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## **Leukemia-related mortality in towns lying in the vicinity of metal production and processing installations**

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**Abbreviations:**

IARC: International Agency for Research on Cancer

PAHs: Polycyclic aromatic hydrocarbons

EPER: European Pollutant Emission Register

SMR: Standardized Mortality Ratio

ICD: International Classification of Diseases

IPPC: Integrated Pollution Prevention and Control

RR: Relative risk

95%CI: 95% confidence interval

MWFs: Metalworking fluids

ECSA: European Chlorinated Solvent Association

E-PRTR: European Pollutant Release and Transfer Register

## **Abstract**

**Background:** Releases to the environment of toxic substances stemming from industrial metal production and processing installations can pose a health problem to populations in their vicinity.

**Objectives:** To investigate whether there might be excess leukemia-related mortality in populations residing in towns in the vicinity of Spanish metal industries included in the European Pollutant Emission Register.

**Methods:** Ecologic study designed to examine mortality due to leukemia at a municipal level, during the period 1994-2003. Population exposure to pollution was estimated on the basis of distance from town of residence to pollution source. Using Poisson regression models, we analyzed: risk of dying from leukemia in a 5-kilometer zone around installations which had become operational prior to 1990; effect of pollution discharge route and type of industrial activity; and risk gradient within a 50-kilometer radius of such installations.

**Results:** Excess mortality (relative risk, 95% confidence interval) was detected in the vicinity of pre-1990 installations (1.07, 1.02-1.13 in men; 1.05, 1.00-1.11 in women), with this being more elevated in the case of installations that released pollution to air versus water. On stratifying by type of industrial activity, statistically significant associations were also observed among women residing in the vicinity of galvanizing installations (1.58, 1.09-2.29) and surface treatment installations using an electrolytic or chemical process (1.34, 1.10-1.62), which released pollution to air. There was an effect whereby risk increased with proximity to certain installations.

**Conclusions:** The results suggest an association between risk of dying due to leukemia and proximity to Spanish metal industries.

**Key Words:** Leukemia, metal industries, relative risk, EPER, industrial pollution, mortality

## 1. Introduction

Leukemias are a grouping of malignant diseases of hematopoietic cells, acute as well as chronic, which account for around 3.2% of all cancer deaths in Europe (Ferlay et al., 1999). In Spain, there were 1727 leukemia-related deaths among men (2.7% of all tumors) and 1360 among women (3.5% of all cancers) in 2007 (Instituto Nacional de Estadística, 2010). According to the EURO CARE-4 project, relative survival in Spain at five years of diagnosis is 45.9% for men and 44.4% for women, figures similar to the European mean (Istituto Superiore di Sanità, 2010).

Insofar as the etiology of this disease is concerned, the risk factors for which a clearer evidence exists are ionizing radiations and benzene (Boice, Jr. and Lubin, 1997; Clapp et al., 2005; Linet et al., 2006; Siemiatycki et al., 2004), with the latter being associated with the development of non-lymphocytic leukemias in particular (Hayes et al., 2001; Lynge et al., 1997; Siemiatycki et al., 2004). Several studies have reported elevated risks of leukemias among children whose parents had been occupationally exposed to pesticides or had used these in the home or garden (Zahm and Ward, 1998) and a recent meta-analysis found an association between childhood leukemia and prenatal maternal occupational pesticide exposure (Wigle et al., 2009). Furthermore, the International Agency for Research on Cancer (IARC) has classified some reactive chemicals, such as 1,3-butadiene or ethylene oxide, as carcinogens in humans, based on epidemiological findings of increased risks of leukemias in cohorts of exposed workers (Blair and Kazerouni, 1997; IARC, 2008).

In terms of industrial activities, employment in the rubber industry and in boot and shoe manufacture and repair has been associated with these tumors (Kogevinas et al., 1998; Siemiatycki et al., 2004; Ward et al., 1997), and some studies found excess risks among petroleum industry workers (Sathiakumar et al., 1995; Siemiatycki et al., 2004; Ward et al., 1997). Another industrial sector that might be related to an increase in occupational risk of leukemias is that of metal production and processing (Ahn et al., 2006; Gallagher and Threlfall, 1983; Rockette and Arena, 1983; Silverstein et al., 1986). Moreover, some authors have observed excess mortality of leukemias in the vicinity of

aluminum, zinc, and iron/steel foundries (Casella et al., 2005; Knox and Gilman, 1997). These types of installations release numerous carcinogenic substances into the environment, e.g., heavy metals, polycyclic aromatic hydrocarbons (PAHs), asbestos and other carcinogens, such as benzene or dioxins, which have been linked to leukemias. Assessment of the possible relationship between these industries and leukemia-related mortality in their environs would therefore appear advisable.

The European Pollutant Emission Register (EPER) (EPER, 2009), a public inventory of industries set up by the European Commission under the terms of Directive 96/61/EC, is a valuable resource for monitoring industrial pollution, and enables any possible association between residential proximity to these pollutant installations and risk of cancer mortality to be studied (Garcia-Perez et al., 2009; Garcia-Perez et al., 2010; Monge-Corella et al., 2008; Ramis et al., 2009). One of the EPER-designated industrial groups encompasses metal production and processing installations, and the register shows data on the pollutants released by and the geographic coordinates of each installation.

This paper sought to ascertain whether there was excess leukemia-related mortality among the population residing in the vicinity of Spanish metal production and processing installations which reported their emissions to the EPER.

## **2. Materials and methods**

An ecologic study was designed to model standardized mortality ratios (SMRs) for leukemia in 8073 Spanish towns for the period 1994 through 2003. Separate analyses were performed for the overall population and for each sex.

SMRs were calculated as the ratio of observed to expected deaths. Observed municipal mortality data were drawn from the records of the National Statistics Institute for the study period, and corresponded to deaths coded as leukemias (lymphoid leukemia, myeloid leukemia, monocytic leukemia, other specified leukemia, and leukemia of unspecified cell type), namely, codes 204-208 (International Classification of Diseases, 9<sup>th</sup> Revision/ICD-9) and C91-C95 (ICD-10). Expected cases

were calculated by multiplying the specific rates for Spain as a whole, broken down by age group (18 groups: 0 – 4, 5 – 9, ..., 80 – 84, 85 and over), sex, and five-year period (1994-1998, 1999-2003), by the person-years for each town, broken down for the same strata. For calculation of person-years, the two five-year periods were considered, with data corresponding to the 1996 municipal roll and 2001 census being taken as the estimator of the population.

Population exposure to industrial pollution was estimated by reference to the distance from the centroid of subjects' town of residence to the industrial facility. Data on industries were obtained from the EPER-Spain (Ministerio de Medio Ambiente y Medio Rural y Marino, 2007). We selected the 118 Integrated Pollution Prevention and Control (IPPC) category-2 metal production and processing installations: which included production of pig iron or steel (17 facilities) – category 2.2, hot-rolling mills (steel) (5 facilities) – category 2.3.a, galvanizing (3 facilities) – category 2.3.c, ferrous metal foundries (18 facilities) – category 2.4, production of non-ferrous crude metals (7 facilities) – category 2.5.a, smelting of non-ferrous metals (19 facilities) – category 2.5.b, and surface treatment of metals and plastic materials using an electrolytic or chemical process (49 facilities) – category 2.6; and which reported their releases to air and water in 2001, including previously validated geographic coordinates of their location (Garcia-Perez et al., 2008). Data on date of commencement of industrial operations were obtained from official websites of the metal industries analyzed.

Initially, we conducted an exploratory "near vs. far" analysis to estimate the relative risks (RRs) of towns situated at a distance of less than 5 kilometers from metal industries. The exposure variable was coded as a "dummy", with three levels, namely:

- 1) exposed group ("near"), consisting of towns having their municipal centroid at  $\leq 5$  km from a metal production and processing installation;
- 2) intermediate group, consisting of towns at  $\leq 5$  km from any industrial installation other than metal production and processing; and,

3) unexposed group ("far"), consisting of towns having no EPER-registered industry within 5 km of their municipal centroid (reference level).

RRs and their 95% confidence intervals (95% CIs) were estimated on the basis of a mixed Poisson regression model (Gelman and Hill, 2007), including province as a random effects term, to enable geographic variability and extra-Poisson dispersion to be taken into account and unexposed towns belonging to the same geographic setting (province) to be considered as the reference group in each case. We used expected cases as offset for the total population, men, and women, and estimations were adjusted for the following standardized sociodemographic indicators, chosen for their availability at a municipal level: population size; percentages of illiteracy, farmers and unemployed persons; average persons per household according to the 1991 census; and, mean income as a measure of income level (Ayuso Orejana et al., 1993).

To ensure that the record of pollutant emissions was sufficiently reliable over time for each installation, the analysis was replicated, by confining the above model to the 105 industries that entered into operation prior to 1990. Furthermore, separate analyses were performed for industries that had released some type of pollutant to air (61 facilities) and for those that had released pollutants exclusively to water (44 facilities). Similarly, in order to stratify the risk by type of industrial activity, we created a variable of interest with the following levels:

- 1) group 1, i.e., towns lying at  $\leq 5$  km from more than one IPPC category-2 metal installation (multiple pollution sources);
- 2) group 2, i.e., towns lying at  $\leq 5$  km from a single IPPC category-2.2 or -2.3.a metal installation (steel production and hot-rolling mills);
- 3) group 3, i.e., towns lying at  $\leq 5$  km from a single IPPC category-2.3.c metal installation (galvanizing);
- 4) group 4, i.e., towns lying at  $\leq 5$  km from a single IPPC category-2.4 metal installation (ferrous metal smelters);

- 5) group 5, i.e., towns lying at  $\leq 5$  km from a single IPPC category-2.5.a or -2.5.b metal installation (non-ferrous metal smelters and producers);
- 6) group 6, i.e., towns lying at  $\leq 5$  km from a single IPPC category-2.6 metal installation (surface treatment using an electrolytic or chemical process);
- 7) intermediate group, i.e., towns lying at  $\leq 5$  km from any industry other than metal production and processing; and lastly,
- 8) unexposed group, i.e., towns having no EPER-registered industry within a radius of 5 km from the centroid (reference level).

Finally, in view of that fact that the characteristics of the respective metal installations vary (years of operation, production volume, type and amount of emissions), installations that had commenced operations prior to 1990 were analyzed individually, with the analysis being confined to an area of 50 km surrounding each installation so as to have a local comparison group, and with the RRs being estimated using a Poisson regression model proposed by Breslow and Day (Breslow and Day, 1987), as an external standard. In this model, the regression coefficient of the exposure term gave us the logarithm of the ratio between the respective SMRs for the exposed and reference zones, which we called "RR". To take into account the problem of multiple comparisons, p-values were also suitably adjusted, by controlling for the expected proportion of false positives (False Discovery Rate) as proposed by Benjamini (Benjamini and Hochberg, 1995; Benjamini and Yekutieli, 2001). The risk gradient in the vicinity of each facility was likewise studied, with distance from town to installation as an explanatory variable categorized in concentric rings (0-5, 5-10, 10-20, 20-30 km; and 30-50 km as reference). This was included in all models as both a categoric and a continuous variable, thereby making it possible for: the effect of the respective distances to be estimated by the former; the existence of radial effects to be ascertained by the latter (rise in RR with increasing proximity to an installation); and, by applying the likelihood ratio test, the statistical significance of such distance-related effects to be computed. RR estimates were adjusted for the abovementioned

sociodemographic variables, and towns that had some industry other than metal production and processing within a radius of 5 kilometers of the municipal centroid were excluded.

### 3. Results

From 1994 to 2003 there were 27,765 leukemia-related deaths in Spain among men and 12,285 among women.

Figure 1 depicts the geographic distribution of the 118 metal industries studied, along with their EPER code. The pollutants and amounts emitted by these installations as a whole, as well as the percentage with respect to the total emitted by all industrial sectors included in the EPER-Spain in 2001, are shown in Table 1. Among the substances with greatest emissions to air were CO<sub>2</sub>, CO and SO<sub>2</sub>; and among those with greatest emissions to water were chlorides and nitrogen.

Table 2 shows the RRs for towns with metal production and processing installations at a distance of less than 5 km, estimated using Poisson mixed regression models. As will be seen, analyses of the installations overall and of those which went into operation before 1990 showed a slight statistically significant excess risk of dying due to leukemias across the sexes. When foci that released pollutants to air were analyzed, the significant excess risk was observed for males, whilst in the case of installations that released pollutants solely to water, a slight significant risk was observed for the entire population.

Table 3 shows RRs of leukemia in towns lying at less than 5 kilometers from one or more pre-1990 metal production and processing installation, by type of industrial activity and pollution discharge route (air or only water). It will be seen that, in the case of installations that released some type of pollutant to air in the vicinity of electrolytic or chemical surface-treatment and galvanizing installations, the statistically significant excess risk was concentrated in women (RRs=1.34 and 1.58 respectively), and in towns affected by more than one installation or by multiple pollution sources, the statistically significant excess risk was concentrated in men. With regard to metal production and processing

industries that released pollution solely to water, the highest excess risk was concentrated among women in the vicinity of non-ferrous metal installations (RR=1.69). In men too there were elevated excess risks in the environs of galvanizing installations and ferrous and non-ferrous metal production facilities, but these failed to attain statistical significance. This analysis stratified by type of industrial activity served to highlight significant results that were masked in the analysis of Table 2.

Lastly, Table 4 shows the RRs for areas ( $\leq 5$  km) surrounding metal industries which commenced industrial activity prior to 1990, and for ever-decreasing radiuses within a 50-kilometer circle drawn round each installation. Data are shown for installations having a statistically significant excess risk in the "near vs. far" analysis and/or for those in which the test for trend proved significant in the risk gradient analysis, suggesting a positive association. In the former analysis, the nine facilities covered by the table registered statistically significant elevated excess risks in their respective environs, and six of them, namely, facilities '30' (Cantabria), '1478' (Corunna), '1606' (Cadiz), '2076' (Cantabria), '2494' (Teruel) and '3645' (Guipuzcoa), also displayed significant risk gradients. Their geographic positions are depicted in Figure 2.

In the above table, the "near vs. far" analyses were performed separately for each pre-1990 facility, as were their respective corrections using multiple comparisons (see Supplementary Material).

#### **4. Discussion**

This study is one of the first to use publicly accessible information available in the EPER to explore the effects of the metal sector on cancer mortality among neighboring populations. Our results indicate a slight excess leukemia-related mortality among men and women living in the vicinity of metal production and processing installations. Analysis by pollution discharge route shows that installations which release pollutants to air pose a greater excess risk with residential proximity than do those which release pollutants solely to water. Whereas in the former group, statistically significant excess risk is found in the environs of electrolytic or chemical surface-treatment and galvanizing

installations, in the latter this excess risk arises in the environs of non-ferrous metal smelters and producers, with -rather curiously- significant excess risk being exclusively confined to women.

In the individualized analysis, it should be noted that most of the installations which displayed excess risk in the "near vs. far" analysis also displayed significant results in the risk gradient analysis, something that supports the hypothesis of a "real" association between residence near these types of facilities and a greater risk of dying of leukemia. Another aspect to be borne in mind is that in some specific installations, excess risks solely affect men, which may be indicative of a possible source of occupational exposure.

Recent studies reinforce the idea of an association between residential exposure to pollutant industries and excess risk of malignant tumors (Casella et al., 2005; Garcia-Perez et al., 2009; Garcia-Perez et al., 2010; Parodi et al., 2005; Tsai et al., 2009). Ecologic studies, such as the one presented here, may suggest new avenues of research with respect to exposure to industrial pollution and risk of developing or dying from different tumors. One of the advantages of the design chosen is its high power for including a great number of subjects. A further advantage lies in the fact that the analysis can be repeated in future, which is crucial for monitoring and controlling the effects of pollution, and that this study can be reproduced using leukemia incidence data broken down by age group in certain specific locations. Nevertheless, in this type of studies conclusions can neither be obtained in terms of cause – effect, nor do individuals inferences from studies of groups, since it might incur the ecological fallacy.

One of this study's limitations is the use of mortality instead of incidence, in view of the fact that it involves a type of tumor with a high survival, particularly in children. In the absence of a population-based leukemia incidence registry in Spain, we chose to use mortality data, the quality of which is regarded as good (Perez-Gomez et al., 2006).

This study uses distance to the pollution source as a proxy of exposure, assuming an isotropic model, something that could introduce a problem of misclassification, since real exposure is critically dependent on prevailing winds, geographic landforms and releases into aquifers. A further possible

bias in the allocation of exposure is the use of centroids as coordinates to pinpoint the entire population of a town, when, in reality, the population may be fairly widely dispersed. Nevertheless, these problems would be posed in all cases, limiting the capacity to find positive results but in no way invalidating the associations found.

In an attempt to reduce possible biases deriving from confounding variables not included in the study, mixed Poisson regression models were fitted with "province" as the random effects term, something that constitutes a more conservative option. Another point to be borne in mind is that some installations for which statistically significant RRs were observed, are situated in areas with numerous industries releasing pollution into the environment, a problem when it comes to interpreting the results. For instance, situated around facility '1606' are industries that emit benzene (chemical industries and oil refineries) and that might thus be linked to the excess risk detected in neighboring towns. Including towns exposed to other EPER installations as the "intermediate group" in the statistical analyses goes some way to solving this problem.

One aspect addressed in the analyses is that of multiple comparisons. In the supplementary material, we provide adjusted p-values, though from an epidemiologic point of view we prefer to discuss the resulting RRs in the light of a series of factors, namely, the magnitude of risk *per se*, the consistency of the associations observed, and biologic plausibility. Furthermore, on studying the facilities on a one-by-one basis, it has been estimated that for  $\alpha=0.05$ , random chance would account for 2.6 associations (number of comparisons x percentage of statistically significant  $RR>1$  expected under the null hypothesis) for each of the analyses by sex, a figure lower than the number of associations observed.

Of all the industrial groups registered in the EPER-Spain, metal production and processing installations are the principal emitters to air of cadmium, hydrogen cyanide, CO, chromium, copper, lead, perfluorocarbons, tetrachloroethylene and zinc, and the principal emitters to water of benzene, toluene, ethylbenzene, xylenes, cyanides, dichloromethane, phenols, fluorides, PAHs and nickel (Table 1).

Although the metal industries analyzed in this study reported pollution data in 2001, the date when such industries commenced operations was taken into account for analysis purposes: of the total of 118 facilities, 105 started up before 1990 and the great majority went into operation prior to the 1960s, so that surrounding populations could have been exposed continuously to their emissions for long periods of time.

Emissions from metal sector installations, which encompass several types of industrial activities, arouses social alarm due to the health problems that may be generated among their workers and the surrounding population. Indeed, there are studies that have linked excess leukemias with residential proximity to industrial plants (Benedetti et al., 2001; Linos et al., 1991; Shore et al., 1993; Weng et al., 2008), including metal industries (Casella et al., 2005; Knox and Gilman, 1997). Moreover, a Canadian study covering over 10,000 metal workers detected a statistically significant excess risk of dying from leukemia (Gallagher and Threlfall, 1983), and a cohort of Korean steel workers was found to display a significant excess incidence associated with lymphohematopoietic cancer, including leukemias (Ahn et al., 2006). Silverstein too observed excess risk of leukemia in another cohort of ferrous foundry workers (Silverstein et al., 1986). Nevertheless, occupational exposure levels might well be very different to those reported in the environments of towns close to these installations.

One of the most interesting results of our study was the excess leukemia-related mortality in the vicinity of galvanizing installations which release pollutants to air (Table 4). The galvanizing sector is one of the industrial activities that releases dioxins to air (ATEG-Grupo Interlab, 2005) and is included in the Spanish National Dioxin and Furane Inventory (Martinez et al., 2008). Dioxins are recognized by the IARC as carcinogens in humans (IARC, 2009) and, due in great measure to the industrial accident in Seveso (Italy), studies have been conducted which have reported a connection between exposure to such substances and increased risk of leukemias (Bertazzi et al., 1997; Bertazzi et al., 2001; Collins et al., 2009; Consonni et al., 2008; Read et al., 2007), a finding that could be related to the excess risk observed by us.

Another noteworthy result is the high excess mortality found in the environs of electrolytic or chemical surface-treatment installations that release pollutants to air (Table 4). These types of metal industries (many of which belong to the automobile sector) use metalworking fluids (MWFs), a range of oils and other chemicals substances used to cool and/or lubricate metal workpieces when they are being machined, ground, milled, etc., and known to be carcinogens in humans (Savitz, 2003). Some occupational studies have found excess leukemia-related mortality among workers exposed to certain types of MWFs (Eisen et al., 1992; Eisen et al., 2001; Tolbert et al., 1992).

Lastly, it should be noted that the primary metal industry is a major environmental contributor of chlorinated solvents, which are potential chemical leukemogens (Shore et al., 1993). According to European Chlorinated Solvent Association (ECSA), chlorinated solvents are defined as methylene chloride (dichloromethane), perchloroethylene (tetrachloroethylene) and trichloroethylene (Chlorine Online, 2010), and are mainly used in metal degreasing. Both tetrachloroethylene and trichloroethylene are recognized as probable carcinogens according to the IARC (IARC, 2009) and there are studies which have linked exposure to drinking water contaminated by these substances to an increase in incidence of leukemias exclusively among women (particularly elevated for certain histologic types in the case of trichloroethylene), with no such effect being observed for males (Cohn et al., 1994; Fagliano et al., 1990). Likewise, risk of acute lymphocytic leukemia in childhood was significantly increased among girls but not among boys. This could be related to the significant excess risks found by us for women alone. It should be stressed that chlorinated solvents are released into the environment, chiefly as toxic waste discharged into water drainage areas by the metal sector, and that on the whole, effluents from metal industries are genotoxic, in that they induce cytogenetic damage, mutations, and DNA damage in repair processes (Claxton et al., 1998; Houk, 1992).

Although publicly accessible EPER information enables the type of emissions coming from pollutant industries to be established, there are no data available on the actual amounts of hazardous waste discharged by these installations. However, the updating of the EPER in the form of the new

European Pollutant Release and Transfer Register (E-PRTR) will incorporate additional information on releases of such waste.

## **5. Conclusion**

The results of this study indicate a possible ecologic association between residential proximity to Spanish metal industries as a whole and excess risk of leukemia-related mortality among men and women alike. Furthermore, when pollution discharge routes and types of industrial activity were studied, there were excess risks associated with certain activities that proved statistically significant among women alone. Lastly, in the environs of a number of specific installations, significant results were observed in both the "near vs. far" and risk gradient analyses.

The study of cancer mortality in areas surrounding industrial pollution sources is beginning to assume growing importance, and industrial pollutant emission registers such as the EPER and E-PRTR afford a useful and valuable tool for studying industrial pollution that affects the health of the population.

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## **Figure legends**

Figure 1: Geographic distribution of Spanish metal industries.

Figure 2: Geographic location of pre-1990 metal installations with statistically significant excess mortality in the "near vs. far" analysis and/or significant test for trend in the risk gradient analysis.