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ABSTRACT

Background: Industrial activity is one the main sources of ambient pollution in developed countries. However, research analyzing the effect of industrial pollution on birth outcomes is scarce. **Objective:** To analyze the association between proximity of mother's municipality of residence to industries and risk of Very Preterm Birth (VPTB), Moderate Preterm Birth (MPTB), Very Low Birth Weight (VLBW), Moderate Low Birth Weight (MLBW) and Small for Gestational Age (SGA) in Spain during the period 2004-2008. **Methods**: Ecological Study. A "near vs. far" analysis was carried out to explore the association between residential proximity (≤3.5 km) to industries from 24 different activity groups and risk of adverse birth outcomes by means of Hierarchical Bayesian models allowing spatial correlation implemented via Integrated Nested Laplace Approximation (INLA). **Results:** VPTB risk was estimated to be 10% higher for mothers living near pharmaceutical companies. Proximity to galvanization and hazardous waste management industries increased the estimated risk of MPTB by 10% and 8% respectively. Estimated risk of VLBW was 9%, 13% and 15% higher for mothers with residence near pharmaceutical and non-hazardous or animal waste management industries respectively. For MLBW many associations were found, being notable the proximity to mining, biocides and animal waste management plants. Associations for SGA were weaker, with estimated effects associated with proximity to management animal waste plants as the strongest. **Conclusions:** Our results highlight the importance of further research on the effects of proximity to industrial sites in birth outcomes especially for the case of pharmaceutical and animal waste management activities.

Key Words: preterm; birth weight; gestational age; industrial pollution; INLA; Besag, York and Mollié.

Abbreviations Used:

BYM: Besag, York and Mollié.

ccd: Central composite design

CrI: Credible interval

INE: Spanish national institute for statistics

INLA: Integrated nested Laplace approximation

IPPC: Prevention and integrated pollution control

LBW: Low birth weight (<2500 grams)

MAGRAMA: Spanish ministry for agriculture, food and environment

MLBW: moderate low birth weight (1500-2499 grams)

MPTB: Moderate preterm birth (33-36 weeks)

PTB: Preterm birth (≤36 weeks)

RR: Risk ratio

SGA: Small for gestational age (birth weight below the 10th percentile for local babies of the same gender and gestational age).

SIGPAC: Spanish farm plot geographic information system

VLBW: Very low birth weight (<1500 grams)

VPTB: Very preterm birth (≤32 weeks)

HIGHLIGHTS

- Innovative Integrated Nested Laplace Approximation used for fitting BYM mod els
- Proximity to chemical, pharm and waste industries increase RR of numerous outcomes
- Proximity to animal waste industries showed increased risk of all outcomes
- Proximity to industry showed bigger effect on birth weight than on gestational age
- No associations found for refineries and coke ovens, metallurgical or shipyards
- No associations found for ceramic, fertilizers or textile industries

INTRODUCTION

The prenatal period encompasses the most rapid and most important phase of human development. Poor intrauterine growth is an important predictor of survival and morbidity in childhood and can also result in negative impacts on adult health (Lawn, Cousens et al. 2005; Varvarigou 2010; Calkins and Devaskar 2011). Prenatal development appears to proceed largely under instruction and direction of individuals' genes but this does not mean that it is immune to external influences. Indeed, numerous studies have demonstrated a high risk of abnormal fetal development and adverse birth outcomes associated with unfavorable socio-economic conditions, mothers' life-style and health status (McCowan and Horgan 2009; Blumenshine, Egerter et al. 2010; Shah 2010). However, although etiologic research has focused mainly on these proximate risk factors, individual characteristics and behaviors, it seems that individual-level factors have only been able to partially explain poor birth outcomes in some populations.

In recent years, many epidemiologists have pointed out the neglected importance of environment as a major contributor to reproductive risk. Humans are exposed to environmental pollution at home, in the workplace, or in the community via contaminated soil, air, water or food. Pregnant women and developing fetuses are particularly vulnerable to the adverse impact of environmental aggressions (Miranda, Maxson et al. 2009; Shah and Balkhair 2011).

One of the main sources of pollution is industrial activity and related potential health effects are of a growing concern. Research studies exploring the association between residential exposure to industrial pollution and adverse birth outcomes have appeared regularly in the reproductive epidemiology literature. However, there is not a general agreement about results with some studies suggesting possible associations between proximity to industrial installations and adverse birth outcomes (Elliott, Briggs et al. 2001; Yang, Cheng et al. 2002; Mohorovic 2004; Tsai, Yu et al. 2004; Brender, Maantay et al. 2011) and others dismissing such association (Bhopal, Tate et al. 1999; Parker, Mendola et al. 2008; Brender, Maantay et al. 2011). The large variability across studies in design, exposure assessment methods and type of industrial activities considered, limits the strength of the evidence found, emphasizing the need for a systematic, thorough examination of potential impacts of proximity to industrial sites across categories of industries.

In Spain, assessment of the effect of environmental pollution on health is of increasing interest. However, research has mainly focused on its effects on mortality and cancer, especially in the case of industrial pollution (Garcia-Perez, Pollan et al. 2009; Ramis, Vidal et al. 2009; Garcia-Perez, Lopez-Cima et al. 2010), and only recently has attention turned to assessment of potential effects on reproductive health (Fernandez, Sunyer et al. 2007). Important results regarding exposure to certain pollutants and its effects on length of gestation and birth size had already been published (Ballester, Estarlich et al. 2010; Llop, Ballester et al. 2010). However, the number of pollutants explored and the number of geographical areas considered is still limited leaving many potential harmful exposures and high risk areas unexplored.

Since 2007, the regulatory framework of Prevention and Integrated Pollution Control (IPPC 2002) requires inscription of all industries with potential pollutant activities to legally operate in Spain, providing a comprehensive registration of such sites. The existence of this source of information allows linkage of industrial pollution with births and population data, opening a new door for research in this area.

The objective of this study was to ascertain whether any excess risk of having a very or moderate preterm delivery, a newborn with very or moderate low weight or a small for gestational age baby was present among the women residing near industrial facilities of various types.

MATERIAL AND METHODS

We designed an ecological study using municipalities as the units of observation, based on links between data from birth and industry registries as detailed below.

1. Data Sources

1.1 Birth data

The Spanish National Institute for Statistics (INE 2011) provided us with a database containing all single live births registered in the country between 2004 and 2008. Data in this registry meet a documented high standard of reliability (Rio, Castello et al. 2010). Individual socio-demographic and sanitary information included: maternal age at birth (<20 years; 20-35 years; >=35 years), mother's country of origin (Spain; immigrants from low income countries; immigrants from medium-high income countries. See Supplemental Material, Table 1 for description of groups), maternal educational level (completed primary school or higher education; illiterate or did not complete primary school), mother's profession (non-manual labor; manual labor; not working; and not classified) and municipality of maternal residence (at time of birth); sex, gestational age (weeks, determined by last menstrual period and confirmed using ultrasound) and birth weight (grams) of the newborns.

Using data on sex, gestational age and birth weight of all live singleton births, we defined the following adverse birth outcomes of interest: very preterm birth (VPTB: <33 weeks of gestation); moderate preterm birth (MPTB: 33-36 weeks of gestation); very low birthweight (VLBW: <1,500 grams); moderate low birth weight (MLBW: 1,500-2,499 grams); small for gestational age (SGA: Birth weight below the national 10^{th} percentile for babies of the same gender and gestational age).

1.2 Census and municipal register data

INE publishes yearly information about population size for all Spanish municipalities (INE 2011). These data were used to calculate a unique population size for each municipality as an average of the population size between 2003 and 2008. Population size was afterwards classified in 3 categories: <2,000, 2,000-10,000 and ≥10,000 inhabitants.

From the 2001 INE census we obtained and included in the analyses the following socio demographic characteristics of the municipalities: habitability index (0-100), unemployment rate, socioeconomic level (0-3), percentage of single parent families and number of vehicles per household. More information about these variables is available at the INE webpage (INE 2001, see Supplemental Material, Table 2 for more detailed description).

1.3 Industrial pollution exposure data

Mothers' exposure to industrial pollution was estimated by taking the distance from the centroid of municipality of residence to the pollution source (using a purpose-designed distance matrix between all industrial installations and municipalities). Data on industries for 2007 included in the IPPC were provided by the Spanish Ministry for Agriculture, Food and Environment (MAGRAMA 2007). It contained geographical coordinates and industrial activity groups of the 2458 industries legally operating in Spain releasing pollution to the air (see Supplemental Material, Table 2 for description). Activity groups with less than 5 installations and the intensive rearing of poultry or pigs were excluded.

Geographic coordinates of industrial facilities' location recorded in the MAGRAMA database were validated by carrying out a thorough revision of industrial localizations using Google Earth (with aerial images and the Street View application), the Spanish Farm Plot Geographic Information System – SIGPAC (MAGRAMA 2007) (which includes orthophotos of the entire surface of Spanish territory, along with topographic maps showing the names of the industries, industrial estates, roads, buildings and streets), the GoogleMaps server (Google 2011) (which allows for a search of address and companies, and offers high-quality aerial photographs), Yellow Pages web page (Páginas Amarillas 2011) (which allows for a search of addresses and companies), Internet aerial photographs, and the websites of the industries themselves, to ensure that localization of the industrial facility was exactly positioned (Garcia-Perez, Boldo et al. 2008).

1.4 Municipal coordinates and maps

The geospatial vector data (shape-files) of municipalities were obtained from the 2004 version of Spanish Vital Statistics cartography. Municipality administrative centroids were defined as the town administrative center. Given the irregularity in the size and shape of Spanish municipalities, adjacencies were defined by neighboring municipalities sharing a boundary.

Modification of the 2004 municipal INE maps, assignation of municipality administrative centroids and definition of adjacencies was carried out with the same protocol as that for industry location in order to have comparably accurate geographical information.

2. Database Transformation

Datasets of births, population size and population and housing census data, were aggregated at a municipal level and combined into one database with information for the 8098 Spanish municipalities on: number of live births with complete information on gestational age (VPTB and MPTB rates denominator), number of live births with complete information on birth weight (VLBW and MLBW rates denominator), number of live births with complete information on weight and gestational age (SGA rate denominator), and number of VPTB, MPTB, VLBW, MLBW and SGA births, proportion of adolescent mothers (maternal age <20 years), proportion of mature mothers (maternal age ≥35 years), proportion of immigrant mothers from low income countries, proportion of illiterate mothers or without primary school education completed, proportion of mothers developing manual work, population size (<2,000 (rural zone); 2,000-

10,000 (semi-urban zone); ≥10,000 inhabitants (urban zone)), habitability index, unemployment rate, socioeconomic index, proportion of single parent families and mean number of vehicles per household.

3. Analysis

Characteristics of the mother and the newborn were described by means of basic descriptive statistics.

It was assumed that the observed number of cases of VPTB, MPTB, VLBW, MLBW and SGA for each municipality followed a Poisson distribution. The expected number of cases for each municipality and outcome of interest were calculated as:

$$\text{Expected}_{\text{i}} = \textit{National Raw Rate of Outcome} \times \frac{\textit{Number Live}}{\textit{Births Municipality}_i^{*}}, \quad i = 1...8098$$

Where the national rate was defined as:

$$\textit{National Raw Rate of Outcome} = \frac{\textit{Number of Cases of Outcome}}{\textit{Number of Live Births}^{*}} \times 1000$$

*****With complete information about the outcome of interest.

In order to measure the effect that proximity of mother's residence to industrial pollutant facilities has in birth outcomes, an exploratory "Near vs. Far" analysis was proposed to estimate the relative risks (RRs) of towns according to their exposure (proximity) to the facilities. For that purpose we calculated Euclidean distances between each 8098 of the municipality centroids (x_i, y_i) and each of the 2458 industrial facilities coordinates (x_j, y_j).

In Spain, the threshold distance used in published point sources studies exploring the association between industrial pollution and cancer or mortality based on municipality data varies from 2 to 5km (Garcia-Perez, Pollan et al. 2009; Ramis, Vidal et al. 2009; Garcia-Perez, Lopez-Cima et al.

2010). To remain consistent with this literature, we defined "near" as those municipalities within a radius of 3.5 km and 24 new categorical variables were created, one for each industrial group *k*. For every municipality *i*, such variables take the following three possible levels:

a) Non-exposed (reference group): Municipality *i* has no industries within a 3.5 km radius from its centroid.

b) Exposed to other activities: Municipality *i* has one or more industries within a 3.5 km radius from its centroid but none of type *k*.

c) Exposed: Municipality *i* has at least one industry of type *k* within a 3.5 km radius from its centroid.

To obtain the adjusted RR of VPTB, MPTB, VLBW, MLBW and SGA associated to proximity to each of the industrial activity groups, a Besag, York and Molliè (BYM) model (Besag, York et al. 1991) was fitted for each combination of the 5 outcomes and 24 industrial activity groups. The BYM model for a given outcome was formulated as follows:

$$O_i \sim \text{Po}(\mu_i = E_i \lambda_i) \qquad i = 1 \ldots 8098$$

$$\log(\mu_i) = \log[E_i] + \beta_1 x_i + \sum_j (\beta_j SOC_{ij}) + h_i + b_i \qquad j = 1 \ldots 11$$

$$h_i \sim \text{Normal}(\mu, \tau_h)$$
$$b_i \sim \text{Car.Normal}(\eta_i, \tau_b)$$

$$\tau_h \sim \text{Gamma}(\alpha, \varphi)$$
$$\tau_b \sim \text{Gamma}(\gamma, \delta)$$

Where:

λ_i represents the relative risk in municipality *i*

O_i represents the number of observed cases of the corresponding outcome in area *i*.

E_i represents the expected number of cases of the corresponding outcome in area *i*.

x_i represents the indicator variable for proximity of municipality i to industrial facility group under analysis.

SOC_{ij} represents the 10 potential confounders (j=2…11) in municipality i.

h_i represents a random effect capturing spatially unstructured heterogeneity.

b_i represents a random effect capturing spatially structured heterogeneity.

τ_h and τ_b represent hyperparameter corresponding to prior variance components associated with the two types of random effects.

Variables included in the model as potential confounders were: proportion of adolescent mothers, proportion of mature mothers, proportion of immigrant mothers coming from countries with low income, proportion of mothers who were illiterate mothers or did not complete primary school education, population size, habitability index, unemployment rate, average socioeconomic level, percentage of mono-parental families and number of vehicles per household.

RRs and their 95% credible intervals (CrI) resulting from models were summarized by means of forest plots.

We used R software version 2.14.1 (R 2012) for database management and modeling. January 12th 2012 version of INLA with the option of Gaussian estimation of the parameters and the standard central composite design (ccd) approach was used as the integration strategy (Rue, Martino et al. 2009).

RESULTS

During the period 2004-2008, 2,319,555 singleton live births were registered in the 8098 municipalities of the Spanish territory. Data on gestational age and birth weight were missing for

15.17% and 4.71% of live births respectively and, consequently, data on SGA was not calculated for 17.06% of births. Data on municipality of residence and mother age was complete for all records, while proportions of mothers in each of origin, profession and educational level categories were estimated based in a 99.86%, 96.90% and 40.75% and of completeness respectively.

Table 1 summarizes the distribution of the characteristics of newborns and the mothers. Prevalence of VPTB and MPTB was 0.95% and 5.24% respectively, while 0.60% and 5.07% of newborns had VLBW and MLBW and 10.06% were classified as SGA. The proportion of women migrating from low income countries was 15.59%. Regarding maternal age, education level and type of work, 2.92% and 24.26% of deliveries were from adolescent and mature mothers respectively, 14.60% of mothers were illiterate or did not finish primary school and 24.00% developed manual work. 93,738 (4.04%) births were inscribed in small municipalities with <2,000 inhabitants, 349,492 (15.07%) in municipalities between 2,000 and 10,000 inhabitants, and 1,876,325 (80.89%) in municipalities with more than 10,000 inhabitants.

Table 2 summarizes the main characteristics of Spanish municipalities according to the last census, elaborated in 2001. Despite the fact that most births occur in municipalities with more than 10,000 inhabitants, these represent only the 8.65% of the Spanish municipalities, followed by a 19.25% of municipalities having a population size between 2,000 and 10,000 inhabitants, and a majority (72.10%) of municipalities having less than 2,000 inhabitants.

The mean habitability index was 57.53 (from a range of 0 to 100) and socioeconomic level mean score was 0.93. The median unemployment rate was 9.30%, 15% of the families have a single parent and the mean number of vehicles per household was 0.95.

Figure 1 summarizes the RR and 95% CrI of VPTB and MPTB by residential proximity to sites within each one of the industrial groups adjusted by characteristics of mothers and municipalities. A slight excess risk for VPTB was observed for mothers living in municipalities within a 3.5km radius from plants of pharmaceutical products (RR=1.10, 95% CrI=1.00-1.20). Results also suggest an elevated (but not statistically significant) risk of VPTB in the vicinity of disposal or recycling of animal waste industries (RR=1.11, 95% CrI=0.98-1.26). When compared with women living in municipalities with no industries within a 3.5km radius, a significant excess risk of MPTB for mothers living within 3.5km of galvanization industries (RR=1.10, 95% CrI=1.00-1.21) or near recovery or disposal of hazardous waste industries (RR=1.08, 95% CrI=1.00-1.17) was detected. In addition, suggestive associations were observed between mothers with municipality of residence close to inorganic chemical industries (RR=1.07, 95% CrI=0.99-1.16) or industries dealing with disposal or recycling of animal waste (RR=1.08, 95% CrI=0.97-1.19).

Figure 2 summarizes the adjusted RR and 95% CrI of VLBW and MLBW by industrial activity group. Mothers living in municipalities close to pharmaceutical industries and management of non-hazardous or animal waste showed a significant excess risk of VLBW (RR=1.09, 95% CrI=1.00-1.19, RR=1.13, 95% CrI=1.01-1.25 and RR=1.15, 95% CrI=1.01-1.31, respectively). Excess risk of MLBW seemed to be associated with residential proximity to facilities from most of the industrial groups. Thus, a positive association was found for mothers living near combustion installations (RR=1.05; 95% CrI=1.01-1.09), galvanization (RR=1.07; 95% CrI=1.02-1.13), surface treatment of metals (RR=1.06; 95% CrI=1.03-1.09), mining (RR=1.09; 95% CrI=0.99-1.21), glass and mineral fibres (RR=1.06; 95% CrI=1.01-1.11), organic (RR=1.06; 95% CrI=1.02-1.09) and inorganic chemical industries (RR=1.04; 95% CrI=1.00-1.09). Similar increased risk of MLBW was found for maternal residential proximity to industries of biocides (RR=1.08; 95% CrI=1.00-1.16), pharmaceutical products (RR=1.06; 95%

CrI=1.02-1.11), hazardous (RR=1.06; 95% CrI =1.01-1.10), non-hazardous (RR=1.05; 95% CrI=1.00-1.10), or disposal or recycling of animal waste (RR=1.09; 95% CrI=1.03-1.16), paper and board (RR=1.06; 95% CrI=1.02-1.11), food and beverages sector (RR=1.05; 95% CrI=1.02-1.08) or organic solvents (RR=1.04; 95% CrI=1.01-1.08) .

Results of the risk for SGA analyses are summarized in Figure 3. Most industries associated with an excess risk of MLBW were also associated with an increased risk of SGA. Hence, a slight significant excess risk was also found for pregnant women leaving near combustion installations (RR=1.03; 95% CrI=1.00-1.07), metallic surface treatment (RR=1.04; 95% CrI=1.01-1.07) or cement an lime industries (RR=1.05; 95% CrI=1.00-1.09), and also for those with municipality of residence near organic (RR=1.05; 95% CrI=1.02-1.09) or inorganic chemical industry (RR=1.05; 95% CrI=1.01-1.09) or explosives and pyrotechnic industrial facilities (RR=1.06; CrI95%=1.01-1.12). Proximity to management of hazardous (RR=1.04; 95% CrI=1.00-1.08), non-hazardous (RR=1.06; 95% CrI=1.02-1.11), animal (RR=1.07; 95% CrI=1.01-1.13) or water (RR=1.03; 95% CrI=1.00-1.07) waste or to paper and board (RR=1.03; 95% CrI=1.00-1.07), food and beverages (RR=1.04; 95% CrI=1.01-1.06) and organic solvents facilities (RR=1.04; 95% CrI=1.00-1.07) during pregnancy constituted also a higher risk for having SGA newborns.

DISCUSSION

Residential proximity to pharmaceutical industries and management of animal waste plants was found to be significantly associated with excess risk of many of the outcomes under study (VLBW, MLBW, and SGA). Proximity to management of non-hazardous waste plants was also associated with an increase in the risk of VLBW. In terms of number of associations detected, proximity to inorganic chemical, pharmaceutical and waste management industries seem to be the associations most consistently reported across outcomes. Especially striking is the case of residential proximity to disposal or recycling of animal waste industries that is positively associated with an increase in the risk for all the outcomes showing the strongest associations.

On the contrary, no associations were found between the reproductive outcomes under study and residential proximity to refineries and coke ovens, metallurgical industry, ceramic, fertilizers, textile activities or shipyards.

Direct comparison of our results to those from previous studies was not always possible. To our knowledge, no results on the specific effects of industrial pollution on birth outcomes have been published in Spain. Regarding research on environmental industrial pollution and human reproduction in other countries, between-country differences in the types of industrial activities analysed constituted a limitation for comparisons. However, when no comparable environmental studies existed, we used (if available) results from occupational exposure as a basis of comparison. For most previous studies exploring the effects of proximity to industrial facilities and adverse birth outcomes mentioned in this section, the magnitude of the associations were, as in our results, weak even though some are statistically significant.

Overall, our results are consistent with previous research showing evidence of association between air pollution and risk of low birth weight and inconclusive results regarding associations with preterm birth (Sram, Binkova et al. 2005). Similarities also exist between our research and association studies of birth outcomes and other exposures to toxic fumes such as environmental tobacco (Salmasi, Grady et al. 2010).

Evidence of an association between PTB and LBW and proximity to combustion plants (Mohorovic 2004; Tsai, Yu et al. 2004) and occupational exposure to welding fumes and metal dusts (generated in galvanization processes) (Quansah and Jaakkola 2009) was also found in other studies. In addition, proximity to mining areas has previously been associated with high risk of LBW (Ahern, Mullett et al. 2011). As shown in our results, significant associations of LBW and SGA with exposure to chemical substances at the workplace were found in the literature (Yan 1990; Seidler, Raum et al. 1999), even though chemicals are usually explored in general (not differentiating organic and inorganic) and never associated specifically to industrial pollution. Some previous research assessing exposure to agricultural pesticides showed a positive association with risk of LBW (de Siqueira, Braga et al. 2010) and our finding of significant associations between the estimated risk of MPTB and proximity to recovery or disposal of hazardous and municipal waste was supported for other studies (Johnson 1999). Finally, previous work support our results identifying an increased risk of LBW and SGA due to proximity to incineration of non-hazardous waste and landfill sites (Morgan, Vrijheid et al. 2004; Gilbreath and Kass 2006) or organic solvents occupational exposure (Ahmed and Jaakkola 2007; Sorensen, Andersen et al. 2010).

Research supporting our results of no association between adverse birth outcomes and proximity to refineries and coke ovens (Bhopal, Tate et al. 1999; Oliveira, Stein et al. 2002), metallurgical plants (Bhopal, Tate et al. 1999; Parker, Mendola et al. 2008) or textile activity (Savitz, Whelan et al. 1989; Savitz, Brett et al. 1996) has been published. We also found scientific literature supporting our findings of no significant evidence of excess risk of PTB related to the use of organic solvents in industrial processes (Ahmed and Jaakkola 2007; Sorensen, Andersen et al. 2010).

We were not aware of any studies exploring the association between risk of adverse birth outcomes and proximity to industries of metal and plastic surface treatment, cement and lime, glass and mineral fibers, ceramic, fertilizers, pharmaceutical products, explosives, management of animal waste, treatment of urban waste-water, paper and board, food and beverages or shipyards,. Catches the attention the absence of literature regarding to pharmaceutical companies (associated with high risk of 3 of the 5 adverse outcomes under study including the most extreme ones) and management of animal waste industries (the only activity associated to the occurrence of all outcomes showing the stronger associations).

Insofar as the limitations of our study, it seems reasonable to consider that missing values (15.17% and 4.71% of data on gestational age and birth weight) could affect our results, especially if data are not missing at random, particularly if the probability of missingness increased in women with poorer birth outcomes (underestimated risks). In order to check this possibility we calculated the distribution of birth weight among babies with no data for gestational age: 67% of them were bigger than 2,500 grams and only 4% were low birth weight babies (0.4% VLBW). The other 29% had missing data for both measures. This distribution of birth weight does not support non-randomly missing gestational age data, with respect to birth weight.

One of the most important limitations of our study is the potential for ecological bias, which occurs when information on within-area variability in exposures and confounders is lost but a number of distinct consequences occur as a result of this variability (Wakefield 2008). While the available data do not allow direct assessment of this potential bias, we do note the value of ecological studies in defining hypotheses of interest for future research when, as is the case here, the area of study is still largely unexplored.

Decision on the distance threshold depends greatly on the information available about pollutant resources and health data. Different approaches are used depending on geographical information available (Gilbreath and Kass 2006). In Spain, distances from 2km to 5km are the most commonly used for studies using MAGRAMA data to explore the association between industrial pollution and cancer outcomes or mortality using municipality as the geographical unit of analysis (Elliott, Briggs et al. 2001; Tsai, Yu et al. 2004; Brender, Maantay et al. 2011). In order to include enough municipalities to obtain stable results but trying to avoid the dilution of the effect resulting from taking a threshold too wide we elected to use a value falling between those two distances (3.5km).

Several methodological difficulties presented themselves in the course of our study. On one hand, sources of pollution are not unique which makes the selection of non-exposed individuals very difficult. We chose mothers whose residence was established in municipalities with no industrial plants within 3.5km from its centroid as our reference group, independent of any traffic-related pollution of such municipality or other occupational exposure to which the mother was exposed. Therefore, control mothers were exposed to environmental toxins, but they are further from putative industrial sources than the exposed mothers. Adjusting by number of vehicles per household and percentage of mothers doing manual work (including production workers), might attenuate this problem but, given that we are using aggregated data, part of it still remains. On the other hand, industrial facilities tend to be grouped geographically, as a result some mothers can live within 3.5km of more than one type of facility, and hence their risk is not consequence of emissions from an only source. Interaction effect of industries might be possible and should also be explored in further studies.

Another factor that could be influencing the associations found is our use of isotropic models to fit our regressions. These assume exposure is equally distributed in all directions, which is usually untrue due to factors such as temperature, precipitation or wind predominance which affect the direction and intensity of potential emissions. Municipalities located in one specific direction might receive more pollutants than others within the same radius but in a different direction from the source. Therefore, counts including exposed and unexposed municipalities in the same radius might dilute any observed harmful effect that industrial pollution has on birth outcomes. More sophisticated anisotropic models or individual measurements could be considered as possible solutions to this problem in future work.

As mentioned in the introduction, adequacy of prenatal care, cigarette consumption or substance abuse are factors closely related to adverse birth results but this information was not available in our study. However, it has become popular to attempt to control for these variables using area-level measures of socioeconomic status (Elliott, Briggs et al. 2001; Morgan, Vrijheid et al. 2004; Gilbreath and Kass 2006; Garcia-Perez, Pollan et al. 2009; Garcia-Perez, Lopez-Cima et al. 2010). Even if they cannot pick up the subtleties of the real measurements such adjustments can sometimes ameliorate these problems since socioeconomic level is highly correlated with lifestyle variables (Berry and Bove 1997).

Despite the potential limitations outlined above, it is important to highlight several strengths in our study. First, one of the most important strengths of environmental studies in reproductive health is that fetal development is a clearly delimited period so most relevant exposure times are similarly limited. We used all births occurred in Spain between 2004 and 2008 linked with exposure data of 2007, therefore, the exposure information is relevant to our study of these characteristics. Second, our study utilizes high-quality registry data for births, population demographics, and industry exposure groups. Third, despite the fact of being an ecological study, the extensive population size makes results considerably reliable. Fourth, our protocol for assigning location minimizes chances of misspecification in our proximity-based exposure surrogate. Finally, to our knowledge, there are no other studies relating industrial pollution to adverse birth outcomes across so broad a list of industry types.

We believe that the originality and scope of the results above, the high quality of the data, and the intriguing results provide a solid base for future research relating to proximity to industrial sites and adverse reproductive outcomes.

CONCLUSIONS

Our results indicate an association between residential proximity to certain types of pollutant industrial facilities and increased risk of some adverse birth outcomes. The high number of associations found between municipal proximity to industries and risk of MLBW and SGA suggests that the industrial activity might be more strongly associated with birth weight than with a reduction of the gestational age. Given the information available and the shortness of the induction periods, studies evaluating effects of exposure in reproductive results can provide very useful insight for environmental vigilance in Spain.

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TABLES

Table 1.- Main characteristics of newborns and mothers of all singleton births occurring in Spain in 2004-2008

Variable	n (%)[a]
Gestational Age	
≤32 weeks	18,693 (0.95%)
33-36 weeks	103,201 (5.24%)
>36 weeks	1,845,779 (93.81%)
Birth Weight	
<1500 grams	13,287 (0.60%)
1500-2499 grams	112,038 (5.07%)
≥2500 grams	2,084,916 (94.33%)
Newborn small for gestational age	
Small for gestational age	193,543 (10.06%)
Normal for gestational age	1,730,386 (89.94%)
Origin of the mother	
Spain	1,921,219 (82.94%)
Immigrant from medium-high income country	33,995 (1.47%)
Immigrant from Low Income country	361,115 (15.59%)
Mother age	
<20	68,033 (2.92%)
20-34	1,693,926 (72.82%)
≥35	564,485 (24.26%)
Educational level	
Primary school finished or more	807,334 (85.40%)
Illiterate or without primary school finished	137,993 (14.60%)
Profession of the mother	
No Manual Work	824,437 (36.68%)
Manual Work	539,546 (24.00%)
Doesn't Work	535,774 (23.84%)
Not Classified	347,888 (15.48%)
Size of municipality of residence	
<2000 inhabitants	93,738 (4.04%)
2000-10000 inhabitants	349,492 (15.07%)
≥10000 inhabitants	1,876,325 (80.89%)

[a]Figures do not sum to 100% due to missing values

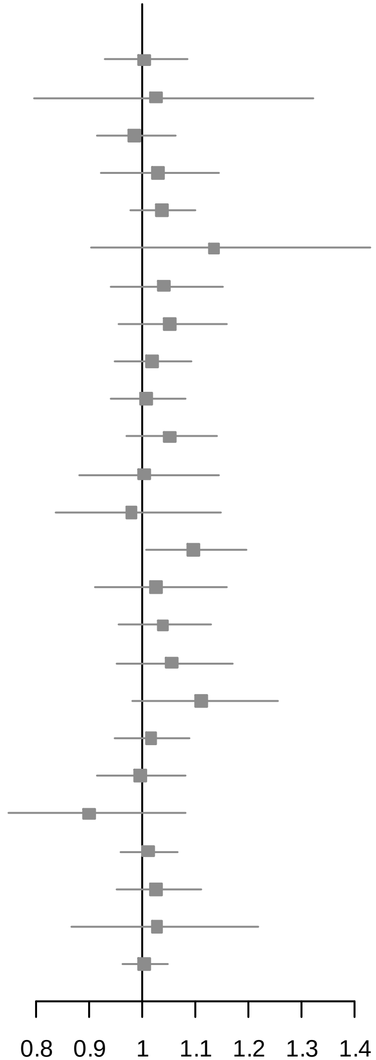
Table 2.- Main characteristics of Spanish municipalities (population census 2001 and 2008 and population and housing census 2001)

Variable	Descriptive
Size of municipality of residence n (%)	
<2000 inhabitants	5,839 (72.10%)
2000-10000 inhabitants	1,559 (19.25%)
≥10000 inhabitants	700 (8.65%)
Habitability Index mean(sd)	57.53 (11.25)
Socioeconomic Level mean(sd)	0.93 (0.20)
Unemployment Rate median(IQ)	9.30 (5.79-14.18)
Proportion of mono-parental families mean(sd)	0.15 (0.07)
Number of vehicles per household mean(sd)	0.95 (0.30)

FIGURE CAPTIONS

Figure 1.- Adjusted relative risk of VPTB and MPTB by industrial activity group.

	VPTB OBS	VPTB RR (95%CrI)	MPTB OBS	MPTB RR (95%CrI)
Combustion	1370	1.00 (0.93-1.08)	7666	1.00 (0.94-1.07)
Refineries and coke ovens	152	1.02 (0.79-1.32)	784	1.00 (0.80-1.26)
Metallurgical	1805	0.98 (0.91-1.06)	10151	1.01 (0.94-1.08)
Galvanization	601	1.03 (0.92-1.14)	3407	1.10 (1.00-1.21)
Surface treatment metals/plastic	3922	1.04 (0.97-1.10)	21823	1.03 (0.97-1.08)
Mining	89	1.14 (0.90-1.43)	481	1.08 (0.92-1.27)
Cement and lime	657	1.04 (0.94-1.15)	3546	0.99 (0.91-1.08)
Glass and mineral fibres	910	1.05 (0.96-1.16)	4898	1.07 (0.97-1.17)
Ceramic	1573	1.02 (0.95-1.09)	9388	1.01 (0.96-1.06)
Organic chemical industry	2157	1.01 (0.94-1.08)	12028	1.03 (0.96-1.09)
Inorganic chemical industry	1359	1.05 (0.97-1.14)	7539	1.07 (0.99-1.16)
Fertilizers	445	1.00 (0.88-1.14)	2552	1.04 (0.92-1.18)
Biocides	274	0.98 (0.83-1.15)	1429	1.05 (0.92-1.21)
Pharmaceutical products	1244	1.10 (1.00-1.20)	6156	1.03 (0.94-1.12)
Explosives and pyrotechnic	379	1.02 (0.91-1.16)	2072	1.01 (0.92-1.10)
Hazardous waste	1257	1.04 (0.95-1.13)	6773	1.08 (1.00-1.17)
Non-hazardous waste	626	1.06 (0.95-1.17)	3307	0.98 (0.90-1.06)
Disposal or recycling of animal waste	443	1.11 (0.98-1.26)	2379	1.08 (0.97-1.19)
Urban waste-water treatment plants	1816	1.02 (0.95-1.09)	9861	0.98 (0.92-1.05)
Paper and board	1459	0.99 (0.92-1.08)	8352	1.04 (0.97-1.12)
Pre-treatment or dyeing of textiles	143	0.90 (0.75-1.08)	831	0.92 (0.81-1.04)
Food and Beverages sector	4197	1.01 (0.96-1.06)	23571	1.02 (0.98-1.07)
Organic Solvents Use	1476	1.03 (0.95-1.11)	8421	1.04 (0.97-1.11)
Shipyards	387	1.03 (0.86-1.22)	2218	1.04 (0.83-1.30)
OVERALL	10560	1.00 (0.96-1.05)	59377	1.01 (0.98-1.05)



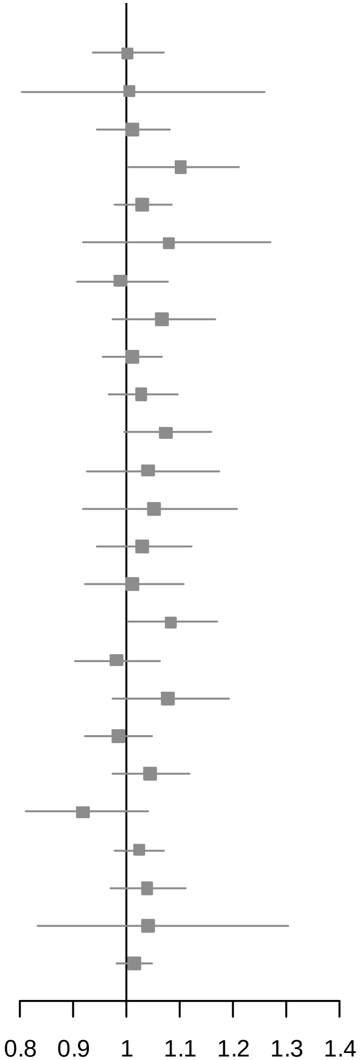
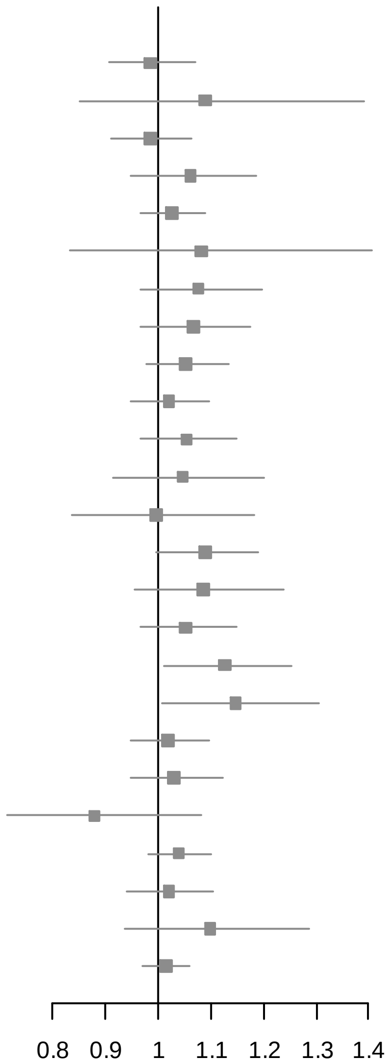


Figure 2.- Adjusted Relative risk of VLBW and MLBW by industrial activity group.

	VLBW		MLBW	
	OBS	RR (95%CrI)	OBS	RR (95%CrI)
Combustion	948	0.99 (0.91-1.07)	8215	1.05 (1.01-1.09)
Refineries and coke ovens	107	1.09 (0.85-1.39)	827	1.08 (0.95-1.22)
Metallurgical	1270	0.98 (0.91-1.06)	10835	1.02 (0.99-1.06)
Galvanization	446	1.06 (0.95-1.19)	3862	1.07 (1.02-1.13)
Surface treatment metals/plastic	2809	1.03 (0.97-1.09)	24843	1.06 (1.03-1.09)
Mining	62	1.08 (0.83-1.41)	546	1.09 (0.99-1.21)
Cement and lime	493	1.08 (0.97-1.20)	4055	1.03 (0.98-1.08)
Glass and mineral fibres	653	1.07 (0.97-1.18)	5415	1.06 (1.01-1.11)
Ceramic	1166	1.05 (0.98-1.14)	9859	1.02 (0.99-1.06)
Organic chemical industry	1548	1.02 (0.95-1.10)	13664	1.06 (1.02-1.09)
Inorganic chemical industry	972	1.05 (0.97-1.15)	8096	1.04 (1.00-1.09)
Fertilizers	311	1.05 (0.91-1.20)	2620	1.03 (0.96-1.09)
Biocides	183	1.00 (0.84-1.18)	1772	1.08 (1.00-1.16)
Pharmaceutical products	861	1.09 (1.00-1.19)	7385	1.06 (1.02-1.11)
Explosives and pyrotechnic	283	1.09 (0.96-1.24)	2215	0.99 (0.94-1.05)
Hazardous waste	900	1.05 (0.97-1.15)	7608	1.06 (1.01-1.10)
Non-hazardous waste	472	1.13 (1.01-1.25)	3688	1.05 (1.00-1.10)
Disposal or recycling of animal waste	322	1.15 (1.01-1.31)	2566	1.09 (1.03-1.16)
Urban waste-water treatment plants	1272	1.02 (0.95-1.10)	10998	1.00 (0.97-1.04)
Paper and board	1056	1.03 (0.95-1.12)	9480	1.06 (1.02-1.11)
Pre-treatment or dyeing of textiles	99	0.88 (0.71-1.08)	1030	1.01 (0.94-1.09)
Food and Beverages sector	3104	1.04 (0.98-1.10)	26728	1.05 (1.02-1.08)
Organic Solvents Use	1054	1.02 (0.94-1.11)	9267	1.04 (1.01-1.08)
Shipyards	289	1.10 (0.94-1.29)	2224	1.01 (0.92-1.10)
OVERALL	7606	1.01 (0.97-1.06)	65503	1.03 (1.01-1.05)



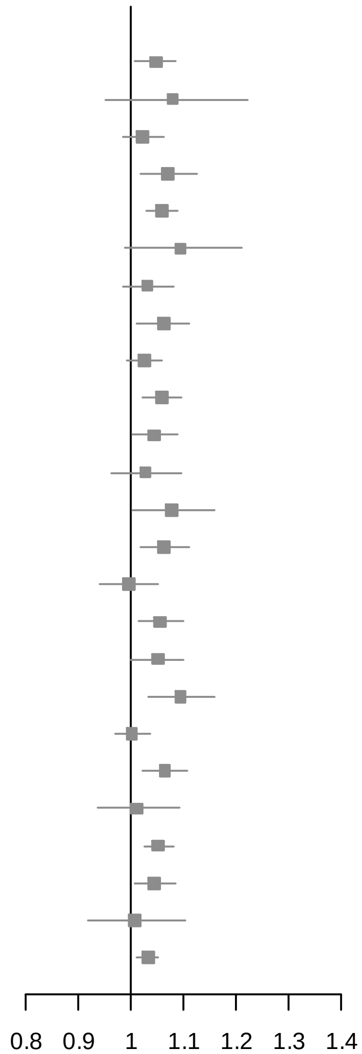
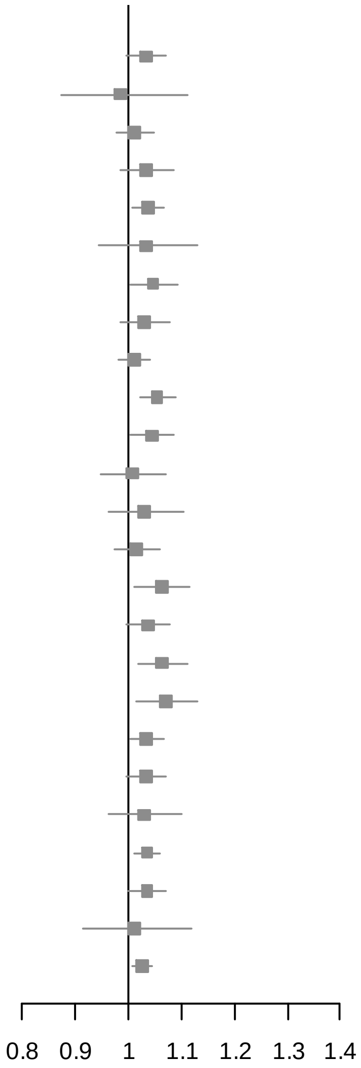


Figure 3.- Adjusted Relative risk of SGA by industrial activity group.

	OBS	RR (95%CrI)
Combustion	14198	1.03 (1.00-1.07)
Refineries and coke ovens	1302	0.98 (0.87-1.11)
Metallurgical	19468	1.01 (0.98-1.05)
Galvanization	6594	1.03 (0.98-1.08)
Surface treatment metals/plastic	42539	1.04 (1.01-1.07)
Mining	915	1.03 (0.94-1.13)
Cement and lime	7455	1.05 (1.00-1.09)
Glass and mineral fibres	9605	1.03 (0.99-1.08)
Ceramic	16865	1.01 (0.98-1.04)
Organic chemical industry	23935	1.05 (1.02-1.09)
Inorganic chemical industry	13481	1.05 (1.01-1.09)
Fertilizers	4573	1.01 (0.95-1.07)
Biocides	3126	1.03 (0.96-1.11)
Pharmaceutical products	12238	1.01 (0.97-1.06)
Explosives and pyrotechnic	4351	1.06 (1.01-1.12)
Hazardous waste	13136	1.04 (1.00-1.08)
Non-hazardous waste	6633	1.06 (1.02-1.11)
Disposal or recycling of animal waste	4816	1.07 (1.01-1.13)
Urban waste-water treatment plants	19430	1.03 (1.00-1.07)
Paper and board	16598	1.03 (1.00-1.07)
Pre-treatment or dyeing of textiles	1872	1.03 (0.96-1.10)
Food and Beverages sector	45448	1.04 (1.01-1.06)
Organic Solvents Use	15725	1.04 (1.00-1.07)
Shipyards	3931	1.01 (0.92-1.12)
OVERALL	113597	1.03 (1.01-1.04)



APPENDIX I: Classification countries in low and medium-high income.

Low income countries: Albania, Bulgaria, Hungary, Poland, Romania, Ukraine, Latvia, Moldova, Belarus, Georgia, Estonia, Lithuania, Czech Republic, Slovak Republic, Bosnia and Herzegovina, Croatia, Slovenia, Armenia, Russia, Serbia and Montenegro, Macedonia, Burkina Faso, Algeria, Angola, Benin, Botswana, Burundi, Cape Verde, Cameroon, Comoros, Congo, Ivory Coast, Djibouti, Egypt, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Equatorial Guinea, Kenya, Lesotho, Liberia, Libya, Madagascar, Malawi, Mali, Morocco, Mauritania, Mauritius, Mozambique, Namibia, Niger, Nigeria, Central African republic, South Africa, Rwanda, Sao Tome and Principe, Senegal, Seychelles, Sierra Leone, Somalia, Sudan , Swazi, Tanzania, Chad, Togo, Tunisia, Uganda, Democratic rep. of Congo, Zambia, Zimbabwe, Mexico, Antigua and Barbuda, Bahamas, Barbados, Belize, Costa Rica, Cuba, Dominica, El Salvador, Grenada, Guatemala, Haiti, Honduras, Jamaica, Nicaragua, Panama, St. Vincent and the Grenadines, Dominican Republic, Trinidad and Tobago, St. Lucia, St. Kitts and Nevis, Argentina, Bolivia, Brazil, Colombia, Chile, Ecuador, Guyana, Paraguay, Peru, Suriname, Uruguay, Venezuela, Afghanistan, Saudi Arabia, Bahrain, Bangladesh, Myanmar, China, UAE, Philippines, India, Indonesia, Iraq, Iran, Israel, Japan, Jordan, Cambodia, Kuwait, Laos, Lebanon, Malaysia, Maldives, Mongolia, Nepal, Oman, Pakistan, Qatar, South Korea, North Korea, Syria, Sri Lanka, Thailand, Turkey, Vietnam, Taiwan, Brunei, Yemen, Azerbaijan, Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, Uzbekistan and other countries without diplomatic relations.

Immigrants from medium-high income countries: Austria, Belgium, Cyprus, Denmark, Finland, France, Greece, Ireland, Iceland, Italy, Liechtenstein, Luxembourg, Malta, Monaco, Netherlands, Norway, Portugal, Andorra, United Kingdom, Germany, San Marino, Holy See, Sweden, Swiss, Canada, United States of America, Australia, New Zealand, Papua New Guinea and Tonga.

APPENDIX II: Description of census variables.

Data on population and housing was provided at a census section level. Average municipal values were calculated by computing, for each municipality, the weighted average of all census section's values that comprise it.

Habitability index (0-100): Sum of the scores of habitability in the census section / Total primary residences. Each housing starts with a value of 100 and a certain amount is subtracted, to a minimum of 0, according to the following conditions:

	Scores
Initial	100
External noise, pollution and bad smells, dirty streets, poor communications, scarce green areas, crime or vandalism, lack of toilet services inside the house, no piped gas, no lift for houses in 3^{rd} and $4r^{th}$ floor, not wheelchair accessible for houses on the ground level or year of construction of the building between 1951 and 1970.	-5
Lack of hygiene inside the house, no lift for houses in floor-higher than 4^{th}, lack of sewerage, running water available only from private supply, only mobile heating devices available (for provinces that require it), between 5 and 10 square meters average area per capita (slightly cramped), year of construction of the building prior to 1951.	-10
Deficient status of the building.	-15
No evacuation of residual waters, no running water, dwellings above ground level not accessible to wheelchairs, not heating devices available of any kind (for provinces that require it), less than or equal to 5 square meters average area per capita (severe overcrowding).	-20
Bad status of the building.	-30
Dilapidated status of the building.	-50
Accommodation: Room that does not respond fully to the definition of family home, either because it is mobile, semi-permanent or improvised.	-100

Unemployment rate: Percentage of population unemployed ≥16 years old, among the total active population ≥16 in each of the census section. A person is unemployed if simultaneously:

1. Has no paid employment.

2. Looking for a job (registration in the unemployment office, workplace arrangements, responding to newspaper advertisements, etc.).

3. Available to work.

Economically active population is all persons ≥16 who are eligible for inclusion among the employed or unemployed groups. A person is employed if during the reference week had a payment for work.

Average socioeconomic level (0-3): Socioeconomic status was grouped according to individuals' occupation, activity and employment status and a score was assigned for each category as follows

	Scores
< 16 years	0
≥16	
Unemployed seeking first job, other inactive	0
Unemployed who have previously worked, other pensioners	0.5
Residents groups, other farm workers, other personnel from service sector, unskilled workers in non-agricultural establishments, retired.	1
Agricultural employers without employees, members of agricultural cooperatives.	1.5
Rest of the administrative and commercial personnel, foremen and boatswains of non-agricultural establishments, skilled and specialized workers from non-agricultural establishments, members of non-agricultural cooperatives, agricultural employers with employees, professionals from Armed Forces, no classified.	2
Government employees with exclusive dedication, professionals, technicians and similar that work for others, non-agricultural employers without employees, directors and heads of farms	2.5
Directors and managers of non-agricultural establishments, senior government employees, professionals, technicians and similar that operate on their own, with or without employees non-agricultural employers with employees.	3

The resulting average socioeconomic level of the census section is an arithmetic mean of the socioeconomic level of the persons residing in the census section. 0 represents the lower socioeconomic level, and 3, the highest.

Percentage of single parent families: Family comprised of a father or a mother with one or more children without a partner.

Number of vehicles per household: Calculated by dividing, for each census section, the number of vehicles (cars or vans) for the number of households.

APPENDIX III: Description of industrial activity groups and total number of municipalities within a radius of 3.5km from each type of industry

Activity Groups	Description	N
Non Exposed	Municipalities with no industries of any type within a 3.5 km radius from its centroid	6735
Exposed	Municipalities with, at least one industry of any type within a 3.5 km radius from its centroid	1363
Combustion	Thermal power stations and other combustion installations with a power superior of 50MW	130
Refineries and coke ovens	Mineral refineries and coke ovens	11
Metallurgical	Production and transformation of metals	328
Galvanization	Plants for galvanization of metals	47
Surface treatment of metals and plastic	Surface treatment of metals and plastic materials using an electrolytic or chemical process	488
Mining	Underground mining industry and related operations	32
Cement and Lime	Installations for the production of: cement clinker in rotary kilns, lime in rotary kilns, cement clinker or lime in other furnaces	94
Glass and mineral fibers	Installations for the manufacture of glass, including glass fibers and installations for melting mineral substances, including the production of mineral fibers	72
Ceramic	Installations for the manufacture of ceramic products by firing, in particular roofing tiles, bricks, refractory bricks, tiles, stoneware or porcelain	589
Organic chemical industry	Chemical installations for the production on an industrial scale of basic organic chemical industry	255
Inorganic chemical industry	Chemical installations for the production on an industrial scale of basic Inorganic chemical industry	105
Fertilizers	Chemical installations for the production on an industrial scale of phosphorous-, nitrogen- or potassium-based fertilizers (simple or compound fertilizers)	37
Biocides	Chemical installations for the production on an industrial scale of basic plant health products and of biocides	21
Pharmaceutical products	Installations using a chemical or biological process for the production on an industrial scale of basic pharmaceutical products	119
Production of explosives	Installations for the production on an industrial scale of explosives and pyrotechnic products	75
Hazardous waste	Installations for the recovery or disposal of hazardous waste	126

Non-hazardous waste	Installations for the incineration of non-hazardous waste in the scope of Directive 2000/76/EC of the European Parliament and of the Council of 4 December 2000 on the incineration of waste and Landfills.	116
Disposal or recycling of animal waste	Installations for the disposal or recycling of animal carcasses and animal waste and independently operated industrial waste-water treatment plants which serve one or more activities of this appendix.	68
Urban waste-water treatment plants	Urban waste-water treatment plants	120
Paper and board	Industrial plants for the production of paper and board and other primary wood products	184
Pre-treatment or dyeing of textiles	Plants for the pre-treatment (operations such as washing, bleaching, mercerization) or dyeing of fibers or textiles	53
Food and beverages sector	Food and beverages sector	427
Organic solvents use	Installations for the surface treatment of substances, objects or products using organic solvents, in particular for dressing, printing, coating, degreasing, waterproofing, sizing, painting, cleaning or impregnating	131
Shipyards	Installations for the building of, and painting or removal of paint from ships	7