1 Cancer mortality and chemical exposure in a retrospective zinc and lead smelter cohort: A 48-year follow-up

Ariane Leroyer, Harry Gomajee, Romain Leroy, Muriel Mazzuca, Bruno Leleu, Catherine Nisse

Version of Record: https://www.sciencedirect.com/science/article/pii/S1438463922000384
Manuscript_67c4e9514d89dc704044060f96b1dc5a

Cancer mortality and chemical exposure in a retrospective zinc and lead smelter cohort: A 48-year follow-up

Ariane LEROYER[a,b], Harry GOMAJEE[b,c], Romain LEROY[b,c], Muriel MAZZUCA[b,d], Bruno LELEU[c1], Catherine NISSE[b,c,d]

[a] Univ. Lille, Inserm, CHU Lille, Lille Inflammation Research International Center (LIRIC), UMR 995, F-59000 Lille, France.

[b] Occupational Health Department, Faculty of Medicine, F-59000 Lille, France

[c] Center for Occupational and Environmental Diseases, CHU Lille, F-59000 Lille, France

[d] Univ. Lille, CHU Lille, Institut Pasteur Lille, ULR 4483 - IMPECS - IMPact de l'Environnement Chimique sur la Santé humaine, F-59000 Lille, France.

Corresponding author:

Ariane LEROYER

Département Universitaire de Médecine et Santé au Travail

Faculté de médecine, pôle recherche

1 place de Verdun

59045 LILLE Cedex

ariane.leroyer@univ-lille.fr

[1] Present address: ASTBTP13, La Palmeraie du Canet, 22 bd Charles Moretti, Bâtiment Vaena, 13014 Marseille, France

Abstract

Introduction: Very few studies to date have investigated cancer mortality in non-ferrous metal smelters. Existing studies mainly focus on lead exposure and have reported inconsistent results. The aim of this study was to investigate the risk of excess cancer mortality in the employees of a lead and zinc smelter located in the north of France by 1) comparing mortality in this cohort of employees with that of the regional population; 2) studying the associations between occupational exposure and cancer deaths.

Methods: The study cohort was composed of male workers, born in France, who had been employed by the company in question for at least 365 consecutive days. A company-specific job-exposure matrix was produced in order to calculate a cumulative exposure index for 15 toxic agents. Deaths of smelter employees which occurred between January 1, 1968 and December 31, 2015 were compared to those in the regional population (standardized mortality ratio, SMR). The relationships between the cumulative exposure indexes and mortality by cancer site were studied using Cox regression models with age and the 20-year lagged cumulative exposure index as time-dependent variables.

Results: Vital status was found for 2,177 of the employees in the cohort (98%). Median follow-up was 34.8 years (interquartile interval = 24.3 - 44.8), totaling 74,437 person-years. Compared to the regional population, no excess risk of all-cause mortality (n=913, SMR=0.96, 95%CI:0.90-1.02), nor of cancer mortality (n=338, SMR=0.97, 95%CI:0.87-1.08) was found. An overall significant excess risk of cancer mortality was found for employees who worked in this non-ferrous metal smelter for a period of between 15 and 29 years (n=139, SMR=1.23, 95%CI:1.04-1.45). Asbestos exposure was found to be associated with an increased risk of mortality for all cancer sites (p=0.0012), lip-oral cavity-pharynx malignant neoplasms (MN) (p=0.0141) and trachea-bronchus-lung MN (p=0.0018); lead exposure was associated with the same risk for lip-oral cavity-pharynx (p=0.0378) and liver MN (p=0.0155); aromatic amine exposure with bladder MN (p=0.0002); chromium exposure with colon-rectum-anus MN (p=0.0057) and colon MN (p=0.0315); bismuth exposure with rectal MN (0.0011) and sodium hydroxide vapor exposure with laryngeal MN (0.0150).

Conclusion: Including occupational exposure to numerous toxic agents other than lead in this study of smelter mortality has made it possible to identify associations between different toxic agents and cancers, opening up new avenues for future research.

Keywords:

Retrospective cohort, cancer mortality, smelter, lead, cadmium, asbestos

Highlights

- Increased risk of death from liver cancer with cumulative exposure to lead
- Increased risk of death from larynx cancer for workers exposed to sodium hydroxide vapor
- Increased risk of death from bladder cancer for workers exposed to aromatic amines
- Asbestos exposure in smelter workers linked to deaths from several types of cancer
- A broad range of toxic agents should be taken into account when studying causes of death in smelter workers

Introduction

Cancer is the leading cause of mortality in men in France (Boulat et al., 2019). Currently, occupational exposures represent a substantial proportion of the new cancer cases in France, around 4% in men (Marant Micallef et al., 2019). In France, a program for monitoring mortality by sector of activity has found a significant excess risk of cancer mortality in male employees in the metal industry, with a relative risk of 1.16 (Santé Publique France, 2018). The lead and zinc smelter investigated in this study, located in the north of France, operated for over a century and was shut down in 2003. Given the very high levels of lead to which the smelter employees were exposed, questions were raised regarding mortality rates. There was a particular concern regarding cancer mortality, even though the precise carcinogenic effects of lead have not yet been clearly established in humans (Fu and Boffetta, 1995; IARC Monographs, 2006). In the literature, several cohorts of smelter workers exposed to lead have already been studied, with each study coming to different conclusions. One Italian cohort (Cocco et al., 1997) studied 1,388 workers and laborers in the production and maintenance units of a primary lead-smelting plant. Mortality from all cancers, stomach cancer, and lung cancer was lower than expected, and mortality from kidney cancer was not significantly elevated. A Swedish study followed a cohort of 3,979 workers at a copper and lead smelter, with follow-up last updated in 1997 (Lundström et al., 1997). This study found significant excess mortality for all cancers and for lung cancer, an association which was ultimately attributed to arsenic exposure (Lundström et al., 2006). Furthermore, in a cohort of 2,300 U.S. workers at 6 lead smelters, no significant excess mortality was found overall, despite the non-significant elevated risk found for certain cancer sites, in particular digestive and respiratory cancer (Wong and Harris, 2000). Finally, mortality in another cohort of 1,990 U.S. workers at a primary lead smelter in Idaho has recently been reassessed (Bertke et al., 2016). Significant excess all-cause, cancer and lung cancer mortality were found in the cohort compared to mortality rates for the State of Idaho. A non-significant elevated mortality rate for kidney and stomach cancer was also found but no relationship to the level of cumulative lead exposure established. It is difficult to compare results between these cohorts due to the disparities in terms of production processes and lead exposure levels, and due to the combined exposure to multiple toxic agents which is often ignored or partially taken into consideration. A specific study of the lead and zinc smelter in the north of France was therefore deemed necessary in order to investigate the impact of the exposures workers were subjected to in this particular firm.

The aim of this study was to assess the risk of excess cancer mortality in the employees of a lead and zinc smelter by comparing mortality in this cohort of employees with that in the regional population, and by studying the associations between occupational exposures and causes of cancer deaths.

Material and methods

The lead and zinc smelter

This study was conducted in a metallurgy firm involved in the primary processing of precious and non-ferrous metals, specialized in lead and zinc production, implanted in the north of France from 1894 to 2003. This company was one of the largest employers in the area. It operated two pyrometallurgical smelters, a smelter using the imperial smelting process for mixed zinc-lead ore, and a water jacket furnace for lead ore. In its final years of operation annual production was 160,000 tons of lead and 105,000 tons of zinc. A quarter of its supply of raw materials came from metal recycling. At certain points in its history the company also had a germanium production workshop (1976-2003) and an indium workshop (1982-2003).

The company was liquidated in March 2003. At this time the company had 830 employees, not including temporary workers and subcontractors.

Producing lead and zinc using pyrometallurgical processes involves roasting ore to remove the sulfur, followed by reduction smelting in an adapted furnace (a water jacket shaft furnace or imperial smelting process blast furnace). After reduction the raw lead and zinc are refined ready for sale. These processes not only expose workers to metals (namely lead, cadmium, arsenic, bismuth, mercury, antimony, thallium, zinc), but also to heat, carbon monoxide, sodium hydroxide, sulfur dioxide and sulfuric acid. There are five different sectors within the firm:

1) *Production:* lead and zinc production (including roasting, smelting and refining), sulfur dioxide workshop (where liquid sulfur dioxide is produced, using aromatic amines - toluidine and xylidine), sulfuric acid workshop, hydrometallurgy workshop (production of rare metals - germanium, gallium)

2) *Technical and purchasing units*: purchasing, supply chain, warehouse, maintenance and servicing workshops, electrical and instrumentation unit, design unit, civil engineering, fluids-energy, and garage for maintaining the site vehicles.

3) *Control and development*: metallurgy studies (for the continuous improvement of metal production techniques), sampling (taking and preparing samples for analysis), laboratory (carrying out chemical analyses) and investigations (various measurements taken in the plant).

4) *Logistics*: transporting raw materials, intermediate and finished products around the plant.

5) *Administrative sector*: administrative roles, security, IT unit, training.

Biomonitoring of lead exposure in the company's employees was introduced at the start of the 1970s, by monitoring urinary delta-aminolevulinic acid levels. The monitoring of blood lead levels was introduced in 1985. In France, the regulatory monitoring of lead exposure with blood lead level testing officially came into force with the decree dated 1 February 1988. Cadmium exposure monitoring was also implemented in the 1990s by monitoring urinary cadmium levels in exposed workers.

The biomonitoring results were anonymised and we were unable to link them to each of the employees in the cohort. However, averages per period and per sector were available. The workshops where workers were the most exposed to lead were the lead and zinc smelters. Blood lead levels decreased gradually over time until a mean level of around 500 $\mu g\ L^{-1}$ for workers at these stations was reached at the start of the 2000s. Employees with blood lead levels approaching 800 $\mu g\ L^{-1}$ (the upper regulatory biological limit value since 1988) were temporarily moved to less exposed workstations. In some rare cases, employees with blood lead levels over 800 $\mu g\ L^{-1}$ with consequences in terms of renal function were declared unfit for positions exposed to lead and were moved permanently to the less exposed sectors on the site.

Atmospheric measurements were also taken as of the 1990s onwards. Mean exposure levels could reach 3000 $\mu g\ m^{-3}$ for Pb and more than 100 $\mu g\ m^{-3}$ for Cd for some workstations. This collective, atmospheric and biological data was synthesised by workstation, and enabled exposure levels to be estimated when a company-specific job-exposure matrix was produced.

Population

The cohort studied was composed of all former employees of the company who met the following inclusion criteria: male subjects, born in France, employed by the company on the site for at least 365 consecutive days and who worked there during the period from 1 January 1968 to 24 March 2003 (the date of the

company's liquidation). Temporary workers and subcontractors were not included in the study (as there were no records of these workers).

When the firm closed, the association of former workers on the site entrusted the hard copies of the former employees' administrative files to the French national labor archives (*ANMT*). The list of employees included in the cohort was established based on the information in these files.

Data collection

The following information was collected for each employee included: the administrative data required to obtain vital status from the National Institute of Health and Medical Research (*INSERM*) (surname, first name, sex, date and place of birth), their work history with the firm (official dates of entry and departure, positions held and sectors occupied by the employee during his time working on the site).

The vital status and individual medical causes of death were investigated for all subjects in the cohort. Only the initial causes of death (causes which triggered the process resulting in death) were considered in the data analysis. The causes of death were coded based on the classifications in force at the time of death: International Classification of Diseases, 8th revision (ICD-8) from 1968 to 1978; 9th revision (ICD-9) from 1979 to 1999; and the 10th revision (ICD-10) since 2000.

Assessment of occupational exposure in the company

A company-specific job-exposure matrix was created by former employees of the firm in collaboration with the research team. Exposure to fifteen toxic substances was assessed for the cancer mortality analysis: lead (Pb), cadmium (Cd), arsenic (As), bismuth (Bi), chromium (Cr), antimony (Sb), thallium (Tl), asbestos, aromatic amines (ortho-toluidine and xylidine), diesel exhaust, sodium hydroxide vapor, solvents, sulfur dioxide (SO_2), dust, silica (SiO_2). The assessment of exposure was carried out for each of the 2,210 positions in the company identified as being held by employees during their time of employment. Temporal changes in exposure were taken into account by way of job titles, which evolved over the course of time. This enabled us to distinguish different exposure levels successively, within the same profession. The exposure assessment was based on an understanding of the production process, atmospheric exposure data, bioavailability (of the different chemical forms of lead) and/or biological data from former employees working in different roles. Four categories of exposure were defined for Pb, based on atmospheric Pb levels: 0-50 µg m^{-3}, 51-100 µg m^{-3}, 101-150 µg m^{-3} and >150 µg m^{-3}. These were coded as 1, 3, 5 and 8 respectively to approximately reflect the increase in mean levels in each of these groups. Similarly, four categories of exposure were defined for Cd, based on atmospheric Cd levels: 0-10 µg m^{-3}, 11-30 µg m^{-3}, 31-50 µg m^{-3} and >50 µg m^{-3} which were also coded as 1, 4, 8 and 12 respectively. For the other toxic agents investigated, four categories of exposure were defined: no exposure, possible exposure, indirect exposure and direct exposure, coded as 0, 1, 2 and 4 respectively. The coherency of the matrix as a whole was validated by the former occupational health physician for the firm. For each toxic substance, a cumulative exposure index was assigned to each employee, corresponding to the sum of the numbers of years of exposure weighted by the levels of exposure.

Legal and ethical requirements

The ethics committee (Advisory Commission on Information Processing in Health Research, *CCTIRS*) approved the terms and conditions for implementing the project on 10 June 2015. The French National Commission for Information Technology and Civil Liberties (*CNIL*) approved the study on 16 December 2016

(deliberation no. 2016-389 dated 8 December 2016). The *ANMT* approved the consultation of the firm's archives on 26 January, 2017.

Statistical analysis of data

Person-time began on whichever was the earliest date between 1 January 1968 or one year after the hire date and continued until whichever was the most recent date between the date of death or 31 December 2015.

For each of the causes of death studied, the corresponding list of disease codes established according to the relevant version of the international classification of diseases is set out in detail in the Supplementary Materials, Table S1.

Deaths of former employees of the firm which occurred between 1 January 1968 and 31 December 2015 (endpoint) were compared to those in the regional population (the North and Pas-de-Calais departments). Mortality rates for the region were applied to the study cohort, taking into account age (by 5-year age groups) and the year of death (calculation of the standardized mortality rate, SMR). The SMR are presented with the 95% confidence interval, calculated using the exact method for 5 or fewer observed deaths and Byar's approximation method for more than 5 deaths (Breslow et al., 1987; Sahai and Khurshid, 1996). Comparisons were made for all employees and according to: 1) the date of hire in the company, with 3 periods defined based on the company's production history: 1921-1936 (very high exposure to lead), 1937-1969 (high exposure to lead), and 1970-2003 (more moderate exposure to lead); 2) the duration of employment in the company, in 3 categories: less than 15 years, from 15 to 29 years, and 30 years or more; 3) the following four job sectors: production, technical and purchasing units, control and development, logistics. The employees taken into account were those who worked exclusively in one of these four sectors (for at least one year) and possibly in the administrative sector (where employees were considered not to be exposed). This analysis by sector therefore did not take into account employees who worked exclusively in the administrative sector nor those who worked in different sectors (excluding the administrative sector).

The relationship between the cumulative exposure to the 15 toxic agents and mortality by cancer site was investigated using Cox regression modelling with age and cumulative exposure index as time-dependent variables. This model enables us to take account of changes both in the age and the cumulative exposure index of employees, for each year's monitoring. For each toxic agent, a cumulative exposure index was incremented for each year of follow-up, first with no lag and then with a lag of 10, 15 and 20 years. Different cumulative exposure categories were constituted: three categories for Pb, Cd, asbestos and dust; two categories (exposed/non exposed) for all other substances (See Supplementary Materials, Tables S2-S3). Age-adjusted analyses were conducted for the causes of death for which at least ten deaths were found (that is 12 locations). For Pb, Cd, asbestos and dust, the median cumulative exposure index for each of the three categories was used to compute the linear trend tests. The overall statistical significance and linear trend (expressed as a global P-value and trend P-value, respectively) were assessed with a likelihood ratio statistic. Subsequently, for each of the 12 causes of death, we created a first multivariable Cox model in which we fitted all of the covariates for which global p-value was <0.15 in the age-adjusted model. Then we used a backward step-by-step procedure based on Akaike's information criteria (AIC), so as to finally keep only significant exposures ($p<0.05$) in the final models. In the presence of collinear variables, a reasoned choice was made to select the toxicant to be retained in the model. The absence of violation of proportional hazard assumption was tested for each model.

All analyses were conducted using the R 3.6 software program (epitools and survival packages).

Results

Population description

The cohort of employees was composed of 2,226 men born in France. Vital status and cause of death were established for 2,177 of them (97.8%). Median follow-up was 34.8 years (interquartile interval = 24.3 - 44.8), totaling 74,437 person-years. A total of 2,210 job titles were identified by examining the work histories conserved in the firm's administrative archives.

These employees were born between 1902 and 1980 (median year of birth: 1944) (Table 1) and started working for the firm between 1921 and 2002. Almost 60% were hired before 1970. Just over a quarter of the employees worked for the firm for less than 10 years and over 60% for 30 years or more. More than 40% of them had worked exclusively in the production sector and 22% in the technical and purchasing units. On 31 December 2015, 913 of them had died. Cancer was the most common cause of death (338 deaths, 37.0%) (Table 2). Almost one-third of these cancer deaths were caused by trachea-bronchus-lung cancers (98 deaths, 10.7%).

Comparison with mortality in the regional population

Compared to the regional population, no excess risk of all-cause mortality (913 deaths, SMR=0.96, 95%CI:0.90-1.02), nor of cancer mortality (338 deaths, SMR=0.97, 95%CI:0.87-1.08) was found (Table 3). An excess risk of death from malignant neoplasms (MN) was observed in employees who had worked for the firm for between 15 and 29 years, SMR=1.23, 95%CI:1.04-1.45. An excess mortality from colon-rectum-anus MN was observed in employees hired between 1921 and 1936 (6 deaths, SMR=2.84, 95%CI: 1.04-6.18). Two deaths from gallbladder MN were found. Both of these employees had worked exclusively in the production sector (SMR=11.50, 95%CI: 1.39-41.52), were hired between 1937 and 1970 (SMR=4.68, 95%CI: 0.57-16.89), and had worked for the firm for between 15 and 29 years (SMR=11.77, 95%CI: 1.42-42.24). Eight deaths from pancreatic MN were found, with an excess risk for employees having worked exclusively in the logistics sector (3 deaths, SMR=6.20, 95%CI: 1.28-18.10). Deaths from leukemia (n=8) were over-represented in employees having worked exclusively in the technical and purchasing units (7 deaths, SMR=3.34, 95%CI: 1.34-6.88).

Cancer mortality by exposure category

Of all the exposures identified within the firm, exposure to Pb, Cd, asbestos and dust were those which affected the largest number of employees. For all the other toxic substances studied, more than 75% of the cumulative exposure indexes with a 20-year lag were null (See Supplementary Materials, Tables S2-S3). High positive correlations (correlation coefficients >0.60) were found between Pb, Cd, asbestos and dust, between As, Sb and sodium hydroxide vapor, between solvents and silica, Cr and silica, and between aromatic amines and sulfur dioxide (See Supplementary Materials, Figure S1).

The study of the associations between the cumulative exposure indexes and the risk of death showed similar results regardless of the time lag applied (none, 10, 15 or 20 years). The 20-year lag analysis is presented in Table 4. When several different exposures were associated with a specific cause of death ($p<0.15$) the final results of the multivariate analysis are summarized in Table 5.

Taking age into account (Table 4), a significant excess risk of death from MN was found in subjects exposed to Cd and asbestos. In the final model, only exposure to asbestos was significantly associated with an

excess risk of death from MN (HR=1.76, 95%CI: 1.29-2.41 and HR=1.42, 95%CI: 1.03-1.96 for the intermediate and high exposure categories, respectively) (Table 5). Deaths from trachea-bronchus-lung MN were significantly associated with Pb, Cd, asbestos and dust exposure (age-adjusted analysis); in the final model, only exposure to asbestos showed a significant excess risk of death from trachea-bronchus-lung MN (HR=2.01, 95%CI: 1.06-3.83 and HR=2.96, 95%CI: 1.56-5.64, for the intermediate and high cumulative exposure categories, respectively). Deaths from lip-oral cavity-pharynx MN were associated with Pb and asbestos exposure (age-adjusted analysis), which both remained significant in the final model (HR=12.75, 95%CI: 1.42-114.7 and HR=14.87, 95%CI: 1.30-169.6 for the intermediate and high cumulative exposure categories of asbestos, respectively; HR=2.86, 95%CI: 0.69-11.96 and HR=0.79, 95%CI: 0.13-4.80 for the intermediate and high cumulative exposure categories of lead, respectively). Taking age into account, numerous toxic agents were associated with deaths from colon-rectum-anus MN and rectum MN. In the final model, only the relationship to Cr exposure remained for deaths from colon-rectum-anus MN, and bismuth exposure for deaths from rectum MN. Colon cancer deaths were significantly associated with exposure to Cr and silica. The four subjects who died from colon cancer were exposed to both Cr and silica. To be consistent with the results observed with deaths from colon-rectum-anus MN, we chose to keep Cr in the final regression model. . Only Pb exposure was significantly associated with death from liver-intrahepatic bile duct MN and more specifically to deaths from liver cancer (HR=3.26, 95%CI: 0.25-41.72 and HR=13.36, 95%CI: 1.30-137.2 for intermediate and highly exposed workers, respectively). Sodium hydroxide vapor was the only toxic agent significantly associated with death from laryngeal cancer (HR=6.82, 95%CI: 1.45-32.06 for exposed versus unexposed workers). Deaths from bladder MN were significantly linked to aromatic amine and sulfur dioxide exposure; in the final model, only exposure to aromatic amines (HR=4.63, 95%CI: 1.01-21.22) remained significant. Lastly, none of the exposures studied were significantly linked to death from prostate MN nor to death from esophageal neoplasm.

Discussion

Compared to the regional population, an overall excess risk of cancer mortality was found for the employees who worked in this non-ferrous metal smelter for a period of between 15 and 29 years (n=139, SMR=1.23, 95%CI:1.04-1.45). Deaths from leukemia were significantly more frequent in employees having worked in the technical and purchasing units and deaths from pancreatic cancer more common in employees from the logistics sector. Asbestos exposure was found to be associated with an increased mortality risk for all cancer sites (p=0.0012), lip-oral cavity-pharynx malignant neoplasms (MN) (p=0.0141) and trachea-bronchus-lung MN (p=0.0018); lead exposure was associated with the same risk for lip-oral cavity-pharynx (p=0.0378) and liver MN (p=0.0155); aromatic amine exposure with bladder MN (p=0.0002); chromium exposure with colon-rectum-anus MN (p=0.0057) and colon MN (p=0.0315); bismuth exposure with rectal MN (p=0.0011) and sodium hydroxide vapor exposure with laryngeal MN (p=0.0150).

This study has a number of weaknesses, in particular the small number of deaths for some cancer sites which limits the statistical power of the analyses, notably when investigating the relationship to occupational exposure. Furthermore, the absence of data on individual risk factors means factors such as smoking could not be taken into account. However, the study also has a number of strengths: the very low percentage of subjects lost to follow-up (2.2%); the detail and accuracy of the employees' work histories (2,210 jobs identified); and the company-specific job-exposure matrix which makes it possible to take into account a broad range of occupational exposures. Moreover, the levels of exposure to Pb and Cd in the job-exposure matrix were determined based on atmospheric levels.

As in the present study, an overall deficit in all-cause mortality has been found in most studies of non-ferrous metal smelters (Lundström et al., 1997; Marsh et al., 2009; Wong and Harris, 2000) which is

probably due to a healthy worker effect bias. Nonetheless, elevated mortality was reported in a cohort of 1990 lead smelter workers in Idaho (SMR=1.23, 95%CI: 1.17-1.23) with an exposure-response relationship found for cumulative exposure to lead (Bertke et al., 2016; Steenland et al., 1992). In an Italian cohort of 1,388 workers, non-significant excess all-cause mortality was found (SMR=1.05, 95%CI: 0.97-1.14) (Cocco et al., 1997). However, it should be noted that in these two cohorts, unlike the other studies in the literature, smelter employees mainly working in administrative roles were excluded from the analysis. As a point of comparison, our study also found a non-significant excess risk in the production and logistics sectors which were considered to be the most exposed.

Similarly to other mortality studies in smelters, no increase in mortality from all cancers was found (Cocco et al., 1997; Marsh et al., 2009). Nor was an increased incidence of cancer found for lead-exposed workers in a primary lead and copper smelter in Sweden (Englyst et al., 2001). However, excess cancer mortality was reported in other smelter studies. Excess cancer mortality was reported by Bertke et al. (2016) (SMR=1.29, 95%CI: 1.16-1.43) but the study did not establish any relationship with lead exposure levels. Lundström et al. reported excess cancer mortality (SMR=1.2, 95%CI: 1.0-1.5) in a Swedish cohort of 3,979 workers exposed to lead, but this excess was not found to be significant for the workers with the highest levels of lead exposure (SMR=1.2, 95%CI: 0.9-1.5). However, the incidence of cancer in this same cohort was not significantly elevated (SIR=1.1, 95%CI: 0.9-1.2).

Studies of employees in non-ferrous metal smelters usually use lead exposure as their point of reference for occupational exposure. However, smelting operations expose workers to many other toxic substances which should also be taken into consideration. In our cohort, although there was a significant increased risk of overall cancer mortality in workers with moderate and high exposure to cadmium (age-adjusted analysis), only asbestos exposure was significantly associated with excess all-cancer mortality (multivariate analysis). In 2004, the IARC upgraded its classification of inorganic lead compounds to Group 2A carcinogens, based on evidence from studies in experimental animals (IARC Monographs, 2006). Indeed, it is difficult to obtain firm evidence of a causal link between lead exposure and cancer from epidemiological studies in the general and working population due to combined exposures to other suspected or confirmed carcinogens.

Regarding lung cancer mortality, the results from smelter studies are inconsistent. An increased risk of lung cancer mortality was reported for workers in a primary copper and lead smelter in northern Sweden (SMR=2.8, 95%CI: 2.0-3.8) along with increased risk of incidence of lung cancer (SIR=2.9, 95%CI: 2.1-4.0) (Lundström et al., 1997). The latter was even higher for the subgroup with the highest exposure to lead (cumulative blood-lead index). In an update of the same cohort, the increased incidence of lung cancer in the 481 workers exposed in the smelter's lead workshop was confirmed (SIR=2.4, 95%CI: 1.2-4.5); but as the workers were also exposed to arsenic, the effects of these two carcinogens could not be untangled (Englyst et al., 2001). In the Idaho smelter cohort, a significant excess mortality of lung cancer was reported (SMR=1.94, 95%CI: 1.64-2.27), but there was no exposure-response relationship for lead (Bertke et al., 2016). The authors suggested that potential confounders such as arsenic, cadmium or smoking, which were not controlled in the study, might explain this finding. In our cohort, as in other smelter studies, there was no evidence of excess lung cancer mortality (Cocco et al., 1997; Marsh et al., 2009). Our study did however reveal an exposure-response relationship between exposure to lead, cadmium, asbestos, dust and lung cancer mortality. In the multivariate analysis, only asbestos remained significantly associated with lung cancer mortality. The presence of asbestos in the smelter is attested to in the furnaces, buildings and the personal protective equipment used. Asbestos is known to be carcinogenic for the lungs and this is a convincing explanatory factor which probably suffices to explain the increased incidence of lung cancer (IARC Monographs, 2012a). However, asbestos exposure is only rarely taken into consideration in other smelter mortality studies. Naturally, we cannot exclude a synergistic effect from other pulmonary

carcinogens such as tobacco, arsenic, chromium and cadmium. Several studies investigating smelters or other sectors of activity have reported links between lead exposure and lung cancer incidence or mortality (Anttila et al., 1995; Barry and Steenland, 2019; Fu and Boffetta, 1995; McElvenny et al., 2015; Steenland et al., 2017). However, to date there still appears be a lack of conclusive evidence to support such a link, in particular given the exposure to other pulmonary carcinogens.

In our study, lip-oral cavity-pharynx cancer mortality was associated with asbestos exposure. The results from the literature regarding this association are still conflicting whereas the association between laryngeal cancer and asbestos has been proven. As for Marsh et al. (2009) et Wong et Harris (2000), no increase in laryngeal cancer mortality was found for the cohort as a whole. No links were found between asbestos exposure and laryngeal cancer mortality, but there was a significant excess risk related to exposure to sodium hydroxide vapor. Caustic soda was used in the lead refining process, thus exposing employees to sodium hydroxide vapor. Sodium hydroxide is corrosive and can cause severe burns in any tissues it comes into contact with. Irritation of the nose, throat, and respiratory airways is induced by inhalation of low levels of sodium hydroxide as dusts, mists or aerosols. There are no data available on the direct carcinogenicity of sodium hydroxide. However, cancer of the esophagus has been reported to develop on damaged tissue many years after exposure to sodium hydroxide by ingestion. Although the association with laryngeal cancer found here has not been previously reported in the literature, it is plausible from a pathophysiological point of view due to the causticity of these vapors, as for strong inorganic acid mists which are recognized carcinogens due to their corrosivity (IARC Monographs, 2012b). In our study, lip-oral cavity-pharynx cancer mortality was also associated with lead exposure, but without excess risk in the highest exposure category. To date, the literature does not support this association.

Regarding digestive cancers, no significant excess mortality was found in this study. Significant associations were highlighted between lead exposure and liver cancer mortality, chromium exposure and colon-rectum-anus MN and colon MN mortality and between bismuth exposure and rectum cancer deaths.

The finding from our cohort of no excess mortality from esophageal cancer is consistent with the results from other smelter studies (Marsh et al., 2009; Wong and Harris, 2000). Furthermore, we did not find any exposure related to esophageal cancer deaths. In contrast, Steenland et al. (2019) reported a link between lead exposure and esophageal cancer mortality in a large multi-center cohort studying cancer incidence in lead-exposed workers in Finland and Great Britain.

To the best of our knowledge, no smelter studies have reported any significant excess mortality relating to stomach cancer. In our study, the results showed non-significant decreased mortality due to stomach cancer (SMR=0.87, 95%CI: 0.40-1.65) in line with the findings of Cocco et al. (1997) (SMR=0.97, 95%CI: 0.53-1.62) for Italian lead smelter workers, and those of Marsh et al. (2009) in workers at a copper smelter in Tennessee (SMR=0.78, 95%CI: 0.31-1.60). Other studies found a non-significant excess risk (Bertke et al., 2016; Gerhardsson et al., 1986; Wong and Harris, 2000). Similarly, no increased incidence of gastro-intestinal cancers was found in lead-exposed workers in the Swedish cohort (Lundström et al., 1997). Very few smelter studies have specifically investigated the relationship between lead exposure and stomach cancer (Bertke et al., 2016). Nonetheless, increased rates of stomach cancer have been reported for lead-exposed workers in a range of sectors of activity (Fu and Boffetta, 1995; Steenland et al., 2019, 2017; Steenland and Boffetta, 2000; Wong and Harris, 2000). The very small number of cases in our study (n=9) meant it was impossible to study the association between different exposures (including lead) and deaths due to stomach cancer.

Like Marsh et al. (2009) and Wong et Harris (2000) no excess colon cancer mortality was found in our cohort. However, mortality for this cancer site was significantly higher for workers exposed to chromium and silica. To our knowledge, no significant association with chromium exposure has yet been reported in

the literature. A meta-analysis of digestive cancers among workers occupationally exposed to Cr(VI) was published in 2010, including 13 studies with non-significant relative risk estimates for colon cancer ranging from 0.33 to 3.08 (Gatto et al., 2010). The colon cancer meta-SMR was 0.89, 95%CI: 0.70-1.12 for any Cr(VI) exposure. Another meta-analysis also failed to report links between Cr(VI) exposure and colon MN mortality (Deng et al., 2019). To the best of our knowledge, the association with silica is not currently supported by the literature. In our study, chromium exposure was also significantly linked to colon-rectum-anus MN mortality. The recent meta-analysis of Deng et al. (2019) pointed out a meta-SIR of 1.03, 95%CI: 0.96–1.12 for bowel cancer (intestine, colon, and rectum) exposed to hexavalent chromium.

A non-significant excess mortality for rectal cancer was found (SMR=1.78 95%CI: 0.92-3.11) as reported in two other cohorts of smelter workers, with four cases in the cohort investigated by Marsh et al. (2009) (SMR=1.60, 95%CI: 0.44-4.10), and eight cases in the study by Wong and Harris (2000) (SMR=1.23 95%CI: 0.53-2.42). This association has also been found in other sectors of activity involving lead exposure (McElvenny et al., 2015; Steenland et al., 2019). In our study there was no link to lead exposure but a strong association between bismuth exposure and death by rectum MN was found. This association has not yet been reported. Bismuth is not recognised as a carcinogen. This metal is widely used in therapeutics for leishmaniasis and helicobacter pylori treatment, and more recently in cancer therapy. In foundries exposure to bismuth occurs during the refining phase, which also involves exposure to other metallic elements such as lead, arsenic, antimony, as well as carcinogens such as asbestos, for which doubts exist regarding its carcinogenicity to the rectum (Paris et al., 2017).

No excess liver cancer mortality was found in our study, as in other smelter studies (Cocco et al., 1997; Marsh et al., 2009; Wong and Harris, 2000). However, an exposure-response relationship was found in our study between lead exposure and cancer at this site. To date, there is little data to support this association. In one Australian cohort of 4,114 workers exposed to lead in different sectors of activity, not including the primary lead industry, Gwini et al. (2012) found both significant excess liver cancer mortality and incidence. As the link with blood lead levels could not be studied, the authors attributed this increased risk to possible excessive alcohol consumption.

There was no evidence of excess mortality from bladder cancer. This was also the case in other cohorts of smelter workers (Cocco et al., 1997; Englyst et al., 2001; Marsh et al., 2009; Wong and Harris, 2000). The meta-analysis by Fu et Boffetta (1995) reported an association between lead exposure and bladder cancer mortality (meta-SMR=1.41, 95%CI: 1.16-1.71), but this was not supported by the findings of Steenland et al. (2019) in their study of almost 30,000 lead-exposed workers, even at levels of over 400 µg L^{-1}. In our cohort, bladder cancer mortality was not found to be associated with lead exposure but was associated with exposure to aromatic amines. Indeed, ortho-toluidine was used in the smelter to absorb sulfur dioxide from lead and zinc ore roasting workshops. Ortho-toluidine is carcinogenic and there is sufficient evidence that exposure leads to an elevated risk of urinary bladder cancer in humans (IARC Monographs, 2012b).

No evidence was found of excess kidney cancer mortality in our study, as in the majority of smelter worker cohorts (Marsh et al., 2009; Wong and Harris, 2000). Steenland et al. (1992) found a significant excess risk (SMR=2.39, 95%CI: 1.03-4.71) in the smelter workers most severely exposed to lead, but this finding was no longer present in the update by Bertke et al. (2016). Cocco et al. (1997) identified a non-significant elevated risk of kidney cancer (SMR=1.75, 95%CI: 0.46-4.49) with a significant increase in risk in line with duration of employment. Finally, Englyst et al (2001) found no increase in the incidence of kidney cancer in lead-exposed workers (SMR=0.9, 95%CI: 0.1-3.2). The number of kidney cancer deaths in our cohort was too low to study any possible associations with specific exposures. The kidney is, however, a target organ for lead and other metals in smelters, such as cadmium. Several authors have investigated lead's role in kidney

cancer but none have found any significant association (Callahan et al., 2019; Fu and Boffetta, 1995; Gwini et al., 2012; McElvenny et al., 2015; Steenland and Boffetta, 2000).

Most lead smelter cohorts reported no significant excess mortality for cancer of the central nervous system, notably Marsh et al. (2009) (SMR=1.39, 95%CI: 0.69-2.48), Cocco et al. (1997) (SMR=2.17, 95%CI: 0.57-5.57) et Wong et Harris (2000) (SMR=0.74, 95%CI: 0.24-1.74). Similarly, Lundström et al (1997) did not find any significant excess risk of central nervous system cancer in the workers most exposed to lead (SIR=1.6, 95%CI: 0.4-4.2). Our study only identified two deaths for this cause and therefore could not investigate any associations with exposure. A recent meta-analysis found suggestive evidence of an association between lead exposure and malignant brain tumors (pooled OR=1.13, 95%CI: 1.04-1.24) (Ahn et al., 2020), whilst the meta-analysis by Meng et al. found a non-significant elevated risk of meningioma or brain cancer (Meng et al., 2020).

In our study, significant excess leukemia deaths were found for employees who worked in the technical and purchasing sector. Exposure to hematotoxic solvents in this sector cannot be ruled out. However, the titles of the jobs held by these employees, the period of professional activity and the time lag between the end of their working life and death, were not suggestive of work-related cancers.

Conclusion

One of the strengths of this study is that it investigated a broad range of chemical substances present in non-ferrous metal smelters which have not often been considered in other studies conducted to date. Studying mortality in relation to exposure to these substances has confirmed previously-known associations, such as an excess risk of bladder cancer mortality in employees exposed to aromatic amines and lung cancer mortality in those exposed to asbestos. However, these associations have not been reported in previous smelter studies. Furthermore, new associations were found, namely between lead exposure and liver cancer mortality; lead exposure and lip-oral cavity-pharynx cancer mortality; bismuth exposure and rectum cancer mortality; chromium exposure and colon cancer / colon-rectum-anus cancer mortality; and finally sodium hydroxide vapors exposure and laryngeal cancer mortality. These findings should be further consolidated by future studies.

Conflict of Interest

None

Funding

This study was funded by the Regional Council of the Nord-Pas de Calais Region, Agreement N°2014_11312.

Acknowledgements

We would like to thank the *Association Chœurs de Fondeurs*, in particular Raymond CWERZINSKI, Jacques HOUZET, Albert LEBLEU, Serge PRUVOST and Gervais VANHELLE for their invaluable help in understanding the workings of the company and their involvement in producing the job-exposure matrix.

Our thanks also to the *ANMT* (French national labor archives) for giving us access to company data.

We also thank Kim BARRETT for translating the article.

References

Ahn, J., Park, M.Y., Kang, M.-Y., Shin, I.-S., An, S., Kim, H.-R., 2020. Occupational Lead Exposure and Brain Tumors: Systematic Review and Meta-Analysis. Int. J. Environ. Res. Public Health 17, 3975. https://doi.org/10.3390/ijerph17113975

Anttila, A., Heikkilä, P., Pukkala, E., Nykyri, E., Kauppinen, T., Hernberg, S., Hemminki, K., 1995. Excess lung cancer among workers exposed to lead. Scand J Work Environ Health 21, 460–469. https://doi.org/10.5271/sjweh.62

Barry, V., Steenland, K., 2019. Lead exposure and mortality among U.S. workers in a surveillance program: Results from 10 additional years of follow-up. Environmental Research 177, 108625. https://doi.org/10.1016/j.envres.2019.108625

Bertke, S.J., Lehman, E.J., Wurzelbacher, S.J., Hein, M.J., 2016. Mortality of lead smelter workers: A follow-up study with exposure assessment: Mortality of Lead Smelter Workers. Am. J. Ind. Med. 59, 979–986. https://doi.org/10.1002/ajim.22618

Boulat, T., Ghosn, W., Morgand, L., Falissard, L., Roussel, S., Rey, G., 2019. Principales évolutions de la mortalité par cause sur la période 2000-2016 en France métropolitaine. 576–84.

Breslow, N., Day, N., International Agency for Research on Cancer, 1987. Statistical methods in cancer research Vol. 2 The design and analysis of cohort studies. Vol. 2 The design and analysis of cohort studies. International Agency for Research on Cancer, Lyon.

Callahan, C.L., Friesen, M.C., Locke, S.J., Dopart, P.J., Stewart, P.A., Schwartz, K., Ruterbusch, J.J., Graubard, B.I., Chow, W.-H., Rothman, N., Hofmann, J.N., Purdue, M.P., 2019. Case-control investigation of occupational lead exposure and kidney cancer. Occup Environ Med 76, 433–440. https://doi.org/10.1136/oemed-2018-105327

Cocco, P., Hua, F., Boffetta, P., Carta, P., Flore, C., Flore, V., Onnis, A., Picchiri, G., Colin, D., 1997. Mortality of Italian lead smelter workers. Scand J Work Environ Health 23, 15–23. https://doi.org/10.5271/sjweh.173

Deng, Y., Wang, M., Tian, T., Lin, S., Xu, P., Zhou, L., Dai, C., Hao, Q., Wu, Y., Zhai, Z., Zhu, Y., Zhuang, G., Dai, Z., 2019. The Effect of Hexavalent Chromium on the Incidence and Mortality of Human Cancers: A Meta-Analysis Based on Published Epidemiological Cohort Studies. Front Oncol 9, 24. https://doi.org/10.3389/fonc.2019.00024

Englyst, V., Lundström, N.G., Gerhardsson, L., Rylander, L., Nordberg, G., 2001. Lung cancer risks among lead smelter workers also exposed to arsenic. Sci. Total Environ. 273, 77–82. https://doi.org/10.1016/s0048-9697(00)00843-3

Fu, H., Boffetta, P., 1995. Cancer and occupational exposure to inorganic lead compounds: a meta-analysis of published data. Occupational and Environmental Medicine 52, 73–81. https://doi.org/10.1136/oem.52.2.73

Gatto, N.M., Kelsh, M.A., Mai, D.H., Suh, M., Proctor, D.M., 2010. Occupational exposure to hexavalent chromium and cancers of the gastrointestinal tract: A meta-analysis. Cancer Epidemiology 34, 388–399. https://doi.org/10.1016/j.canep.2010.03.013

Gerhardsson, L., Brune, D., Nordberg, G.F., Wester, P.O., 1986. Distribution of cadmium, lead and zinc in lung, liver and kidney in long-term exposed smelter workers. Sci. Total Environ. 50, 65–85. https://doi.org/10.1016/0048-9697(86)90352-9

Gwini, S., MacFarlane, E., Del Monaco, A., McLean, D., Pisaniello, D., Benke, G.P., Sim, M.R., 2012. Cancer incidence, mortality, and blood lead levels among workers exposed to inorganic lead. Ann Epidemiol 22, 270–276. https://doi.org/10.1016/j.annepidem.2012.01.003

IARC (Ed.), 2012. A review of human carcinogens, IARC monographs on the evaluation of carcinogenic risks to humans. International agency for research on cancer, Lyon.

IARC Monographs, 2012a. IARC monographs on the evaluation of carcinogenic risks to humans. Arsenic, Metals, Fibres, and Dusts. Volume 100 C. Lyon, France.

IARC Monographs, 2012b. IARC monographs on the evaluation of carcinogenic risks to humans. Chemical agents and related occupations. Volume 100F. Lyon, France.

IARC Monographs, 2006. IARC monographs on the evaluation of carcinogenic risks to humans. Inorganic and Organic Lead Compounds. Volume 87. Lyon, France.

Lundström, N.-G., Englyst, V., Gerhardsson, L., Jin, T., Nordberg, G., 2006. Lung cancer development in primary smelter workers: a nested case-referent study. J. Occup. Environ. Med. 48, 376–380. https://doi.org/10.1097/01.jom.0000201556.95982.95

Lundström, N.G., Nordberg, G., Englyst, V., Gerhardsson, L., Hagmar, L., Jin, T., Rylander, L., Wall, S., 1997. Cumulative lead exposure in relation to mortality and lung cancer morbidity in a cohort of primary smelter workers. Scand J Work Environ Health 23, 24–30. https://doi.org/10.5271/sjweh.174

Marant Micallef, C., Shield, K.D., Vignat, J., Baldi, I., Charbotel, B., Fervers, B., Gilg Soit Ilg, A., Guénel, P., Olsson, A., Rushton, L., Hutchings, S.J., Cléro, E., Laurier, D., Scanff, P., Bray, F., Straif, K., Soerjomataram, I., 2019. Cancers in France in 2015 attributable to occupational exposures. International Journal of Hygiene and Environmental Health 222, 22–29. https://doi.org/10.1016/j.ijheh.2018.07.015

Marsh, G.M., Esmen, N.A., Buchanich, J.M., Youk, A.O., 2009. Mortality patterns among workers exposed to arsenic, cadmium, and other substances in a copper smelter. American Journal of Industrial Medicine 52, 633–644. https://doi.org/10.1002/ajim.20714

McElvenny, D.M., Miller, B.G., MacCalman, L.A., Sleeuwenhoek, A., van Tongeren, M., Shepherd, K., Darnton, A.J., Cherrie, J.W., 2015. Mortality of a cohort of workers in Great Britain with blood lead measurements. Occup Environ Med 72, 625–632. https://doi.org/10.1136/oemed-2014-102637

Meng, Y., Tang, C., Yu, J., Meng, S., Zhang, W., 2020. Exposure to lead increases the risk of meningioma and brain cancer: A meta-analysis. Journal of Trace Elements in Medicine and Biology 60, 126474. https://doi.org/10.1016/j.jtemb.2020.126474

Paris, C., Thaon, I., Hérin, F., Clin, B., Lacourt, A., Luc, A., Coureau, G., Brochard, P., Chamming's, S., Gislard, A., Galan, P., Hercberg, S., Wild, P., Pairon, J.-C., Andujar, P., 2017. Occupational Asbestos Exposure and Incidence of Colon and Rectal Cancers in French Men: The Asbestos-Related Diseases Cohort (ARDCo-Nut). Environ Health Perspect 125, 409–415. https://doi.org/10.1289/EHP153

Sahai, H., Khurshid, A., 1996. Statistics in epidemiology: methods, techniques, and applications. CRC Press, Boca Raton.

Santé Publique France, 2018. Programme Cosmop : surveillance de la mortalité par cause selon l'activité professionnelle. Analyse de la mortalité et des causes de décès par secteur d'activité de 1976 à 2005. Santé publique France, Saint-Maurice.

Steenland, K., Barry, V., Anttila, A., Sallmén, M., McElvenny, D., Todd, A., Straif, K., 2017. A cohort mortality study of lead-exposed workers in the USA, Finland and the UK. Occup Environ Med 74, 785–791. https://doi.org/10.1136/oemed-2017-104311

Steenland, K., Barry, V., Anttila, A., Sallmen, M., Mueller, W., Ritchie, P., McElvenny, D.M., Straif, K., 2019. Cancer incidence among workers with blood lead measurements in two countries. Occup Environ Med 76, 603–610. https://doi.org/10.1136/oemed-2019-105786

Steenland, K., Boffetta, P., 2000. Lead and cancer in humans: where are we now? Am. J. Ind. Med. 38, 295–299. https://doi.org/10.1002/1097-0274(200009)38:3<295::aid-ajim8>3.0.co;2-l

Steenland, K., Selevan, S., Landrigan, P., 1992. The mortality of lead smelter workers: an update. Am J Public Health 82, 1641–1644. https://doi.org/10.2105/AJPH.82.12.1641

Wong, O., Harris, F., 2000. Cancer mortality study of employees at lead battery plants and lead smelters, 1947-1995. Am. J. Ind. Med. 38, 255–270. https://doi.org/10.1002/1097-0274(200009)38:3<255::aid-ajim4>3.0.co;2-8

Table 1. Description of the cohort of workers studied (n=2,226)

Population characteristics	Numbers (%)
Decade of birth	
≤ 1920	161 (7.2)
1921-1930	275 (12.4)
1931-1940	491 (22.1)
1941-1950	586 (26.3)
1951-1960	417 (18.7)
1961-1970	171 (7.7)
1971-1980	125 (5.6)
Date of hire	
≤ 1950	298 (13.4)
1951-1960	343 (15.4)
1961-1970	687 (30.9)
1971-1980	415 (18.6)
1981-1990	257 (11.5)
1990-2002	226 (10.2)
Employment duration	
< 10 years	592 (26.6)
10-19 years	252 (11.3)
20-29 years	657 (29.5)
30-39 years	612 (27.5)
≥ 40 years	113 (5.1)
Employment sector	
Exclusive employment in production*	940 (42.2)
Exclusive employment in technical and purchasing units*	489 (22.0)
Exclusive employment in control and development*	128 (5.8)
Exclusive employment in logistics*	77 (3.5)
Other situations (various sectors, administrative sector exclusively)	592 (26.5)

*At least 1 year in the sector considered and no other (except administrative sector)

Table 2. Number and distribution of cancer deaths.

Causes of death	N	%
All causes	913	100.0
Neoplasms	338	37.0
Malignant neoplasms (MN)	329	36.0
- MN lip, oral cavity & pharynx	22	2.4
MN lip & oral cavity	7	0.8
MN oropharynx	6	0.7
MN nasopharynx	1	0.1
MN hypopharynx	7	0.8
MN other or unspecified sites	1	0.1
- MN esophagus	23	2.5
- MN stomach	9	1.0
- MN colon, rectum & anus	30	3.3
MN colon	17	1.9
MN rectosigmoid junction	1	0.1
MN rectum	12	1.3
MN anal canal	0	0.0
- MN liver & intrahepatic bile ducts	14	1.5
MN liver	12	1.3
MN intrahepatic bile ducts	2	0.2
- MN gallbladder	2	0.2
- MN other specified sites bile ducts & unspecified sites	2	0.2
- MN pancreas	8	0.9
- MN larynx	13	1.4
- MN trachea, bronchus & lung	98	10.7
- MN pleura	3	0.3
- Malignant melanoma of skin	2	0.2
- MN breast	1	0.1
- MN prostate	22	2.4
- MN kidney	5	0.5
- MN renal pelvis	0	0.0
- MN ureter	0	0.0
- MN bladder	14	1.5
- MN brain & other unspecified central nervous system sites	2	0.2
- MN thyroid	0	0.0
- MN lymphoma	4	0.4
Hodgkin's lymphoma	1	0.1
Non-Hodgkin's lymphoma	3	0.3
- Leukemia	8	0.9
Lymphoid leukemia	2	0.2
-- Acute lymphoblastic leukemia	0	0.0
-- Chronic lymphocytic leukemia	2	0.2
-- Other & unspecified lymphoid leukemia	0	0.0
Myeloid leukemia	4	0.4
-- Acute myelogenous leukemia	2	0.2
-- Chronic myelogenous leukemia	2	0.2
-- Other & unspecified myeloid leukemia	0	0.0
- Other MN of lymphoid and histiocytic tissue, multiple myeloma & immunoproliferative neoplasms	3	0.3

-- Multiple myeloma	2	0.2
- Other MN	42	4.6
Benign neoplasms, carcinoma in situ & neoplasms of uncertain behavior	9	1.0

Table 3. Comparison of mortality in the smelter cohort studied and mortality for the regional population: standardized mortality ratio (SMR) and 95% confidence interval (except for causes of death < 2 events)

Causes of death	Total cohort		Exclusive sector of work*							
			Production		Technical & purchasing		Control & development		Logistic	
	O	SMR [95%CI]	O	SMR [95%CI]	O	SMR [95%CI]	O	SMR [95%CI]	O	SMR [95%CI]
All causes	913	0.96 [0.90-1.02]	341	1.06 [0.95-1.18]	197	0.78 [0.68-0.90]	46	0.85 [0.62-1.13]	46	1.13 [0.83-1.51]
Neoplasms	338	0.97 [0.87-1.08]	119	1.00 [0.84-1.20]	81	0.89 [0.71-1.10]	16	0.79 [0.45-1.28]	18	1.34 [0.79-2.12]
Malignant neoplasms (MN)	329	0.97 [0.87-1.08]	117	1.00 [0.84-1.20]	80	0.89 [0.72-1.11]	15	0.75 [0.42-1.24]	17	1.29 [0.75-2.07]
- MN lip, oral cavity & pharynx	22	0.78 [0.49-1.18]	8	0.78 [0.34-1.54]	6	0.85 [0.31-1.85]	1	_	1	_
MN lip & oral cavity	7	0.64 [0.26-1.32]	4	1.01 [0.27-2.59]	2	0.73 [0.09-2.64]	0	_	0	_
MN oropharynx	6	0.97 [0.35-2.11]	1	_	2	1.32 [0.16-4.77]	1	_	0	_
MN hypopharynx	7	1.29 [0.52-2.66]	3	1.51 [0.31-4.41]	2	1.50 [0.18-5.42]	0	_	0	_
- MN esophagus	23	0.91 [0.58-1.37]	6	0.69 [0.25-1.50]	4	0.61 [0.17-1.56]	1	_	3	3.05 [0.63-8.91]
- MN stomach	9	0.87 [0.40-1.65]	3	0.89 [0.18-2.60]	2	0.74 [0.09-2.67]	1	_	0	_
- MN colon, rectum & anus	30	1.09 [0.74-1.56]	13	1.44 [0.77-2.46]	4	0.53 [0.14-1.36]	2	1.28 [0.15-4.62]	1	_
MN colon	17	0.90 [0.52-1.44]	8	1.31 [0.56-2.58]	3	0.58 [0.12-1.69]	0	_	0	_
MN rectum	12	1.78 [0.92-3.11]	5	2.26 [0.73-5.27]	1	_	2	5.24 [0.63-18.92]	1	_
- MN liver & intrahepatic bile ducts	14	0.79 [0.43-1.33]	8	1.30 [0.56-2.56]	2	0.42 [0.05-1.52]	0	_	0	_
MN liver	12	0.68 [0.35-1.19]	7	1.15 [0.46-2.37]	1	_	0	_	0	_
MN intrahepatic bile ducts	2	1.21 [0.15-4.37]	1	_	1	_	0	_	0	_
- MN gallbladder	2	3.66 [0.44-13.21]	2	**11.50 [1.39-41.52]**	0	_	0	_	0	_
- MN other specified sites bile ducts & unspecified sites	2	1.81 [0.22-6.53]	0	_	0	_	0	_	1	_
- MN pancreas	8	0.61 [0.26-1.20]	2	0.45 [0.05-1.62]	0	_	0	_	3	**6.20 [1.28-18.10]**
- MN larynx	13	0.92 [0.49-1.57]	5	1.04 [0.34-2.42]	3	0.82 [0.17-2.39]	0	_	0	_
- MN trachea, bronchus & lung	98	1.08 [0.88-1.31]	40	1.27 [0.91-1.73]	28	1.19 [0.79-1.72]	3	0.56 [0.12-1.64]	4	1.17 [0.32-3.00]
- MN pleura	3	1.03 [0.21-3.01]	0	_	2	2.53 [0.31-9.13]	0	_	0	_
- Malignant melanoma of skin	2	1.07 [0.13-3.86]	1	_	0	_	0	_	0	_
- MN prostate	22	1.16 [0.73-1.76]	6	1.06 [0.39-2.31]	7	1.27 [0.51-2.62]	1	_	2	2.19 [0.26-7.91]
- MN kidney	5	0.93 [0.30-2.17]	2	1.10 [0.13-3.97]	2	1.39 [0.17-5.02]	0	_	0	_
- MN bladder	14	1.25 [0.68-2.10]	5	1.38 [0.45-3.22]	3	0.96 [0.20-2.80]	1	_	1	_
- MN brain & other unspecified central nervous system sites	2	0.38 [0.05-1.37]	1	_	1	_	0	_	0	_

- MN lymphoma	4	0.88 [0.24-2.25]	2	1.24 [0.15-4.48]	0	_	0	_	0	_
Non-Hodgkin's lymphoma	3	0.85 [0.18-2.48]	1	_	0	_	0	_	0	_
- Leukemia	8	1.03 [0.44-2.03]	1	_	7	**3.34 [1.34-6.88]**	0	_	0	_
Lymphoid leukemia	2	0.99 [0.12-3.57]	0	_	2	3.62 [0.44-13.07]	0	_	0	_
-- Chronic lymphocytic leukemia	2	1.41 [0.17-5.09]	0	_	2	4.96 [0.60-17.91]	0	_	0	_
Myeloid leukemia	4	1.27 [0.35-3.25]	0	_	3	3.55 [0.73-10.37]	1	_	0	_
-- Acute myelogenous leukemia	2	1.14 [0.14-4.12]	0	_	1	_	1	_	0	_
-- Chronic myelogenous leukemia	2	2.12 [0.26-7.65]	0	_	2	7.92 [0.96-28.59]	0	_	0	_
- Other MN of lymphoid and histiocytic tissue, multiple myeloma & immunoproliferative neoplasms	3	0.60 [0.12-1.75]	0	_	0	_	1	_	0	_
-- Multiple myeloma	2	0.67 [0.08-2.42]	1	_	0	_	0	_	0	_

*At least 1 year in the sector considered and in no other (except administrative sector)

- SMR and 95%CI are not presented when specific causes of death < 2

Table 3. (continued)

Causes of death	Period of hire						Employment duration					
	1921-1936		1937-1970		1971-2002		< 15 years		15-29 years		≥30 years	
	O	SMR [95%CI]	O	SMR [95%CI]	O	SMR [95%CI]	O	SMR [95%CI]	O	SMR [95%CI]	O	SMR [95%CI]
All causes	67	0.93 [0.73-1.18]	710	0.99 [0.92-1.06]	136	0.83 [0.70-0.99]	229	1.05 [0.92-1.19]	347	1.10 [0.99-1.22]	337	0.80 [0.72-0.89]
Neoplasms	17	0.88 [0.51-1.41]	271	1.01 [0.90-1.14]	50	0.82 [0.62-1.09]	76	0.95 [0.76-1.19]	139	**1.22 [1.03-1.44]**	123	0.80 [0.67-0.96]
Malignant neoplasms (MN)	17	0.90 [0.52-1.44]	263	1.00 [0.89-1.13]	49	0.83 [0.62-1.09]	74	0.94 [0.75-1.19]	137	**1.23 [1.04-1.45]**	118	0.78 [0.65-0.94]
- MN lip, oral cavity & pharynx	2	2.19 [0.26-7.91]	17	0.79 [0.46-1.26]	3	0.51 [0.11-1.49]	6	0.89 [0.32-1.94]	10	1.04 [0.50-1.91]	6	0.50 [0.18-1.09]
MN lip & oral cavity	1	_	5	0.60 [0.19-1.40]	1	_	1	_	3	0.80 [0.16-2.34]	3	0.64 [0.13-1.87]
MN oropharynx	0	_	6	1.30 [0.47-2.83]	0	_	3	2.01 [0.41-5.87]	1	_	2	0.78 [0.09-2.82]
MN hypopharynx	1	_	4	0.98 [0.27-2.51]	2	1.68 [0.20-6.06]	2	1.52 [0.18-5.49]	4	2.19 [0.60-5.61]	1	_
- MN esophagus	1	_	20	1.01 [0.62-1.56]	2	0.47 [0.06-1.70]	5	0.88 [0.29-2.05]	11	1.31 [0.65-2.34]	7	0.63 [0.25-1.30]
- MN stomach	0	_	6	0.78 [0.28-1.70]	3	2.03 [0.42-5.93]	3	1.33 [0.27-3.88]	3	0.90 [0.19-2.63]	3	0.64 [0.13-1.87]
- MN colon, rectum & anus	6	**2.84 [1.04-6.18]**	18	0.83 [0.49-1.31]	6	1.52 [0.56-3.31]	6	0.97 [0.35-2.11]	11	1.25 [0.62-2.24]	13	1.02 [0.54-1.74]
MN colon	3	2.17 [0.45-6.34]	9	0.60 [0.27-1.14]	5	1.93 [0.63-4.50]	6	1.44 [0.53-3.13]	6	1.00 [0.37-2.18]	5	0.57 [0.18-1.33]
MN rectum	2	3.38 [0.41-12.20]	9	1.75 [0.80-3.32]	1	_	0	_	5	2.31 [0.75-5.38]	7	2.28 [0.91-4.70]
- MN liver & intrahepatic bile ducts	0	_	11	0.78 [0.39-1.40]	3	0.97 [0.20-2.83]	1	_	7	1.25 [0.50-2.58]	6	0.76 [0.28-1.65]
MN liver	0	_	10	0.72 [0.34-1.32]	2	0.65 [0.08-2.35]	1	_	6	1.08 [0.39-2.35]	5	0.64 [0.21-1.49]
MN intrahepatic bile ducts	0	_	1	_	1	_	0	_	1	_	1	_
- MN gallbladder	0	_	2	4.68 [0.57-16.89]	0	_	0	_	2	**11.77 [1.42-42.24]**	0	_
- MN other specified sites bile ducts & unspecified sites	1	_	1	_	0	_	1	_	0	_	1	_
- MN pancreas	0	_	6	0.59 [0.22-1.28]	2	0.87 [0.11-3.14]	1	_	5	1.19 [0.39-2.77]	2	0.35 [0.04-1.26]
- MN larynx	0	_	10	0.88 [0.42-1.62]	3	1.53 [0.32-4.47]	4	1.35 [0.37-3.46]	2	0.42 [0.05-1.52]	7	1.10 [0.44-2.27]
- MN trachea, bronchus & lung	1	_	82	1.19 [0.96-1.47]	15	0.87 [0.49-1.44]	19	0.90 [0.54-1.41]	38	1.26 [0.89-1.73]	41	1.04 [0.75-1.41]
- MN pleura	1	_	2	0.84 [0.10-3.03]	0	_	0	_	2	2.11 [0.26-7.62]	1	_
- Malignant melanoma of skin	0	_	2	1.49 [0.18-5.38]	0	_	0	_	1	_	1	_
- MN prostate	3	1.34 [0.28-3.91]	16	1.07 [0.61-1.74]	3	1.70 [0.35-4.96]	5	1.25 [0.41-2.91]	11	1.91 [0.95-3.42]	6	0.65 [0.24-1.41]
- MN kidney	0	_	4	0.95 [0.26-2.43]	1	_	2	1.63 [0.20-5.88]	3	1.74 [0.36-5.08]	0	_
- MN bladder	0	_	13	1.46 [0.78-2.50]	1	_	3	1.22 [0.25-3.56]	7	1.96 [0.79-4.04]	4	0.77 [0.21-1.97]
- MN brain & other unspecified parts of central nervous system	0	_	2	0.53 [0.06-1.91]	0	_	1	_	0	_	1	_
- MN lymphatohematopoietic system	0	_	3	0.87 [0.18-2.54]	1	_	2	1.77 [0.21-6.39]	2	1.35 [0.16-4.87]	0	_
Non-Hodgkin's lymphoma	0	_	3	1.12 [0.23-3.27]	0	_	1	_	2	1.77 [0.21-6.39]	0	_

- Leukemia	0	_	6	1.00 [0.37-2.18]	2	1.68 [0.20-6.06]	2	1.15 [0.14-4.15]	3	1.20 [0.25-3.50]	3	0.86 [0.18-2.51]
Lymphoid leukemia	0	_	1	_	1	_	1	_	1	_	0	_
-- Chronic lymphocytic leukemia	0	_	1	_	1	_	1	_	1	_	0	_
Myeloid leukemia	0	_	4	1.64 [0.45-4.20]	0	_	0	_	3	2.92 [0.60-8.53]	1	_
-- Acute myelogenous leukemia	0	_	2	1.48 [0.18-5.34]	0	_	0	_	1	_	1	_
-- Chronic myelogenous leukemia	0	_	2	2.72 [0.33-9.82]	0	_	0	_	2	6.53 [0.79-23.57]	0	_
Other MN of lymphoid and histiocytic tissue, multiple myeloma & immunoproliferative neoplasms	0	_	3	0.75 [0.15-2.19]	0	_	2	1.84 [0.22-6.64]	0	_	1	_
-- Multiple myeloma	0	_	2	0.84 [0.10-3.03]	0	_	0	_	1	_	1	_

- SMR and 95%CI are not presented when specific causes of death < 2

Table 4. Cancer mortality according to categories of cumulative exposure index for each exposure studied (Cox regression models with age and 20-year lag cumulative exposure index as time-dependent variables): hazard ratio and 95% confidence intervals for each MN location with more than 10 deaths.

Toxic agents & cumulative exposure †	Malignant neoplasms Eff	HR	[95%CI]	Global p value *(p trend)*	MN lip, oral cavity, pharynx Eff	HR	[95%CI]	Global p value *(p trend)*	MN esophagus Eff	HR	[95%CI]	Global p value *(p trend)*
Pb												
≤500 µg/m³ x years	67	1.00		0.1796	3	1.00		**0.0014**	6	1.00		0.4633
>500 - 2000 µg/m³ x years	125	1.34	[0.97-1.84]	*(0.39)*	14	9.52	[2.28-39.86]	*(0.83)*	10	2.03	[0.62-6.61]	*(0.80)*
>2000 µg/m³ x years	137	1.30	[0.93-1.80]		5	3.48	[0.65-18.57]		7	1.42	[0.39-5.19]	
Cd												
≤50 µg/m³ x years	54	1.00		**0.0385**	6	1.00		0.632	5	1.00		0.127
>50 - 200 µg/m³ x years	115	1.54	[1.08-2.19]	(0.17)	7	1.49	[0.40-5.58]	*(0.37)*	6	1.47	[0.36-5.95]	*(0.046)*
>200 µg/m³ x years	160	1.50	[1.04-2.16]		9	1.96	[0.48-7.99]		12	3.41	[0.85-13.71]	
As												
Non exposed	269	1.00			19	1.00			20	1.00		
Exposed	60	1.02	[0.77-1.35]	0.915	3	0.85	[0.25-2.92]	0.797	3	0.73	[0.21-2.49]	0.614
Bismuth												
Non exposed	303	1.00			21	1.00			23	1.00		
Exposed	26	1.30	[0.87-1.94]	0.203	1	0.85	[0.11-6.41]	0.878	0	0.00	[0-Inf]	0.996
Cr												
Non exposed	302	1.00			21	1.00			22	1.00		
Exposed	27	0.97	[0.65-1.44]	0.865	1	0.64	[0.08-4.84]	0.663	1	0.49	[0.07-3.72]	0.493
Sb												
Non exposed	267	1.00			19	1.00			20	1.00		
Exposed	62	1.02	[0.77-1.34]	0.909	3	0.81	[0.24-2.79]	0.742	3	0.70	[0.21-2.39]	0.569
Tl												
Non exposed	304	1.00			21	1.00			21	1.00		
Exposed	25	0.99	[0.65-1.49]	0.959	1	0.71	[0.09-5.38]	0.738	2	1.20	[0.27-5.24]	0.811
Asbestos												
Non exposed	62	1.00		**0.0012**	1	1.00		**0.0005**	5	1.00		0.362
>0 to <20	140	1.76	[1.29-2.41]	*(0.56)*	14	19.32	[2.4-155.39]	*(0.13)*	11	2.25	[0.71-7.15]	*(0.80)*
20+	127	1.42	[1.03-1.96]		7	12.99	[1.38-121.92]		7	1.73	[0.47-6.37]	
Dust												
0 to <5	138	1.00		0.204	13	1.00		0.853	14	1.00		0.173
5 to <20	82	1.15	[0.87-1.53]	*(0.09)*	4	0.72	[0.22-2.32]	*(0.82)*	2	0.31	[0.07-1.41]	*(0.75)*
20+	109	1.27	[0.97-1.65]		5	0.86	[0.28-2.62]		7	1.09	[0.41-2.87]	
Aromatic amines												
Non exposed	312	1.00			21	1.00			23	1.00		
Exposed	17	1.15	[0.7-1.88]	0.579	1	1.21	[0.16-9.1]	0.852	0	0.00	[0-Inf]	0.997
Diesel exhaust												
Non exposed	281	1.00			20	1.00			21	1.00		
Exposed	48	0.87	[0.64-1.19]	0.394	2	0.65	[0.15-2.89]	0.570	2	0.53	[0.12-2.32]	0.398
Solvents												
Non exposed	318	1.00			20	1.00			23	1.00		
Exposed	11	0.87	[0.47-1.58]	0.641	2	2.92	[0.67-12.69]	0.153	0	0.00	[0-Inf]	0.997
Sulfur dioxide												
Non exposed	260	1.00			18	1.00			18	1.00		
Exposed	69	1.27	[0.97-1.66]	0.0807	4	1.25	[0.42-3.77]	0.690	5	1.46	[0.53-3.99]	0.463
Silica												
Non exposed	296	1.00			20	1.00			21	1.00		

Exposed	33	1.06	[0.74-1.52]	0.760	2	1.14	[0.26-4.94]	0.865	2	0.95	[0.22-4.1]	0.941
Sodium hydroxide vapor												
Non exposed	317	1.00			21	1.00			23	1.00		
Exposed	12	0.99	[0.56-1.77]	0.978	1	1.54	[0.2-11.67]	0.675	0	0.00	[0-Inf]	0.997

† cumulative index of exposure with a 20-year lag, expressed as $\mu g/m^3$ x years for Pb and Cd, and as cumulated scores for asbestos and dust.

Table 4. (continued)

Toxic agents & cumulative exposure †	MN colon, rectum, anus Eff	HR	[95%CI]	Global p value *(p trend)*	MN colon Eff	HR	[95%CI]	Global p value *(p trend)*	MN rectum Eff	HR	[95%CI]	Global p value *(p trend)*
Pb												
≤500 µg/m³ x years	4	1.00		0.0553	4	1.00		0.9677	0	1.00		
>500 - 2000 µg/m³ x years	9	2.54	[0.69-9.35]	*(0.033)*	6	1.20	[0.29-4.99]	*(0.91)*	3			
>2000 µg/m³ x years	17	4.14	[1.16-14.74]		7	1.17	[0.28-4.97]		9	5.86	[1.38-24.95]	**0.0167**
Cd												
≤50 µg/m³ x years	3	1.00		0.0517	3	1.00		0.6881	0			
>50 - 200 µg/m³ x years	12	4.71	[1.20-18.45]	*(0.49)*	6	1.80	[0.39-8.38]	*(0.86)*	6	1.00		
>200 µg/m³ x years	15	3.48	[0.82-14.80]		8	1.25	[0.24-6.47]		6	1.09	[0.31-3.88]	0.8897
As												
Non exposed	21	1.00			14	1.00			7	1.00		
Exposed	9	2.14	[0.97-4.72]	0.0600	3	1.09	[0.31-3.83]	0.8948	5	3.59	[1.12-11.52]	**0.0314**
Bismuth												
Non exposed	25	1.00			16	1.00			8	1.00		
Exposed	5	3.19	[1.21-8.44]	**0.0195**	1	1.05	[0.14-7.99]	0.9642	4	7.70	[2.27-26.14]	**0.0011**
Cr												
Non exposed	23	1.00			13	1.00			9	1.00		
Exposed	7	3.43	[1.43-8.22]	**0.0057**	4	3.56	[1.12-11.31]	**0.0315**	3	3.95	[1.02-15.36]	**0.0472**
Sb												
Non exposed	21	1.00			14	1.00			7	1.00		
Exposed	9	2.07	[0.94-4.57]	0.0715	3	1.05	[0.30-3.71]	0.9340	5	3.48	[1.09-11.16]	**0.0357**
Tl												
Non exposed	24	1.00			14	1.00			9	1.00		
Exposed	6	3.11	[1.23-7.83]	**0.0161**	3	2.67	[0.74-9.63]	0.1338	3	4.45	[1.14-17.39]	**0.0318**
Asbestos												
Non exposed	5	1.00		0.1094	4	1.00		0.2126	1	1.00		0.0996
>0 to <20	12	2.97	[1-8.79]	*(0.45)*	8	2.46	[0.71-8.57]	*(0.49)*	4	5.33	[0.55-51.41]	*(0.12)*
20+	13	2.35	[0.77-7.19]		5	0.99	[0.25-3.96]		7	7.90	[0.82-76.46]	
Dust												
0 to <5	10	1.00		0.1897	8	1.00		0.6952	2	1.00		0.0513
5 to <20	9	2.20	[0.86-5.61]	*(0.23)*	5	1.46	[0.46-4.58]	*(0.71)*	4	5.48	[0.92-32.69]	*(0.07)*
20+	11	1.97	[0.78-4.94]		4	0.83	[0.24-2.91]		6	6.23	[1.09-35.76]	
Aromatic amines												
Non exposed	27	1.00			16	1.00			10	1.00		
Exposed	3	2.31	[0.69-7.7]	0.1738	1	1.35	[0.18-10.29]	0.7726	2	4.09	[0.88-19.13]	0.0733
Diesel exhaust												
Non exposed	21	1.00			13	1.00			8	1.00		
Exposed	9	2.29	[1.01-5.21]	**0.0472**	4	1.62	[0.50-5.21]	0.4172	4	2.87	[0.81-10.2]	0.1031
Solvents												
Non exposed	27	1.00			16	1.00			10	1.00		
Exposed	3	2.84	[0.85-9.51]	0.0901	1	1.63	[0.21-12.49]	0.6366	2	5.06	[1.07-23.82]	**0.0403**
Sulfur dioxide												
Non exposed	21	1.00			13	1.00			7	1.00		
Exposed	9	2.19	[0.99-4.85]	0.0526	4	1.58	[0.51-4.91]	0.4329	5	3.68	[1.14-11.84]	**0.0288**
Silica												
Non exposed	23	1.00			13	1.00			9	1.00		

Exposed	7	3.05	[1.29-7.21]	**0.0113**	4	3.17	[1.01-9.93]	**0.0474**	3	3.39	[0.89-12.85]	0.0728
Sodium hydroxide vapor												
Non exposed	27	1.00			16	1.00			10	1.00		
Exposed	3	2.90	[0.86-9.78]	0.0865	1	1.72	[0.22-13.25]	0.6038	2	5.17	[1.08-24.8]	**0.0399**

† cumulative index of exposure with a 20-year lag, expressed as µg/m^3 x years for Pb and Cd, and as cumulated scores for asbestos and dust.

Table 4. (continued)

Toxic agents & cumulative exposure †	MN liver, intrahepatic bile ducts Eff	HR	[95%CI]	Global p value *(p trend)*	MN liver Eff	HR	[95%CI]	Global p value *(p trend)*	MN larynx Eff	HR	[95%CI]	Global p value *(p trend)*
Pb												
≤500 µg/m³ x years	1	1.00		**0.0121**	1	1.00		**0.0155**	4	1.00		0.9145
>500 - 2000 µg/m³ x years	3	4.89	[0.45-53.62]	***(0.009)***	2	3.26	[0.25-41.72]	***(0.009)***	5	1.02	[0.24-4.37]	*(0.69)*
>2000 µg/m³ x years	10	14.51	[1.49-141.7]		9	13.36	[1.30-137.2]		4	0.78	[0.16-3.76]	
Cd												
≤50 µg/m³ x years	0	1.00			0	1.00			4	1.00		0.9290
>50 - 200 µg/m³ x years	6				5				4	0.74	[0.16-3.42]	*(0.90)*
>200 µg/m³ x years	8	1.90	[0.52-6.96]	0.3300	7	1.98	[0.49-8.05]	0.3384	5	0.82	[0.17-4.02]	
As												
Non exposed	10	1.00			8	1.00			11	1.00		
Exposed	4	2.09	[0.65-6.78]	0.2178	4	2.63	[0.78-8.9]	0.1202	2	0.91	[0.2-4.16]	0.8995
Bismuth												
Non exposed	12	1.00			10	1.00			12	1.00		
Exposed	2	3.06	[0.68-13.8]	0.1450	2	3.65	[0.79-16.82]	0.0973	1	1.46	[0.19-11.37]	0.7176
Cr												
Non exposed	13	1.00			11	1.00			12	1.00		
Exposed	1	1.17	[0.15-9.3]	0.8828	1	1.31	[0.16-10.62]	0.7986	1	1.15	[0.14-9.19]	0.8969
Sb												
Non exposed	10	1.00			8	1.00			11	1.00		
Exposed	4	2.00	[0.62-6.48]	0.2464	4	2.52	[0.74-8.51]	0.1379	2	0.87	[0.19-3.98]	0.8555
Tl												
Non exposed	14	1.00			12	1.00			12	1.00		
Exposed	0	0.00	[0-Inf]	0.9970	0	0.00	[0-Inf]	0.9972	1	1.35	[0.17-10.89]	0.7758
Asbestos												
Non exposed	0	1.00			0	1.00			2	1.00		0.2632
>0 to <20	8				7				8	2.86	[0.57-14.39]	*(0.57)*
20+	6	1.27	[0.39-4.14]	0.6905	5	1.18	[0.33-4.20]	0.8012	3	1.21	[0.18-8.11]	
Dust												
0 to <5	4	1.00		0.2739	3	1.00		0.2167	4	1.00		0.3619
5 to <20	5	2.88	[0.74-11.26]	*(0.37)*	4	3.21	[0.68-15.27]	*(0.20)*	4	2.04	[0.48-8.72]	*(0.20)*
20+	5	2.29	[0.55-9.55]		5	3.25	[0.68-15.61]		5	2.71	[0.64-11.44]	
Aromatic amines												
Non exposed	14	1.00			12	1.00			12	1.00		
Exposed	0	0.00	[0-Inf]	0.9970	0	0.00	[0-Inf]	0.9973	1	2.29	[0.29-17.86]	0.4296
Diesel exhaust												
Non exposed	14	1.00			12	1.00			10	1.00		
Exposed	0	0.00	[0-Inf]	0.9969	0	0.00	[0-Inf]	0.9972	3	2.24	[0.57-8.76]	0.2471
Solvents												
Non exposed	14	1.00			12	1.00			12	1.00		
Exposed	0	0.00	[0-Inf]	0.9970	0	0.00	[0-Inf]	0.9972	1	2.81	[0.36-22.02]	0.3253
Sulfur dioxide												
Non exposed	12	1.00			10	1.00			11	1.00		
Exposed	2	0.92	[0.2-4.15]	0.9127	2	1.09	[0.24-5.03]	0.9137	2	0.98	[0.21-4.46]	0.9745
Silica												
Non exposed	13	1.00			11	1.00			12	1.00		

Exposed	1	0.87	[0.11-6.77]	0.8969	1	1.02	[0.13-8.05]	0.9834	1	0.95	[0.12-7.42]	0.9589
Sodium hydroxide vapor												
Non exposed	13	1.00			11	1.00			11	1.00		
Exposed	1	2.88	[0.37-22.42]	0.3114	1	3.29	[0.42-26.02]	0.2596	2	6.82	[1.45-32.06]	**0.0150**

† cumulative index of exposure with a 20-year lag, expressed as µg/m^3 x years for Pb and Cd, and as cumulated scores for asbestos and dust.

Table 4. (continued)

Toxic agents & cumulative exposure †	MN trachea, bronchus, lung				MN prostate				MN bladder			
	Eff	HR	[95%CI]	Global p value *(p trend)*	Eff	HR	[95%CI]	Global p value *(p trend)*	Eff	HR	[95%CI]	Global p value *(p trend)*
Pb												
≤500 µg/m³ x years	20	1.00		**0.0256**	3	1.00		0.1163	4	1.00		0.2356
>500 - 2000 µg/m³ x years	18	1.34	[0.70-2.59]	***(0.008)***	10	4.20	[0.99-17.74]	*(0.67)*	7	1.17	[0.30-4.63]	*(0.14)*
>2000 µg/m³ x years	50	2.14	[1.13-4.03]		9	3.04	[0.66-13.94]		3	0.39	[0.07-2.06]	
Cd												
≤50 µg/m³ x years	17	1.00		**0.0456**	3	1.00		0.1329	1	1.00		0.0873
>50 - 200 µg/m³ x years	29	1.69	[0.84-3.41]	*(0.023)*	8	3.97	[0.93-16.89]	*(0.89)*	7	7.06	[0.79-63.22]	*(0.88)*
>200 µg/m³ x years	52	2.33	[1.15-4.72]		11	2.29	[0.48-10.89]		6	3.26	[0.31-33.88]	
As												
Non exposed	79	1.00			19	1.00			12	1.00		
Exposed	19	1.15	[0.7-1.91]	0.5802	3	0.76	[0.22-2.58]	0.6558	2	0.76	[0.17-3.43]	0.72
Bismuth												
Non exposed	90	1.00			21	1.00			12	1.00		
Exposed	8	1.40	[0.67-2.89]	0.3689	1	0.77	[0.1-5.78]	0.8020	2	2.62	[0.58-11.82]	0.2109
Cr												
Non exposed	90	1.00			22	1.00			13	1.00		
Exposed	8	1.03	[0.49-2.14]	0.9400	0	0.00	[0-Inf]	0.9966	1	0.78	[0.1-6.06]	0.8108
Sb												
Non exposed	78	1.00			19	1.00			12	1.00		
Exposed	20	1.18	[0.72-1.94]	0.5071	3	0.72	[0.21-2.47]	0.6064	2	0.73	[0.16-3.28]	0.6774
Tl												
Non exposed	90	1.00			22	1.00			13	1.00		
Exposed	8	1.16	[0.56-2.42]	0.6921	0	0.00	[0-Inf]	0.9966	1	0.87	[0.11-6.77]	0.8925
Asbestos												
Non exposed	16	1.00		**0.0018**	6	1.00		0.6491	5	1.00		0.5559
>0 to <20	33	2.01	[1.06-3.83]	***(0.002)***	5	1.34	[0.39-4.52]	*(0.39)*	5	1.01	[0.28-3.6]	*(0.30)*
20+	49	2.96	[1.56-5.64]		11	1.69	[0.55-5.22]		4	0.52	[0.13-2.09]	
Dust												
0 to <5	32	1.00		**0.0026**	9	1.00		0.6161	10	1.00		0.1358
5 to <20	26	1.81	[1.05-3.13]	***(0.001)***	5	1.66	[0.54-5.17]	*(0.50)*	1	0.21	[0.03-1.64]	*(0.23)*
20+	40	2.38	[1.43-3.97]		8	1.51	[0.54-4.26]		3	0.42	[0.11-1.6]	
Aromatic amines												
Non exposed	95	1.00			21	1.00			10	1.00		
Exposed	3	0.71	[0.22-2.23]	0.5531	1	0.99	[0.13-7.41]	0.9914	4	9.06	[2.78-29.49]	**0.0003**
Diesel exhaust												
Non exposed	87	1.00			19	1.00			11	1.00		
Exposed	11	0.70	[0.37-1.33]	0.2747	3	0.72	[0.21-2.51]	0.6113	3	1.30	[0.35-4.87]	0.6983
Solvents												
Non exposed	97	1.00			22	1.00			13	1.00		
Exposed	1	0.28	[0.04-2.01]	0.2062	0	0.00	[0-Inf]	0.9971	1	2.14	[0.28-16.54]	0.4658
Sulfur dioxide												
Non exposed	75	1.00			19	1.00			8	1.00		
Exposed	23	1.55	[0.97-2.49]	0.0685	3	0.83	[0.24-2.84]	0.7697	6	3.67	[1.25-10.8]	**0.0181**
Silica												
Non exposed	88	1.00			22	1.00			13	1.00		

Exposed	10	1.15	[0.6-2.23]	0.6743	0	0.00	[0-Inf]	0.9968	1	0.71	[0.09-5.51]	0.7452
Sodium hydroxide vapor												
Non exposed	97	1.00			22	1.00			12	1.00		
Exposed	1	0.29	[0.04-2.06]	0.2147	0	0.00	[0-Inf]	0.9966	2	4.63	[1.01-21.22]	**0.0482**

† cumulative index of exposure with a 20-year lag, expressed as µg/m³ x years for Pb and Cd, and as cumulated scores for asbestos and dust.

Table 5: Final cancer mortality models according to categories of cumulative exposure index (Cox regression models, with age and 20-year lag cumulative exposure index as time-dependent variables): hazard ratio and 95% confidence intervals for each MN location with more than 10 deaths[a].

	Malignant neoplasms				MN lip, oral cavity, pharynx				MN colon, rectum, anus				MN colon				MN rectum			
Toxic agents & cumulative exposure [b]	Eff	HR	[95%CI]	Global p value *(p trend)*	Eff	HR	[95%CI]	Global p value *(p trend)*	Eff	HR	[95%CI]	Global p value *(p trend)*	Eff	HR	[95%CI]	Global p value *(p trend)*	Eff	HR	[95%CI]	Global p value *(p trend)*
Pb								**0.0378**												
≤500 µg/m³ x years				_	3	1.00		*(0.25)*				NS				_				NS
>500 - 2000 µg/m³ x years					14	2.86	[0.69-11.96]													
>2000 µg/m³ x years					5	0.79	[0.13-4.80]													
Bismuth																				
Non exposed				_				_				NS				_	8	1.00		
Exposed																	4	7.70	[2.27-26.14]	**0.0011**
Cr																				
Non exposed				_				_	23	1.00			13	1.00						NS
Exposed									7	3.43	[1.43-8.22]	**0.0057**	4	3.56	[1.12-11.31]	0.0315				
Asbestos																				
Non exposed	62	1.00		**0.0012**	1	1.00		**0.0141**				NS				_				NS
>0 to <20	140	1.76	[1.29-2.41]	*(0.56)*	14	12.75	[1.42-114.7]	*(0.15)*												
20+	127	1.42	[1.03-1.96]		7	14.87	[1.30-169.6]													
Aromatic amines																				
Non exposed				_				_				_				_				NS
Exposed																				
Sodium hydroxide vapor																				
Non exposed				_				_				NS				_				NS
Exposed																				
Other exposures taken into account in the models but non-significant in the final model	Cadmium, sulfur dioxide								Cadmium, arsenic, antimony, thallium, diesel exhaust, solvents, sulfur dioxide, silica				Thallium, silica				Arsenic, antimony, thallium, dust, diesel exhaust, solvents, sulfur dioxide, silica			

NS: exposures taken into account in the models but non-significant for the specific cause of death

-: exposure not taken into account in the multivariate analysis

[a] Final models for esophagus and prostate MN mortality are not presented due to the absence of any significant exposure linked with.

[b] Cumulative index of exposure with a 20-year lag, expressed as µg/m³ x years for Pb and as cumulated scores for asbestos

Table 5 *(continued)*

Toxic agents & cumulative exposure [b]	MN liver, intrahepatic bile ducts				MN liver				MN larynx				MN trachea, bronchus, lung				MN bladder			
	Eff	HR	[95%CI]	Global p value *(p trend)*	Eff	HR	[95%CI]	Global p value *(p trend)*	Eff	HR	[95%CI]	Global p value *(p trend)*	Eff	HR	[95%CI]	Global p value *(p trend)*	Eff	HR	[95%CI]	Global p value *(p trend)*
Pb																				
≤500 µg/m³ x years	1	1.00		**0.0121**	1	1.00		**0.0155**				_				NS				_
>500 - 2000 µg/m³ x years	3	4.89	[0.45-53.62]	***(0.009)***	2	3.26	[0.25-41.72]	***(0.009)***												
>2000 µg/m³ x years	10	14.51	[1.49-141.7]		9	13.36	[1.30-137.2]													
Bismuth																				
Non exposed				NS				NS				_				_				_
Exposed																				
Cr																				
Non exposed				_				_				_				_				_
Exposed																				
Asbestos																				
Non exposed				_				_				_	16	1.00		**0.0018**				_
>0 to <20													33	2.01	[1.06-3.83]	***(0.002)***				
20+													49	2.96	[1.56-5.64]					
Aromatic amines																				
Non exposed				_				_				_				_	10	1.00		
Exposed																	4	9.06	[2.78-29.49]	**0.0002**
Sodium hydroxide vapor																				
Non exposed				_				_	11	1.00						_				NS
Exposed									2	6.82	[1.45-32.06]	**0.0150**								
Other exposures taken into account in the models but non-significant in the final model						Arsenic, antimony								Cadmium, dust, sulfur dioxide				Cadmium, dust, sulfur dioxide		

NS: exposures taken into account in the models but non-significant for the specific cause of death

-: exposure not taken into account in the multivariate analysis

[a] Final models for esophagus and prostate MN mortality are not presented due to the absence of any significant exposure linked with.

[b] cumulative index of exposure with a 20-year lag, expressed as µg/m³ x years for Pb and as cumulated scores for asbestos