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ABSTRACT

Objective: To study the possible association between iron oxide exposures and lung cancer risk among workers in a French carbon steel-producing factory.

Methods: 16,742 males and 959 females ever employed for at least 1 year between 1959 and 1997 were followed up for mortality from January 1968 to December 1998. Causes of death were ascertained from death certificates. Job histories and smoking habits were available for 99.7% of subjects, respectively. Occupational exposures were assessed by a factory-specific job-exposure matrix (JEM) validated with atmospheric measurements. Standardised mortality ratios (SMRs) were computed using local death rates (external references). Poisson regressions were used to estimate the relative risks (RRs) for occupational exposures (internal references), adjusted on potential confounding factors.

Results: Among males, observed mortality was lower than expected for lung cancer compared to the local population (233 deaths, SMR 0.89, 95% CI 0.78 to 1.01) and higher than expected compared to the French population (SMR 1.30, 95% CI 1.15 to 1.48). No lung cancer excess was observed for exposure to iron oxides (RR 0.80, 95% CI 0.55 to 1.17) and no dose–response relationship with intensity, duration of exposure or cumulative index was found. A significant bladder cancer excess was observed among workers exposed to oil mist (RR 2.44, 95% CI 1.06 to 5.60), increasing significantly with intensity, duration of exposure and cumulative index. Among females, observed mortality was lower than expected for lung cancer compared to the local population (233 deaths, SMR 0.89, 95% CI 0.78 to 1.01).

Conclusion: This study did not detect any relationship between exposure to iron oxides and lung cancer mortality. An excess of mortality from bladder cancer was found among workers exposed to oil mist.

Methods: The research protocol was approved by the Commission Nationale de l’Informatique et des Libertés (Paris, France).

Study population and follow-up

A historical cohort was set up of all male and female workers ever employed in a French carbon steel-producing factory for at least 1 year between 1 January 1959 (the date the factory opened) and 30 June 1997 (the date data were collected). Data relating to civil status (name, sex, birth date, birth place) and work history were abstracted from administrative records (date of hire and a list of successive jobs held in the factory with starting and finishing dates). Data on smoking habits were abstracted from factory medical records. This information had been collected by the occupational physician during the workers’ yearly clinical examinations.
The cohort was followed up for mortality from 1 January 1968 to 31 December 1998. The vital status for all subjects was assessed (i) by searching the national computerised database listing all deceased subjects in France since 1978, (ii) by contacting the registry offices of the birth places for people born in France and (iii) by contacting the registry office for foreign born French subjects. The causes of death were determined by matching the file of the deceased subjects with the French national file of causes of death, which was set up in 1968. As this file is anonymous, matching was carried out using sex, date of birth, date of death and place of death. Causes of death were ascertained from death certificates coded using the WHO International Classification of Disease 8th revision for deaths occurring between 1968 and 1978, and the 9th revision for deaths occurring after 1979.

Exposure assessment
Present and past occupational exposures were assessed by a specific job-exposure matrix (JEM) through the subjects’ job histories. The JEM was developed by a group of eight experts comprising two epidemiologists, two occupational hygienists and four occupational physicians from the factory. It was constructed in four stages.

Definition of the rows and columns of the matrix
Individual work histories contained successive job titles, dates and departments (coke-oven plant, sinter plant, blast furnace plant, steel-making plant, hot rolling mill, heavy plate mill, stocks and warehouses, maintenance, transport, research and support). Job titles were regrouped into 264 similar exposure groups based on the location of the workshop and/or the tasks of the workers. These job groups were separated into different time periods according to the historical evolution of exposure. A total of 590 job periods representing JEM rows were thus defined.

All known potential carcinogens were coded in the matrix (JEM columns) as follows: iron oxides, PAHs, silica, asbestos and oil mist, as well as total dust.

Definition of the coding procedure
An exposure intensity code on a 0–5 scale was defined for total dust and on a 0–3 scale for iron oxides, asbestos, PAHs, silica and oil mist. For each of these agents, the experts identified typical jobs corresponding to each level of the intensity codes (see supplementary online table 1 for examples of intensity scale benchmarks). These job groups were used as reference groups throughout the coding procedure. However, in the course of the coding procedure, the experts introduced an additional category coded “e” between the intensity codes 0 and 1, which corresponded to a very low exposure to iron oxides, asbestos, PAHs and silica.

Furthermore, the exposure frequency was coded according to the percentage of working time, in the following categories: 1%, 1–10%, 10–30%, 30–50%, >50%.

Finally, the experts coded the reliability of the assigned intensity and frequency codes as follows: disagreement between experts, some doubt as to the code, or consensus among the experts.

Coding
For each substance, codes were assigned to each job-period group, based on the collected information, in successive plenary meetings of the experts. The coding decisions were reached by consensus. When the experts disagreed, a minimum-coding consensus was agreed on and the disagreement was coded in the reliability code.

In order to correct a possible drift in coding, the job groups were grouped into the final assigned exposure levels and the homogeneity of the coding was critically re-examined by the group of experts.

Exposures to iron oxides, asbestos, PAHs and silica were expressed in different ways: ever exposed, highest exposure level in the work history, and duration of exposure at a level ≥2, frequency weighted cumulative index defined as the sum of level × duration of exposure × percentage of working time (frequency).

As the experts coding the exposure levels were blind to the results of exposure measurements, the JEM could be validated by comparing the assigned exposure levels and the historical exposure measurements. However, only total dust and B[a]P measurements were in sufficient numbers, although only from 1980 on, to allow such a validation. Correlations between the intensity codes of the JEM and total dust or B[a]P measurements were assessed by regressing the matched corresponding intensity codes on the log-transformed measurements.

In order to present our results in a more quantitative way, both cumulative and mean exposure levels over the job history were computed for each study subject for total dust and B[a]P based on all the available evidence, that is, the individual job history and the quantitative concentration estimates for each JEM code based on the regression predictions on the available historical atmospheric measurements. Moreover, approximate mean exposure levels of total iron were estimated based on some sporadic measurements of percentages of total iron in total dust available for four departments in the factory.

Statistical analysis
External comparisons
We compared the mortality rate of the cohort with local (département du Nord) and French death rates as external reference using standard life tables. The person-years at risk were calculated for each subject from 1 January 1968 or date of hire if later to 31 December 1998, or earlier in the case of death. Subjects deceased or lost to follow-up before 1968 were excluded from the statistical analysis. Subjects lost to follow-up after 1968 were censored at the date they left the factory. Foreign born workers were censored at date of leaving because of incomplete information on vital status. Age and period-standardised expected numbers were obtained using the corresponding reference rates. The numbers of deaths observed were compared with the expected numbers by calculating the standardised mortality ratio (SMR). 95% Confidence intervals (95% CI) were computed using the standard Poisson assumption.

Internal comparisons
Statistical analysis was carried out based on qualitative and quantitative exposure parameters as assessed by the JEM through job histories.
To account for the latency of lung and bladder cancer, a 10-year lag period was introduced into the calculation of the exposure parameters.

Two series of internal statistical analyses were performed: first, a Poisson regression in which age and period effects were taken into account by including expected numbers of cases as offsets and second, a Cox regression with age as the main time variable and time-varying exposure variables. The results of the Poisson regression were expressed as relative risks (RR) of the time-dependent exposure groups among exposed versus non-exposed subjects. The exposure groups were based on a priori cut-points of the different quantitative exposure variables: duration of exposure at a level \( \geq 2 \) (1–10 years, >10 years for iron oxides and asbestos; 1–5 years, >5 years for PAHs and silica), and the quartiles of the cumulative exposure variable among exposed lung cancer cases. For oil mist, exposure parameters were expressed as follows: duration of exposure at a level \( \geq 1 \) recoded into non-exposed, 1–9 years, >9 years, and the median of the cumulative exposure variable among exposed bladder cancer cases. For each discrete exposure variable, the trend between the exposure ranks was fitted using the Poisson regression. Relative risks per added exposure rank and a 95% confidence interval were estimated. The analyses were performed taking into account all available potential confounders, that is, smoking and occupational exposure to JEM carcinogens (asbestos, PAHs, silica). The information on smoking was defined as never, current, former smoker, and an unknown smoking category. As the information on smoking was available only for a subset of the cohort, the confounding effect of smoking on the relationship between exposure and the outcome was evaluated by comparing the crude and the adjusted relative risks among workers with known smoking habits. The over-dispersion in Poisson regression was tested using the deviance. The Cox regression was used to obtain relative risks by units of the (continuous) quantitative exposure variables.

The statistical analyses were performed using STATA software (Stata, College Station, TX, USA).

RESULTS

Cohort descriptions

The cohort comprised 17,701 subjects (16,742 men, 959 women) corresponding to 400,218 person-years (table 1). The mean follow-up time was 22.7 years for men and 21.8 years for women) corresponding to 400 218 person-years (table 1). The total number of deaths was 2567, for 96.5% of which the causes of death were available. Information on smoking was gathered for 12,797 subjects (72.8%).

Among men, the overall observed mortality (Obs) was markedly lower than expected when compared to the local population (Obs = 2383, SMR = 0.81, 95% CI 0.78 to 0.85) and higher than expected when compared to the French population (SMR = 1.10, 95% CI 1.06 to 1.15) (see mortality from most causes in online table 2). For lung cancer, the SMR was 0.89 (Obs = 233, 95% CI 0.78 to 1.01 – local rates) and 1.50 (95% CI 1.15 to 1.48 – French rates). No trend was observed according to period of death, age at death, time since first employment, duration of employment, period of first employment or age at first employment (online table 3).

Among women, mortality from all causes was lower than expected when compared to the local population (Obs = 29, SMR = 0.57, 95% CI 0.38 to 0.82) and to the French population (SMR = 0.75, 95% CI 0.50 to 1.08) (online table 4).

Exposure assessment

For each exposure, typical workshops corresponding to each level of the intensity codes were used as reference in the coding procedure. For iron oxides, the highest exposures occurred on the floor of the steel-making plant or the blast furnace before the installation of a ventilation system. The non-exposed code related to the coke-oven plant. For asbestos, the ore stockyard was considered as non-exposed, while soaking pits had the highest exposure although this was probably much lower than in asbestos industries. The highest PAH exposures were coded for the top of the coke-ovens, whereas no exposure to PAH was assigned to the ore stockyard. For silica, the maximal exposure was linked to bricklaying tasks, whereas blast furnace hands were coded non-exposed to silica. The highest oil mist exposure levels were for machine tools, while sinter plants and blast furnace plants were coded no exposure. Also see online table 1.

The experts reached a consensus for most codings: for the intensity code, the percentages of job groups over which the experts disagreed were 4.6% (iron oxides), 5.6% (asbestos), 9.2% (PAHs), 13.0% (silica) and 2.8% (oil mist). The corresponding percentages for frequency codes were 4.1%, 4.9%, 8.2%, 8.7% and 2.8%, respectively.

A total of 973 measurements of atmospheric total dust (412 individual and 561 area samples) and 372 B[a]P measurements (177 individual and 195 area samples) could be identified (table 2). The geometric and arithmetic means show an increasing trend according to the JEM codes except for level 5 for individual and area measurements of total dust (see also Wild et al(2)) and level 1 for the arithmetic mean of B[a]P area measurements. The high arithmetic mean observed for B[a]P area measurements in job codes coded as level 1 is due to two quite high measurements corresponding to an occasional activity in the blast furnace area. Ignoring these two values, the arithmetic mean for this group is below the exposure in level 2 job codes (B[a]P arithmetic mean: 1.08 µg/m³). Linear regressions of the log-transformed atmospheric measurements by intensity codes assigned in the JEM showed significantly increasing trends for total dust (p<0.001) and for B[a]P (p<0.001).

The total dust atmospheric measurements in the factory showed a large exposure gradient: 10% of the individual measurements and 30% of the area measurements were above 10 mg/m³. Among cohort subjects, 59% were exposed to total dust at an intensity level \( \geq 3 \) where mean measurements exceeded 2.5 mg/m³, and 48.3% were exposed at a level \( \geq 4 \) among whom 39.1% were at a level \( \geq 5 \) where mean measurements exceeded 5 mg/m³ (table 2).

The median of the total dust cumulative exposure index estimated for each subject was 41.2 mg/m³.years and 90% of the exposed subjects were below 205.6 mg/m³.years. The quartiles of the total dust concentrations were 1.78, 3.22 and 8.48 mg/m³, respectively. The percentage of total iron in total dust ranged from 10% to 50% according to factory department (data not shown). The quartiles of the total iron concentrations thus ranged from 0.18, 0.32 and 0.85 mg/m³ for a 10% total iron content to 0.89, 1.61 and 4.24 mg/m³ for a 50% total iron content.

The median of the B[a]P cumulative exposure index was 5.61 µg/m³.years and 90% of the exposed subjects were below 20.1 µg/m³.years. The quartiles of the B[a]P concentrations calculated for each subject were 0.14, 0.34 and 0.56 µg/m³, respectively.


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Smoking habits, asbestos, PAHs, silica and lung cancer

As estimated in the Poisson regression, the crude relative risks were 6.82 for former smokers and 26.22 for current smokers when compared to never smokers (table 3). Similarly, the relative risk increased with the mean number of cigarettes smoked with RRs of 15.1 (95% CI 3.81 to 69.0) for 1–5 cigarettes/day, 22.5 (95% CI 5.39 to 93.6) for 6–10, 24.7 (95% CI 5.73 to 106.4) for 11–15, 29.2 (95% CI 7.10 to 120.0) for 16–20, and 53.5 (95% CI 12.9 to 222.7) for >20 cigarettes/day. At the estimated low exposure level for asbestos, PAHs and silica, the reciprocally adjusted relative risks for asbestos, PAHs and silica were not elevated (table 3) and no dose–response relationship was apparent between any of the exposure metrics for these agents and lung cancer mortality (data shown in online tables 5–7). No confounding by smoking could be detected when adjusting for smoking (online table 8).

Iron oxides and lung cancer

Table 4 gives lung cancer relative risks for iron oxides adjusted on asbestos, PAHs and silica. For all subjects exposed at an intensity level $\geq 2$, the adjusted relative risk, based on 64 exposed cases, was lower than unity (RR 0.80, 95% CI 0.55 to 1.17). No dose–response relationships were observed in the Poisson regression models with the highest exposure level in work history (RR per added level 0.98, 95% CI 0.87 to 1.10), duration of exposure at an intensity level $\geq 2$ (RR 0.82 per duration period, 95% CI 0.62 to 1.07) and by quartile of the frequency weighted cumulative index (RR 1.00, 95% CI 0.89 to 1.12). However, a moderately increased relative risk was observed in the $\epsilon$ category of the highest exposure level (RR 1.39, 95% CI 0.96 to 2.00).

Among workers with known smoking habits, we compared the smoking adjusted and unadjusted relative risks in the Poisson regression models (data available in online table 9). No difference was observed for the four exposure parameters.

Other results: oil mist and bladder cancer

In a systematic analysis of all causes of death, a significant bladder cancer excess was observed among workers exposed to oil mist (RR 2.44, 95% CI 1.06 to 5.60) compared with those non-exposed (table 5). This risk was found to increase significantly with the highest exposure level in work history (RR 1.57, 95% CI 1.13 to 2.19), duration of exposure at an intensity level $\geq 1$ (RR 1.85, 95% CI 1.07 to 3.19) and by quartile of the frequency weighted cumulative index (RR 1.69, 95% CI 1.03 to 2.79). Adjustments for smoking among workers with known smoking habits did not change any results (data available in online table 10).

Using Cox regression, the results obtained for exposure variables in their continuous form were qualitatively similar. However, the increasing trends observed for duration of exposure (RR per 10 years 1.52, 95% CI 0.71 to 3.24) and for the frequency weighted cumulative index (RR per 0.15 level 1.05, 95% CI 0.99 to 1.07) were more attenuated and not statistically significant.

DISCUSSION

This study focused on the possible risk of lung cancer associated with iron oxide exposure. It failed to detect any such relationship
from multiple Poisson regressions


The relevancy of the exposure assessment depends on the precision of the job histories and on the accuracy of job-specific exposure estimates. The individual job histories in the administrative records were complete and quite detailed as they included not only a precise job title and dates but also the location of the job in the factory, the department and the section. A factory-specific JEM was developed by a group of eight experts, all of whom have prior experience in the steel industry. This group included four occupational physicians who had first hand knowledge of the working conditions in this factory. The internal consistency is good as only few disagreements between experts were coded. Moreover, for total dust and B[a]P, for which a sufficient number of exposure measurements were available, mean exposure measurements were ranked as predicted by the JEM, providing an external validation of the intensity codes. Note that this external validation could only be obtained because the expert assessments were blind to the exposure measurements.

Among the qualitative and quantitative exposure parameters, the main metric of interest is cumulative exposure, which corresponds to incremental damage resulting from exposure. However, any increase in the cumulative dose is correlated with the highest dose and duration of exposure. If the detrimental effect of the exposure is restricted to high doses, the maximal dose could allow this to be detected. An effect with duration of exposure, not confirmed by analysis with the maximal dose, might be an indicator of exposure misclassification or a missing confounder associated with the exposure of interest.

Epidemiological methods

The definition of the cohort was the most extensive possible as it comprised all workers employed in the factory since the date of opening and thus included a large number of subjects. Only those employed for less than 1 year were excluded; these consisted of holiday employees (mostly students whose parents belonged to the workforce) and short term workers whose occupational and personal characteristics were different from those of long term workers, and whose mortality patterns are difficult to interpret.22

The results of external comparisons of the cohort mortality are very different depending on the reference populations used (online table 2). However, internal comparisons are not affected by this problem. Thus, we consider that the internal relative risks comprise the main results of this paper.

Exposure assessment

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Table 5  Observed numbers of deaths, crude relative risk and 95% CI among men for bladder cancer according to oil mist from multiple Poisson regression

<table>
<thead>
<tr>
<th>Oil mist</th>
<th>Obs</th>
<th>Crude RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensity level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>18</td>
<td>1.00</td>
</tr>
<tr>
<td>1–3</td>
<td>8</td>
<td>2.44 (1.06 to 5.60)</td>
</tr>
<tr>
<td>Highest exposure level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-exposed</td>
<td>18</td>
<td>1.00</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>0.81 (0.11 to 6.05)</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>3.15 (0.93 to 10.71)</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>3.65 (1.24 to 10.80)</td>
</tr>
<tr>
<td>Trend†</td>
<td></td>
<td>1.57 (1.13 to 2.19)</td>
</tr>
<tr>
<td>Duration of exposure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(intensity level &gt;1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-exposed</td>
<td>18</td>
<td>1.00</td>
</tr>
<tr>
<td>1–9 years</td>
<td>5</td>
<td>2.14 (0.80 to 5.77)</td>
</tr>
<tr>
<td>&gt;10 years</td>
<td>3</td>
<td>3.16 (0.93 to 10.71)</td>
</tr>
<tr>
<td>Trend†</td>
<td></td>
<td>1.85 (1.07 to 3.19)</td>
</tr>
<tr>
<td>Frequency weighted cumulative index</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(intensity level freq.years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-exposed</td>
<td>18</td>
<td>1.00</td>
</tr>
<tr>
<td>&lt;0.15</td>
<td>4</td>
<td>2.27 (0.77 to 6.72)</td>
</tr>
<tr>
<td>&gt;0.15</td>
<td>4</td>
<td>2.63 (0.89 to 7.76)</td>
</tr>
<tr>
<td>Trend†</td>
<td></td>
<td>1.69 (1.03 to 2.79)</td>
</tr>
</tbody>
</table>

*RR per added level.
\( RR \) per added exposure rank: non-exposed = 0, 1–9 years = 1, >10 years = 2.

Non-exposed 18 1.00
1–9 years 5 2.14 (0.80 to 5.77)
>10 years 3 3.16 (0.93 to 10.71)
Trend† 1.85 (1.07 to 3.19)

PAHs and lung cancer

Our study did not show any link between lung cancer mortality and exposures to PAHs. Among studies carried out in coke-oven plants, some found a dose–response relationship, whereas others have proven negative. For groups of exposure with a mean cumulative dose of about 20 pg/m².years, Hurley et al. found a relative risk of less than 1 (RR 0.59, 95% CI 0.29 to 1.06 and RR 0.87, 95% CI 0.60 to 1.22), while Reid et al. found a relative risk close to 1 (RR 1.00, 95% CI 0.55 to 1.88). With estimated exposure levels close to those observed in these studies, we did not find any risk either. On the other hand, in an other study conducted among coke-oven workers, Chau et al. found a relative risk equal to 4.33 (95% CI 1.58 to 9.40) for the same mean cumulative dose.

Silica and lung cancer

The IARC has classified inhaled crystalline silica in the form of quartz or cristobalite from occupational sources as a human carcinogen, based on sufficient epidemiological data, animal data and data on biological mechanisms (group 1). Our study showed an increased relative risk, but it did not reach statistical significance. Furthermore, no dose–response relationship could be detected. As for PAHs and asbestos, this may be a consequence of the relatively low exposure levels. Freeman and Grossman described silica exposures measured in workplaces in the United States between 1980 and 1992 during 1655 OSHA (Occupational Safety and Health Administration) inspections in 255 industries: the industry “steel works, blast furnaces, and rolling and finishing mills” had maximum levels which were 10 times less than the permissible exposure limit for respirable quartz of 0.1 mg/m³ (American Conference of Industrial Hygienists, 1998 threshold limit values for chemical substances).

Oil mist and bladder cancer

A significant excess of bladder cancer was observed among workers exposed to oil mist compared with those non-exposed and consistent dose–response relationships with increasing highest exposure level in work history, duration of exposure, and cumulative index using Poisson regressions. These results were still observed after adjusting for smoking. However, these trends became non-statistically significant when considering continuous exposure parameters in a time-varying exposure Cox model.

Numerous epidemiological studies on the risks of cancer related to exposures to oil mist have already been published.
Main messages

Occupational exposures to iron oxides do not appear to have an effect on lung cancer mortality.

These studies mainly related to exposures to aerosols of fluids used in the machining of metals and were reviewed several times. Bladder cancers seemed to appear more likely among metal machinists or engineers than controls, with odds ratios ranging from 1.5 to 5.0.

In our study, the JEM experts coded the presence of oil mist in grinding and machining operations, close to the mill stands in hot rolling mills, and close to the four-high stands in heavy plate mills, but there is a lack of knowledge on both the qualitative and quantitative characterisation of this oil mist.

Despite the significant dose–response relationship, this result might be due to multiple testing and must be interpreted with caution. An extended study design is currently being planned and includes a detailed description of the exposure.

CONCLUSION

The present study did not detect any relationship between exposure to iron oxides and lung cancer mortality. This result was obtained in a large cohort with a thorough exposure assessment taking into account the major occupational (asbestos, PAHs, silica) and non-occupational (smoking) confounders. An excess of mortality from bladder cancer was found among workers exposed to oil mist.

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Competing interests: None.

The research protocol has been approved by the Commission Nationale de l'Informatique et des Libertés (Paris, France).

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