Lung Function Changes in Workers Exposed to Cobalt Compounds
A 13-Year Follow-up

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The objective of the study was to examine the influence of cobalt exposure on lung function changes in workers from a cobalt-producing plant in a health monitoring program implemented between 1988 and 2001. A total of 122 male workers with at least 4 (median = 6) lung function tests (FEV1 and FVC) during the follow-up period were assessed longitudinally. Cobalt exposure significantly decreased over the follow-up period, as reflected by the measurements in air and urine. The possible association of spirometric changes with cobalt exposure was examined by a random coefficients model, taking into account other potential influential variables, such as smoking, age, previous respiratory illness, exposure to other lung toxicants, or the presence of glutamate in position 69 in the HLA–DP β-chain, an HLA polymorphism possibly associated with hard-metal-induced lung diseases. The main finding of the follow-up study was that cobalt exposure contributed to a decline in FEV1 over time, and only in association with smoking. No influence of glutamate in position 69 in the HLA–DP β-chain polymorphism was detected. Although the amplitude of the additional FEV1 decrement associated with smoking exposure was relatively small (<20%) compared with the expected decline in a non–cobalt-exposed smoker, the results indicate that further efforts to reduce cobalt exposure and to encourage workers to quit smoking are still warranted.

Keywords: respiratory function tests; longitudinal studies; occupational exposure

Cobalt metal and several of its compounds are used for a variety of industrial applications, such as the manufacture of batteries and alloys, and for the diamond polishing and hard metal industries. In these occupational settings, excessive exposure to cobalt compounds has been associated with adverse health effects, which mainly affect the respiratory system. Respiratory disorders that have been related to occupational exposure to cobalt include bronchial asthma, chronic bronchitis, and the so-called hard-metal disease, a fibrosing alveolitis that has mainly been described in workers exposed to a mixture of cobalt metal and carbides in the hard-metal industry (1). Because of the characteristics of the disease, such as its low prevalence in exposed workers, or the lack of correlation with the intensity or duration of exposure, the existence of a possible genetic susceptibility to hard-metal disease has been suggested. Notably, the substitution of a lysine residue by a glutamate in position 69 in the HLA–DP β-chain (Glu69β) has been reported to be weakly associated with hard-metal disease (2, 3). An increased risk of lung cancer has also been reported for workers in the hard-metal industry (4–6).

A cross-sectional study in the late 1980s that was based on chest radiographs, and measurements of lung volumes and diffusing capacity, which was carried out on workers in a plant producing metallic cobalt, and cobalt oxides and salts (7), did not detect signs of fibrotic disease in the 82 workers investigated. However, cobalt-exposed workers complained more often of respiratory symptoms than unexposed subjects, and a negative relationship between lung-function parameters (mainly FEV1) and exposure was found. Technical and hygienic improvements were enforced to reduce cobalt exposure, and a periodic monitoring of the lung function of the workers was implemented and carried out beginning in 1988. Subsequently, workers were examined at intervals for spirometric parameters, and exposure to cobalt was quantitatively assessed at least annually by the measurement of cobalturia. Based on this 13-year surveillance program (1988–2001), enough information was available to investigate in a longitudinal design the possible effect of cobalt exposure on lung-function parameters. The objective of this study was, therefore, to examine the possible impact of cobalt exposure on the lung function of these workers.

Some of the results of this study have been previously reported in the form of an abstract (8).

METHODS

Plant

The cobalt plant is part of a large metallurgical concern that produces fine cobalt metal powders, cobalt oxides, and cobalt salts. A wide variety of starting raw materials is used, ranging from cobalt metal cathodes to residues and scraps. These materials are dissolved in acids, and the solutions are purified in several hydrometallurgical steps. The obtained product is subsequently dried and packaged. Three types of exposure may be sketched: (1) production of cobalt metal powder, cobalt oxides or salts in the dry-stage area (DA); (2) wet-stage area (WA); and (3) mixed exposure (MX) for maintenance workers and foremen who are involved at different steps of the process.

Study Population

A total of 571 workers were hired at this plant between 1988 and 2001, of whom 287 were still active in 2001. To ensure a minimal duration of exposure and observation, workers with at least three lung-function tests between 1988 and 2000 were considered eligible for a longitudinal analysis (n = 135), which included both active workers and those that had left the plant since 1988. They were invited between June 2001 and March 2002 to answer a short questionnaire, to undergo an additional lung spirometry, and to provide a urine and blood sample for exposure assessment and genotyping, respectively. Thirteen (9.6%) of these workers did not agree to participate in the study. Two of those 13 workers were retired, 4 still worked in the company, I suffered from long-term disease (depression), and 6 had left the company. Finally, a total of 122 male workers, each with a total of at least 4 lung-function...
tests (a minimum of three between 1988 and 2001, and one in 2001–2002), were enrolled in the longitudinal survey. Available information about the workers who were not eligible for the follow-up survey was also examined. The study protocol was approved by the Bioethics Committee of the Catholic University of Louvain.

**Questionnaire**

A short questionnaire was used to reconstruct exposure history, to identify simultaneous or previous exposure to other lung toxicants (e.g., acids, sulfur dioxide, chlorine, silica, beryllium, nickel, and arsenic), and to obtain information on respiratory history, such as any previous or current respiratory disease, or use of medication for respiratory disease.

**Exposure Assessment**

Airborne cobalt measurements were performed yearly by personal sampling in the breathing zone of the workers with a CIP10 dust sampler (MSA, St-Ouen-l’Aumône, France) equipped with two 45-grade and one 60-grade polyurethane foam filters (inhalable fraction). Air was sampled at a mean flow rate of 10 L/minute for 6 hours. After dissolution in a 10% sulfuric acid–1% nitric acid solution, the cobalt content of the filters was measured by flameless atomic absorption spectrometry (Zeeman 5000; Perkin Elmer, Norwalk, CT).

Biological exposure to cobalt was assessed in post-shift urine samples taken at the end of a workweek close to the time of the lung-function test, during the period of follow-up, and in 2001. Cobalt in urine was measured by graphite furnace atomic absorption spectrometry (GFAAS). In the analysis, biomonitoring values (log cobalt in urine) were given preference over air values for assessing worker’s exposure as they more closely reflect the overall uptake, take into account various toxicokinetic factors, and, importantly, integrate the fact that protective measures were implemented and respiratory masks worn starting in 1999 at several job positions.

**Lung-Function Measurements**

VC, FVC, and FEV₁ were measured with a rolling seal spirometer (Volutgraph, Mijnhardt, The Netherlands). Workers were asked to refrain from smoking for one hour before performing the test. At least two acceptable curves were obtained on each subject at each testing, and the apparatus was subjected to regular external quality control. The results were expressed as the absolute value and as a percentage of the predicted value calculated on the basis of age, weight and height according to the European Community for Coal and Steel (9).

Smoking status (current nonsmoker = 0 or current smoker = 1) was recorded at the time of each lung-function test as a discrete variable.

**Genotyping**

Genotyping was performed after extraction of genomic DNA from an ethylenediaminetetraacetic acid-anticoagulated blood sample. The presence of the polymorphisms leading to the expression of Glu99β was determined by a reverse-sequence specific oligonucleotide test using a probe specific for the GAG sequence in exon 2 of the *HLA-DPB1* gene (Innolipa, Innogenetics, Gent, Belgium). The results are expressed as the presence or absence of the polymorphisms without consideration of the allelic combinations.

**Statistical Analysis**

Among the 122 selected workers, 24, 23, 36, 27 and 12 workers had, respectively, 4, 5, 6, 7 and 8 lung-function tests (median: 6) during the follow-up period. The interval between two successive lung-function tests ranged from 1–4 years, and the duration to follow-up (including those workers who had left the plant or retired) ranged from 6–13 years (median of 12 years). To investigate the changes in lung-function parameters in repeated-measure data, a mixed-model approach (random coefficients model) was used. This model allows time slopes and intercepts to vary randomly across observations and, thus, observation specific regression lines to be fitted (10).

Because the smoking status of a significant proportion of the 122 workers (20%) changed during the follow-up period, two random coefficients models were fitted after separating observations according to the smoking status recorded at the time of each lung-function measurement (n = 234 and 279 observations in smoking and non-smoking workers, respectively). A linear relationship was assumed between the outcome variables of interest (absolute FEV₁ and FVC values adjusted for height (FEV₁/cm² and FVC/cm²) (11) and time (reflected by time elapsed since the first-lung function test during the follow-up period). Exposure (log cobalt-urine), other toxic exposures, respiratory history, age at the first lung-function test (age at baseline), and Glu99β (absent or present) were included in the regression models as potential influential variables. After selection of the best-fit model, based on the residual plots, 4 of the 513 observations were identified as clearly aberrant values and excluded after examination of the raw data. Statistical analyses were performed with SPSS 10.0 (SPSS, Chicago, IL) and SAS (SAS Institute, Inc., SAS Technical Report P-229, SAS/STAT Software: Changes and Enhancements, Release 6.07, Cary, NC; 1992; PROC MIXED) for the random coefficients model procedure. A p-value < 0.05 was considered significant.

**RESULTS**

**Exposure Assessment**

The air and biological measurements performed over the years of follow-up indicate that cobalt exposure sharply declined with time. Cobalt dust levels decreased in all three exposure patterns (dry-stage, wet-stage, mixed exposure), but the decrease was sharpest in dry-stage exposure, which had the highest values peaking above 1 mg/m³ at the beginning of the 1990s (not shown). Cobalturia values followed the same pattern (Figure 1).

**Data Collected in 2001**

The data are presented in Table 1 for the total population. Seventeen percent of the workers reported to have suffered from respiratory symptoms in the past, mainly from chronic bronchitis and asthma. Seventy percent of the workers had been exposed to other lung toxicants previously or during their employment at the cobalt plant. When considering the whole cohort, the mean FEV₁ was lower in smokers than in nonsmokers (absolute 3.34 vs. 3.45 L, predicted 96 vs. 101%, respectively), but the difference did not reach statistical significance (not shown). No significant differences were found in lung-function values of the three patterns of exposure (dry-area, wet-area, mixed exposure) (not shown).

**Longitudinal Survey**

As expected, both absolute and/or predicted FEV₁ and FVC values decreased significantly between the initial and the last examination (FEV₁, 4.2 ± 0.7 vs. 3.5 ± 1.3 L; FEV₁, predicted,
TABLE 1. POPULATION CHARACTERISTICS IN 2001

<table>
<thead>
<tr>
<th></th>
<th>Total Population (n = 122)</th>
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<tbody>
<tr>
<td>Mean age (range), yr</td>
<td>43.7 (29.9–60.7)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>175.3 (161–199)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>82.5 (55–120)</td>
</tr>
<tr>
<td>Employment duration, mean ± SD, mo</td>
<td>205.8 ± 75.5</td>
</tr>
<tr>
<td>Still active at the plant, n (%)</td>
<td>93 (76.2)</td>
</tr>
<tr>
<td>With previous respiratory disease, n (%)</td>
<td>17 (13.9)</td>
</tr>
<tr>
<td>Exposed to lung toxicants other than cobalt, n (%)</td>
<td>87 (71.3)</td>
</tr>
<tr>
<td>With Glu 69 β present, n (%)</td>
<td>54 (44.3)</td>
</tr>
<tr>
<td>Never-smokers, n (%)</td>
<td>36 (29.5)</td>
</tr>
<tr>
<td>Ex-smokers, n (%)</td>
<td>37 (30.3)</td>
</tr>
<tr>
<td>Current smokers, n (%)</td>
<td>49 (40.2)</td>
</tr>
</tbody>
</table>

The parameters of the random coefficients model for FEV₁ (FEV₁/height², L/cm²) and FVC (FVC/height², L/cm²) according to smoking habit are shown in Table 2. In this best-fit model (Akaike’s information criterion), age at baseline and time elapsed since the first lung-function test significantly and negatively influenced FEV₁ and FVC values over the years. Cobalturia contributed significantly to deterioration of FEV₁, but only in association with smoking. No influence of cobalturia on FVC was observed. The interaction between cobalturia and time was not significant.

To investigate the possibility of a healthy worker effect, lung function results from all the workers present at the cobalt plant during the years with the heaviest dust exposure (1988–1990) were examined to determine whether those who left the plant earlier had the worst lung function results. No significant difference was observed when both absolute and predicted values of FEV₁ and FVC were compared between workers who subsequently stayed at the plant and those who left for reasons other than retirement (Table 3). In addition, the lung function values (FEV₁ and FVC) in the group of workers with only two lung function measurements between 1988 and 2000 (n = 97) were not different from those of included subjects (values measured at the first examination, not shown).

DISCUSSION

The data collected in 2001 did not reveal an effect of cobalt exposure on lung-function parameters in workers associated with any exposure pattern despite marked contrasts in airborne dust levels and cobalturia (Figure 1). Two plausible explanations that are related to the cross-sectional nature of this approach can be offered for this absence of effect: first, the fact that workers have transited during the survey period from one job group (and thus exposure pattern) to another according to the organization of the work; and second, the considerable decrease of exposure over the years. These might have masked the possible influence of exposure type on the lung-function parameters measured in 2001.

The strength of the present study is that the lung function of these workers was followed longitudinally. Reliable measurements were obtained by a regular calibration of the equipment that was used by the same technician over the follow-up period. The use of a random coefficients model allowed a powerful analysis of the data despite the fact that, as in most longitudinal studies, responses were correlated (observations were taken on the same subject at different time points), measurements were taken at unequal time intervals, and some observations were missing (12, 13). The main finding of the longitudinal survey was that cobalt exposure, as reflected by cobalturia, negatively influenced FEV₁ only in association with smoking. Based on the estimates provided by the model and presented in Table 2, an exposure entailing a cobalturia of 10, 20, or 40 μg/g creatinine (which is roughly equivalent to a time-weighted average exposure at 10, 20 or 40 μg/m³) would cause, for a 30-year-old smoking worker, an additional decrement of 64, 84 or 103 ml of FEV₁ after 10 years of work at this plant (Figure 2). The amplitude of this additional decrement is, however, relatively small compared with the expected decline, 518 ml, in a smoking subject over the same period in the absence of occupational exposure (Figure 2). This finding is consistent with our previous observations in 1988 that detected a slight deterioration of the FEV₁ to VC ratio associated with exposure (7). Decreased pulmonary function was

TABLE 2. RANDOM COEFFICIENTS MODEL FOR FEV₁* AND FVC†

<table>
<thead>
<tr>
<th></th>
<th>FEV₁</th>
<th>FVC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Effect</strong></td>
<td><strong>Estimate</strong></td>
<td><strong>SE</strong></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>0.1887</td>
<td>0.0083</td>
</tr>
<tr>
<td>Age at baseline</td>
<td>–0.0017</td>
<td>0.0003</td>
</tr>
<tr>
<td>Log Co-U</td>
<td>–0.0024</td>
<td>0.0011</td>
</tr>
<tr>
<td>Time</td>
<td>–0.0016</td>
<td>0.0002</td>
</tr>
<tr>
<td>Nonsmoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>0.1688</td>
<td>0.0091</td>
</tr>
<tr>
<td>Age at baseline</td>
<td>–0.0010</td>
<td>0.0003</td>
</tr>
<tr>
<td>Log Co-U</td>
<td>–0.0013</td>
<td>0.0011</td>
</tr>
<tr>
<td>Time</td>
<td>–0.0017</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

Definition of abbreviations: Log Co-U = log cobalt in urine; NS = not significant.

* (FEV₁ [L]/height² [cm²] × 1,000).
† (FVC [L]/height² [cm²] × 1,000).
also reported by Nemery and colleagues (14) in a group of workers from the diamond-polishing industry exposed to metallic cobalt-containing dusts examined in a cross-sectional design.

There is also strong evidence that cobalt can cause occupational asthma with prevalence rates of 5–15% (15). Among the 122 workers examined in the present study, only two (retired) workers were treated for asthma, however, cobalt was not implicated as the causal agent.

The fact that in the present study the decline in the pulmonary function associated with cobalt exposure, although limited in amplitude, was found specifically in association with smoking points to a possible interaction between both exposures. This observation is reminiscent of previous surveys conducted in workers exposed to respiratory irritants that reported a stronger association between symptoms and exposure in smokers than in current nonsmokers (16, 17). It should also be noted that in a biomonitoring study, De Boeck and colleagues (18) reported that workers who both smoked and were exposed to cobalt in a hard-metal plant had elevated biomarkers of genotoxicity (urinary levels of 8-hydroxydeoxyguanosine and micronuclei frequencies in circulating lymphocytes). In a lung cancer–mortality study of workers from the hard-metal industry in France, Moulin and coworkers (4) reported that the interaction between exposure and smoking was non-significantly associated with an increased risk for lung cancer.

An additional objective of this study was to explore the possible involvement of Glu69β, a genetic-predisposing factor previously reported to be associated with beryllium sensitization (19). In hard-metal plants, a possible involvement of immunologic mechanisms has also been suggested, and an association of hard-metal disease with the presence of Glu69β has been reported (2, 3). When, as in the plant used in this study, exposure is to cobalt alone, only a few isolated and poorly documented cases of this interstitial lung disease have been reported (1). No cases of lung fibrosis were identified in this workforce during the follow-up period, and the presence of the Glu69β polymorphisms did not influence the evolution of FVC or FEV1.

The next issue to be discussed is the possibility of a healthy-worker effect and/or selection bias in this survey. First, it should be acknowledged that individuals with preexisting asthma or allergy are not employed at the cobalt plant. Second, the study subjects were selected among the production workers of the plant with at least four lung-function tests over the surveillance period. This allowed us to focus on the analysis of those workers with a sufficient duration of exposure, but this selection excluded workers employed for shorter periods who could have left the cobalt plant because of respiratory problems. This possibility could be excluded by examining the lung-function values of workers who left the plant earlier (Table 3).

The implementation of the regular monitoring of workers also allowed the occupational-health staff of the plant to remove from exposure those workers exceeding cobalturia limits, or with altered lung-function results and to reappoint them to other parts of the plant. While this is, of course, the primary function of a health-monitoring program, it could have led to a weakening of the association between exposure and health effects. Examination of the medical records of workers of this plant indicated that when removal from exposure or reappointment to the wet area of the plant occurred because of respiratory problems (seven cases during the follow-up period), no causal relationship with cobalt exposure could be established. Therefore, while a healthy-worker effect could not be formally excluded, it probably had a limited impact on the results, if any.

Overall, although the hygienic controls enforced since the first study have successfully contributed to the improvement of working conditions, cobalt exposure still appears as a weak contributing factor for adverse lung-function changes, specifically in association with smoking. Further efforts to reduce exposure and to encourage workers to quit smoking are still warranted.

**Conflict of Interest Statement**: V.V. does not have a financial relationship with a commercial entity that has an interest in the subject of this article; A.M. is an employee of UMICORE, the metallicurgic concern that owns the cobalt refinery; J.P.B. does not have a financial relationship with a commercial entity that has an interest in the subject of this article; B.S. is an employee of UMICORE, the metallicurgic concern that owns the cobalt refinery; D.L. does not have a financial relationship with a commercial entity that has an interest in the subject of this article.

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**References**


