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Effects of occupational exposure to poorly soluble forms of beryllium on biomarkers of pulmonary response in exhaled breath of workers in machining industries

Anca Radauceanu[a,*], Michel Grzebyk[a], Jean-Louis Edmé[b,c], Nathalie Chérot-Kornobis[b,d], Davy Rousset[a], Mathieu Dziurla[a], Virginie De Broucker[b,c], Guy Hédelin[a], Annie Sobaszek[b,d], Sébastien Hulo[b,c]

[a] *Institut National de Recherche et de Sécurité pour la prévention des accidents de travail et des maladies professionnelles (INRS) : 1, rue du Morvan, CS 60027, 54519Vandœuvre-lès-Nancy Cedex, France*

[b] *Université de Lille, EA 4483 : 1, place de Verdun, 59045 Lille, France*

[c] *Centre Hospitalier Universitaire de Lille, Service des Explorations Fonctionnelles Respiratoires : 2, avenue Oscar Lambret, 59037 Lille Cedex, France*

[d] *Centre Hospitalier Universitaire de Lille, Service de Médecine du Travail du Personnel Hospitalier : 2, avenue Oscar Lambret, 59037 Lille Cedex, France*

HIGHLIGHTS

- We studied the pulmonary inflammatory response to low exposure to beryllium (Be).
- TNF-α and nitrogen reactive species were assayed in exhaled breath condensate (EBC).
- Cumulative exposure to Be was correlated with TNF-α in EBC of machining operators.
- No relationship between exposure to Be and nitrogen reactive species was found.
- Low air exposure to Be is associated with pulmonary inflammation involving TNF-α.

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ABSTRACT

Objective: To analyze the effects of occupational exposure to poorly soluble forms of beryllium (Be) on biomarkers of pulmonary inflammation using exhaled breath condensate (EBC) in workers employed in machining industries.

Methods: Twenty machining operators were compared to 16 controls. The individual exposure to Be was assessed from the work history with several indices of exposure calculated on the basis of task-exposures matrices developed for each plant using historical air measurements. Clinical evaluation consisted in a medical questionnaire, measurements of biomarkers in EBC (tumor necrosis factor alpha (TNF-α), total nitrogen oxides (NOx)), measurement of the fraction of exhaled nitric oxide (FeNO) and resting spirometry. Adjusted multiple linear regressions were used to study the effect of the exposure to Be on inflammatory biomarkers.

Results: Levels of TNF-α and NOx in EBC were not statistically different between exposed and controls. We found a statistically significant relationship between levels of TNF-α in EBC and both index of cumulative exposure and duration of exposure to Be. No other statistically significant relationships were found between exposure to Be and pulmonary response.

Conclusion: Our results suggest that machining-related exposure to Be is related to pulmonary inflammation involving TNF-α. These findings must be confirmed by larger studies.

* Corresponding author at: Département Epidémiologie en entreprise, INRS, 1 rue du Morvan, 54519, Vandœuvre lès Nancy Cedex, France.

E-mail addresses: anca.radauceanu@inrs.fr (A. Radauceanu), michel.grzebyk@inrs.fr (M. Grzebyk), jledme@univ-lille2.fr (J.-L. Edmé), nathalie.cherot@univ-lille2.fr (N. Chérot-Kornobis), davy.rousset@inrs.fr (D. Rousset), mathieu.dziurla@inrs.fr (M. Dziurla), virginie.debroucker@chru-lille.fr (V. De Broucker), guy.hedelin@inrs.fr (G. Hédelin), annie.sobaszek@univ-lille2.fr (A. Sobaszek), sebastien.hulo@univ-lille2.fr (S. Hulo).

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1. Introduction

Beryllium (Be) is a naturally occurring metal whose physical and mechanical properties are much sought-after in high technology industries, especially in the aeronautics, aerospace, energy, electrical, electronic and medical sectors. The Be industry produces 3 primary poorly soluble forms of Be: metallic Be, alloys of Be and oxides of Be. Exposure to Be and its compounds has been known to cause chronic beryllium disease (CBD), so called berylliosis, a long latency granulomatous disorder resembling sarcoidosis, that requires a prior Be sensitization phase (BeS) and primarily affects the lung (Balmes et al., 2014). The immunological reactions observed in affected individuals are Be-specific hypersensitivity responses involving CD4+ T-lymphocytes, production of T helper 1 (Th1) type cytokines and the subsequent generation of granulomatous inflammation in the lungs (Muller et al., 2011). Tumor necrosis factor-alpha (TNF-α), a Th1-type cytokine, may exert effects on cell recruitment at site of inflammation and induce granulomatous structures (Semenzato et al., 2000).

Despite an increased understanding of the pathogenesis of BeS and CBD, little is known about relationships between external exposure, internal exposure and early respiratory effects. Once Be is deposited in a region of the respiratory tract, its chemical form and solubility are important exposure factors to pulmonary injuries (Stefaniak et al., 2004). Relatively insoluble Be compounds as well as copper-beryllium alloys were associated with development of CBD even in workers exposed at airborne concentrations of Be below the occupational exposure limit of $2\,\mu g\,m^{-3}$ (Schuler et al., 2005). Thus, poorly soluble species are thought to be responsible for local effects whereas soluble compounds are readily taken up and excreted with urine.

The use of a local matrix to monitor target tissue dose and effects occurring in the respiratory tract can be suggested when exposure to pneumotoxic substances occurs by inhalation (Mutti and Corradi, 2006). Exhaled breath condensate (EBC) represents one of these promising matrices. EBC collection is a completely noninvasive method for obtaining samples that reflect airway lining fluid composition through non-volatile substances (Kubáň and Foret, 2013). Biomarkers of local inflammation and oxidative stress – cytokines, nitric-oxide-related products, arachidonic acid metabolites, hydrogen peroxide, aldehydes – were reported as potential sensitive endpoints when identifying early biochemical changes in the airways of workers exposed to various pneumotoxic subtances (Chérot et al., 2012). Nitric oxide (NO) is an important mediator involved in several physiological processes that induces respiratory tract injuries via the interaction of NO with reactive oxygen species resulting in reactive nitrogen intermediates (Sugiura and Ichinose, 2011; Robbins et al., 2000). NO-related products, which are found in EBC, are formed in the airways by oxidation of NO in nitrogen oxides (NOx, namely nitrite and nitrate) (Kubáň and Foret, 2013).

We recently reported that it was possible to quantify beryllium in the EBC of workers exposed mainly to water soluble forms of beryllium in a primary aluminum production plant (Hulo et al., 2016a,b). We also shown that concentrations of Be in EBC and cumulative beryllium exposure index were significantly correlated.

To our knowledge, there have been no published data on exhaled biomarkers to assess respiratory tract effects in workers exposed to beryllium yet. Thus, the aim of the present study was to analyze the effects of occupational exposure to poorly soluble forms of Be on pulmonary inflammation using EBC in workers employed in machining industries.

2. Material and methods

2.1. Study population

We conducted an exposed-control study in a population of 20 workers exposed to poorly soluble forms of Be and 16 control subjects. Exposed subjects worked in three French plants (A, B and C) that machined:

- low beryllium alloys (copper – beryllium (Cu-Be) alloys with beryllium content 2% for plant A and 3% for plant B). Eight exposed workers were recruited from plants A and B
- high beryllium alloy with aluminum (Al-Be) (beryllium content 62%) and beryllium metal for plant C. Twelve exposed workers were recruited from plant C.

Machining operations within the plants consist mainly in lathe work, milling, grinding, deburring, filling, polishing, sanding and electrospark machining. Plants were identified from a French assessment survey of exposure associated with occupational use of Be and its compounds (Vincent et al., 2009) and recruited on a voluntary basis of their management boards. Within each recruited plant, we identified workrooms and workstations with potential exposure to beryllium. All the operators working in these workrooms and workstations were proposed to participate to the study. The voluntary participants were informed about the protocol study and signed an informed and free consent form before enrollment.

Controls were enrolled at the same plants as the exposed subjects and were recruited on the statement of no current or previous Be exposure. We checked during onsite plant visits that controls' activities were disconnected from Be-exposed working areas and were performed in specific buildings far from Be-exposed working areas. Seven controls were recruited from plants A and B, and nine controls from plant C

2.2. Study protocol

The study protocol was approved by the French national data protection commission and by the East ethics committee on protection of persons. All the subjects were recruited in 2010–2011 and answered an interviewed questionnaire in two parts:

- A medical questionnaire to assess medical history and treatment, in particular respiratory health and smoking habits. We used the questionnaire of the European Community for Steel and Coal on respiratory symptoms (Minette, 1989).
- A questionnaire to gather occupational history, focusing on the type, the duration and frequency of Be exposed operations as well as occupational exposure to other pneumotoxicants such as aluminum, titan, zirconium, welding fumes, copper, cobalt, antimony, iron, silica, asbestos, oil mist, nickel, chrome, refractory ceramic fibers, chlorine, solvents.

Then we collected the following samples in that order:

- collection of EBC samples
- measurement of fraction of exhaled nitric oxide (F_eNO)
- spirometric measurements

All clinical data were collected during the workshift.

2.3. Assessment of exposure to beryllium

Workers' exposure to Be was related to machining tasks performed on alloys Cu-Be 2-3% in plants A and B, and on alloy Al-