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OCCUPATIONAL EXPOSURE AND RESPIRATORY DISEASES

FROM THE CLINIC TO THE WORKPLACE, AND BACK

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Content

General introduction and outline of the thesis

During the 20th century coal workers' pneumoconiosis—or *anthraco-silicosis*—and asbestos-related diseases were the major occupational respiratory diseases among Belgian workers, both in terms of public health impact as well as public visibility. Except for asbestos-induced mesothelioma, the occurrence of these occupational diseases has been declining in recent decades, due to improved prevention but to a certain extent also because many hazardous industries, such as coal mining, were closed or have moved to the global south.[1] In Europe, this has led many to think that occupational respiratory diseases can be considered diseases 'of the past'. However, workplace exposures can still contribute substantially to respiratory diseases.[2]

On the one hand, well-known occupational diseases can re-emerge. Outbreaks of silicosis are still occurring, often in new production processes or industries, because the collective memory of the disease repeatedly appears to fall below a critical point of awareness.[3,4] One of the worst recent outbreaks occurred in Turkey in workers sandblasting denim jeans to give them a 'worn-out' look.[5] Sandblasting was done mostly by young men in unregistered workplaces without any protection, leading to high exposures to fine silica dust and extremely high rates of silicosis, many leading to death. In recent years, silicosis is emerging in yet another industry. Several reports have highlighted silicosis in workers fabricating and installing artificial stone kitchen and bathroom countertops in Spain, Australia, Israel, Italy, United States, New Zealand, China, and also Belgium.[6,7] Artificial stones are composed of a high percentage of crystalline silica (70-95% quartz or cristobalite) in a synthetic resin. Workers producing, cutting, drilling, grinding or polishing these stones are exposed to high levels of respirable crystalline silica dust, leading to an increased risk of silicosis in a sector in which few seem to have expected it.

On the other hand, workplace exposure can contribute to respiratory diseases by being a source of new causes of *known* diseases, such as

asthma. Work-related asthma is the most commonly reported work-related respiratory disorder in many industrialized countries.[2] "Work-related asthma" includes *occupational asthma*—defined as asthma "caused" by workplace exposures—, and *work-exacerbated asthma*, meaning pre-existing asthma worsening due to occupational exposure to irritants or physical stimuli. Occupational asthma can be caused by sensitizers (*sensitizer-induced*) but also by exposure to airborne irritants (*irritant-induced asthma*). The role of irritants in the induction (de novo) of occupational asthma is an ongoing scientific debate as it does not correspond well with the traditional paradigm of asthma as an allergic disease.[8] Both a single high level exposure (an acute inhalation injury) as well as long-term exposure to "low-to-moderate levels" of irritants have been shown to induce asthma, with the latter, however, more difficult to "prove" on the individual level.[9]

The association between the use of cleaning products and work-related asthma is a major ongoing debate.[10] Cleaning products are complex chemical mixtures containing a vast range of ingredients, including both irritants and potential sensitizers.[11,12] A number of studies have shown associations between asthma and certain types of products, most commonly sprays, bleach, ammonia and inhalation injuries resulting from the mixing of incompatible products.[13–15] Moreover, respiratory health effects of cleaning products are not limited to (sensitizer or irritant-induced) asthma but include rhinitis, inducible laryngeal obstruction (previously known as vocal cord dysfunction) and chronic bronchitis.[16] Studying respiratory health effects of cleaning products in domestic cleaners is challenging, not only due to the complexity of the exposures but also because domestic cleaners are a difficult to reach and socio-economically vulnerable population.[17] Nevertheless given the huge population of workers in domestic cleaning and the use of cleaning products by "consumers" the public health impact can be large.

The occupational contribution to the burden of respiratory disease extends beyond the 'classic' occupational diseases. A recent Official American Thoracic Society (ATS) and European Respiratory Society (ERS) Statement

showed that for asthma, chronic obstructive pulmonary disease (COPD), and chronic bronchitis the occupational population attributable fraction (PAF) is estimated to be 15–20%.[2] Also, there is evidence for a substantial occupational contribution to the burden of idiopathic pulmonary fibrosis (PAF 26%), hypersensitivity pneumonitis (PAF 19%) and sarcoidosis (PAF 30%).

The PAF is an important epidemiological parameter as it teaches us something about the impact of occupational exposures on health at the level of the population. The PAF corresponds to the percentage of cases that *could have been* prevented if (hypothetically) there had not been any occupational exposures. However, in most cases, attributing—in an individual patient—a disease to a particular exposure is difficult (or impossible). On the one hand, the clinical presentation of most respiratory diseases does often not differ between those caused by occupational exposure and those not. On the other hand, in some of these diseases the causative agents are not entirely understood.

The ATS/ERS Statement on the Burden of Occupational Diseases estimated that 30% of the cases of sarcoidosis—a systemic disease characterized by the formation of immune granulomas in various organs—were attributable to occupational exposure.[2] This high fraction is surprising, because almost any book chapter or review on the topic starts with the obligatory sentence "*sarcoidosis is a disease of unknown etiology*".[18,19] Over the past decade, however, this paradigm has been shifting.[20] Several lines of evidence indicate that the disease results from an immune reaction in genetically susceptible hosts upon exposure to one or several antigens. Many occupational and environmental exposures have been associated with sarcoidosis: inhaled organic dust, inorganic dust—including metals, silica and other minerals—and infectious agents—such as mycobacteria and *Cutibacterium acnes.*[21]

Aims and outline of the thesis

Occupational respiratory diseases are not purely medical problems. Their occurrence is largely determined by socio-economic and technological factors at the level of the workplace and society. Paraphrasing Irving Selikoff—"Occupational diseases are social problems, with medical aspects".[3] Therefore, we need to bridge the gaps between the clinical world, academic research, and the workplace to understand the relation between hazardous exposures and adverse health effects and, most importantly, to have an impact on the prevention of these effects.

In my doctoral dissertation, I have tried to link the improvement of our knowledge on occupational respiratory disease with a direct societal impact by involving and reaching out to different societal actors—workers, employers, occupational physicians, pulmonologists, occupational hygienists, and others. I will cover 3 topics approaching the theme of occupational respiratory diseases from different angles: (1) the search for a cause of an enigmatic disease—sarcoidosis, (2) the re-emergence of an "old" disease in a new industry—silicosis in artificial stone workers, and (3) respiratory health effects of cleaning products in domestic cleaners.

Chapter 1. Occupational and environmental exposures and sarcoidosis
In the first chapter, I first provide an overview of the literature linking the occurrence of sarcoidosis with occupational and environmental exposures. Next, I describe two cases of sarcoid-like granulomatous lung disease that occurred among employees in a small production unit of about 30 workers making metal-halide lamps, who were exposed to amorphous fused silica dust originating from the lamp tubes. Finally, I present our research article on the associations between occupational and environmental exposures and organ involvement in sarcoidosis. Given, the diverse clinical manifestations and the wide range of exposures that have been associated with the disease, an intriguing hypothesis remains: do different exposures lead to different phenotypes of sarcoidosis? The aim in this retrospective study was to establish *if* and *how* occupational and environmental exposures—such as

inorganic dust, organic dust and infectious agents—relate to organ involvement in sarcoidosis patients.

Chapter 2. Old hazards in new places—Silicosis in artificial stone workers

In the second chapter, I describe the hazards of silica exposure and highlight the ongoing outbreaks of silicosis in artificial stone workers that have occurred around the globe.

The aim of this chapter is first to describe the initial Belgian cases of artificial stone-associated silicosis encountered at our clinic at the University Hospitals Leuven. Secondly, I describe an outbreak of silicosis in a Belgian company producing silica-based artificial kerbstones and discuss how the outbreak was initially missed, and how this could be prevented.

Chapter 3. Respiratory health effects of cleaning products in domestic cleaners

In the third chapter, I will provide a review of the literature on the respiratory health effects of cleaning products, including epidemiological and toxicological studies. Next, I describe how we have set up a joint project with the Belgian service voucher sector (“dienstenchequesector”), using a participatory research methodology, and I will present the research article resulting from the first phase of this project.

The aim of the study described in this chapter was to investigate, among professional domestic cleaners, the associations of a range of respiratory outcomes with the use of specific categories of cleaning products at work and with the ability to choose their own products.

Epilogue. The history of the Colinet-Caplan syndrome

The first description of an association between rheumatoid arthritis and pneumoconiosis is generally attributed to Anthony Caplan, who had reported it in South Wales coal miners in 1953. However, in 1950 Émile Colinet, a Belgian rheumatologist at the Saint-Pierre Hospital in Brussels (Belgium), had already described a case of concomitant rheumatoid arthritis and

pneumoconiosis in a 30-year-old woman working at a silica-based scouring powder factory. This case was the first of a series of reports on autoimmune diseases in scouring powder workers. In this epilogue, I explore this largely undocumented history of young scouring powder workers—mainly women—developing autoimmune diseases after relatively short periods of exposure to high airborne concentrations of finely milled silica, in the scouring powder industry.

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Chapter 1 —
Occupational and environmental exposure and sarcoidosis

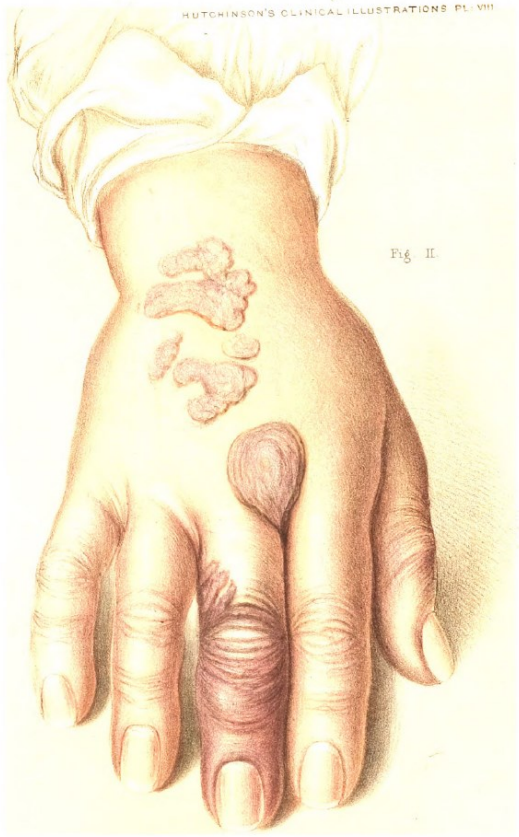

Figure 1—In January 1869, John W, a 58-year-old coal-wharf worker, visited Dr Jonathan Hutchinson, at the Blackfriars Hospital for Skin Diseases (London, UK) complaining of purple skin plaques that had gradually developed over the preceding 2 years. In 1877, Hunchinson described the case in his *Illustrations of Clinical Surgery*, calling it a "*case of livid papillary psoriasis".*[1] *This was* the first description of a patient with skin sarcoidosis. The case report is accompanied by this illustration of the patient's hand. Unfortunately, Dr Hunchinson was not entirely satisfied with it and states that "[t]he artist has, I am sorry to say, not been very successful in representing the peculiarities described." [figure reproduced from Hutchinson J. Illustrations of Clinical Surgery. J & A Churchill; 1877][1]

1.1. Introduction

1.1.1. Background

Sarcoidosis is a systemic disease characterized by the development of epithelioid-cell-rich, non-necrotizing granulomas. The annual incidence is estimated to be 1 to 35 per 100,000 adults, depending on the geographical area.[2] Sarcoidosis is more common in women than in men, and generally diagnosed at a later age in women.[2] The clinical manifestations of sarcoidosis can be very heterogeneous. The lungs and lymph nodes are the most commonly affected organs, but also the eyes, skin, liver, spleen, heart, nervous system, bones, and other organs can be involved.[3] Moreover, the disease may present and evolve with various degrees of severity: from rather benign with reversible mediastinal lymph node enlargement and mild pulmonary impairment, to multisystem organ failure and death.[3]

Pathophysiology and genetic susceptibility

Although sarcoidosis is considered to be a disease of unknown etiology, several lines of evidence support the idea that the disease results from exposure of genetically susceptible hosts to one or several antigen(s), which leads to T-cell immunity against these antigens and to the formation of granulomas.[4] The initial detection and processing of antigens occurs by antigen presenting cells such as macrophages and dendritic cells.[5] Processed antigens are subsequently presented via human leukocyte antigen (HLA) Class II molecules (HLA-DR, -DP and –DQ) on the surface of antigen-presenting cells to a restricted set of T-cell receptors (TCRs) on naive $CD4^+$ T lymphocytes. The interplay of antigen, HLA class II molecules, and TCR is thought to be essential for sarcoidosis to develop.[6]

Various HLA gene alleles have been associated with the development and disease course of sarcoidosis. For example, in the ACCESS (A Case Control Etiologic Study of Sarcoidosis) study, the HLA-DRB1*1101 allele was significantly associated with the occurrence of sarcoidosis.[7] HLA-DRB1*0401 has been associated with ocular sarcoidosis.[7] HLA-DRB1*03 was found to

predispose to disease with spontaneous resolution while HLA-DRB1*14 or HLA-DRB1*15 have been associated with a chronic disease course.[8]

TCRs are heterodimers mostly composed of an α- and a β-chain, the variable regions of which are involved in antigen recognition. In sarcoidosis, accumulation of T-cells expressing distinct TCR Vα or Vβ genes in the lung suggests the presence of *specific* antigens.[9,10] Grunewald *et al* have shown accumulation of large clonal populations of specific Vα2.3/Vβ22 TCR-expressing $CD4^+$ T-cells in the lungs of HLA-DRB1*03^+ sarcoidosis patients, and found that a vimentin-derived peptide matched perfectly into both the HLA peptide-binding pocket and the TCR Vβ22 CDR3 loop.[10] Moreover, they showed that the same vimentin peptide could induce strong proliferative responses in peripheral blood T-cells of HLA-DRB1*03^+ sarcoidosis patients.[11]

Occupational and environmental exposure

Many occupational and environmental exposures have been linked to sarcoidosis—such as inhaled bioaerosols and organic dust,[7,12–14] combustion products,[15,16] and metal/mineral dust.[17–24] Metals such as beryllium, aluminium, titanium and zirconium, have been reported to induce sarcoid-like granulomatous disease.[25,26,20,27]. Also, infectious agents—such as mycobacteria and *Cutibacterium acnes* (previously *Propionibacterium acnes*)—have been suspected as being possible causes of sarcoidosis.

One of the largest studies that has explored exposures occurring in the workplace as possible causes of sarcoidosis was the ACCESS study.[13,22] ACCESS was a US-based multicentre case-control study in which 706 matched case-control pairs were enrolled between 1996 and 1999. Cases had been diagnosed with sarcoidosis by biopsy within 6 months of study enrolment. [22] In accordance with the rest of the literature on this subject, the ACCESS data do not suggest a single cause of sarcoidosis attributable to occupation, but identified multiple possible occupations and exposures associated with sarcoidosis.[13,22]

A recent Official American Thoracic Society and European Respiratory Society Statement stated that the occupational population attributable fraction (PAF) for sarcoidosis is estimated to be 30%.[28] Although occupational exposures tend to differ between women and men, there is insufficient data to estimate a separate PAF for women and men.

Occupational and environmental exposures that have been associated with sarcoidosis might 1) act as antigens themselves, 2) induce neo-antigen formation through the modification of self-peptides,[5] or 3) or induce immune dysregulation (which is thought to be the mechanism by which immune checkpoint inhibitors induce sarcoidosis/sarcoid-like granulomas).[29]

Chronic Beryllium Disease—a model of sarcoid-like illness caused by occupational exposure

Chronic beryllium disease (CBD) is the prototypical example of a sarcoid-like granulomatous lung disorder with a known cause that is pathologically and clinically almost indistinguishable from pulmonary sarcoidosis, except through the use of immunologic testing, such as the beryllium lymphocyte proliferation test (BeLPT).[27] Beryllium (Be) is a lightweight metal that is often used in association with other metals such as copper or aluminium. The major applications of beryllium are in automotive electronics, telecommunications, computers, aerospace, and defence equipment.[27] Chronic beryllium disease has been shown to be caused by specific cell-mediated immunity to beryllium, which in some cases progresses to the formation of granulomas in the lung and lymph nodes.

According to an official statement of the American Thoracic Society,[27] the BeLPT is the cornerstone of medical surveillance and diagnosis of Be sensitization and CBD. This *ex vivo* test (also called lymphocyte transformation test or LTT) consists in measuring the proliferation of lymphocytes (generally obtained from peripheral blood, but possibly also from bronchoalveolar lavage) after they have been incubated for a number of days (e.g. six days) with a soluble beryllium salt ($BeSO_4$) in a range of concentrations. Cell proliferation traditionally is quantified by measuring the

incorporation of ^{3}H-Thymidine into DNA and the proliferation is expressed as a stimulation index (SI), calculated as the amount of the nucleoside (i.e. counts per minute) incorporated by lymphocytes incubated with beryllium divided by the amount incorporated by control lymphocytes incubated without beryllium. The threshold above which the SI is considered abnormal depends on laboratory conditions, but two abnormal values (e.g. SI>3) may be considered as evidence for sensitization to beryllium.

CBD is diagnosed in persons when in addition to sensitization to beryllium, there is proven granulomatous lung inflammation.[27] Clinical-epidemiologic studies have indicated that when the BeLPT is used, a substantial proportion of patients with "sarcoidosis" in fact prove to have CBD, with their exposure to Be having taken place in a large variety of jobs (including metallurgy, military industry, electronics, dental technicians, etc.).[30,31] The paradigm of the BeLPT has been applied to other metallic agents and this has been found to be useful to detect sensitization to metals such as zirconium, aluminium, chrome or cobalt, in patients with sarcoid-like lung disease however still with less evidence than for beryllium.[20,26,32,33]

Chronic beryllium disease has been linked to HLA-DP alleles that contain a glutamic acid at amino acid position 69 (βGlu69).[34] HLA-DP molecules expressing βGlu69—but not HLA-DP molecules with a lysine at that position—have been shown to bind beryllium *in vitro* with high affinity.[35] Recently, Falta *et al* discovered that the major antigenic targets in HLA-DP2–expressing patients with chronic beryllium disease were Be-modified chemokine-derived peptides (C-C motif ligand 4 [CCL4] and CCL3).[36]

The role of infectious agents

Infectious agents—such as mycobacteria and *Cutibacterium acnes*—have been suspected as being possible causes of sarcoidosis. Molecular techniques have identified mycobacterial components in sarcoidosis tissues in some studies[5,37] and T-cell responses to mycobacterial antigens, such as *Mycobacterium tuberculosis* catalase–peroxidase (mKatG), have been

demonstrated in peripheral blood mononuclear cells and bronchoalveolar lavage fluid of sarcoidosis patients.[38,39]

Many researchers have attempted to culture mycobacteria from sarcoid tissues unsuccessfully,[40,41] suggesting that, in some patients, sarcoidosis might represents the result of an immune response to poorly degraded mycobacterial antigens without the presence of viable mycobacteria.[5,41] *C. acnes*, however, is part of the normal skin microbiota and may be found in peripheral lung tissue and mediastinal lymph nodes of healthy individuals as well as of sarcoidosis patients.[42] It has been hypothesized that *C. acnes* may exist in several organs in a latent form, until a hypersensitive immune response is triggered, which can cause systemic sarcoidosis.[43] Nishiwaki *et al* were able to induce lung, liver and spleen granulomas in mice by sensitizing them through repeated subcutaneous injections of *C. acnes*.[44] In sarcoidosis patients, T-cell responses to mycobacterial antigens, such as mKatG, and heat-killed *C. acnes* have been demonstrated in peripheral blood mononuclear cells and bronchoalveolar lavage fluid.[38,39,45] The involvement of microbial agents in the development of sarcoidosis in some patients might explain the associations found in many epidemiological studies with occupations having no obvious dust exposures, such as teachers, educators[12,13,22] and health care workers.[13,46–48]

Exposure and sarcoidosis phenotypes

The diverse clinical manifestations of sarcoidosis and the wide range of exposures associated with the disease suggest that sarcoidosis has more than one cause, each of which may promote a different phenotype and disease course.[49] Some evidence supporting this hypothesis comes from patients with CBD. CBD patients have fewer extrapulmonary manifestations—hepatic, splenic and cardiac involvement have been rarely reported; neurological impairment and uveitis have never been reported. CBD with granulomatous skin involvement has been reported but never erythema nodosum or lupus pernio. Moreover, spontaneous resolution of CBD is rare.[27,50,51]

The association between other occupational exposures and sarcoidosis phenotype has been less well studied. In the ACCESS study, patients who were exposed to agricultural organic dust and wood burning were less likely to have extrapulmonary involvement.[52] Also, several studies have shown that men and women have different organ involvements—whereas women are more prone to skin, eye and involvement, men tend to have higher rates of pulmonary and cardiac involvement.[52–55] As occupational exposures differ in men and women, these findings may provide indirect support for the hypothesis that certain occupational exposures lead to different disease phenotypes. With regards to the association between occupational exposures and the clinical disease course, a recent study showed that sarcoidosis-related mortality was generally higher among patients who had "any type" of occupational exposure.[56]

1.1.2. Evidence for associations between silica/silicates and sarcoidosis

A growing literature on the association between silica/silicates and sarcoidosis has emerged in the past two decades.[57,58] In the next paragraphs, I will summarize the evidence for the association between silica/silicates and sarcoidosis. I will also discuss how "markers" of exposure to silica/silicates and lymphocyte proliferation testing could be useful to strengthen the evidence of this association. Next, I will go deeper into what is the minimally needed dose to induce sarcoidosis and what is the latency period expected between exposure and disease onset. Lastly, I will summarize what is known on the sarcoidosis phenotype associated with silica/silicate exposure and I will discuss the difficulties in differentiating between silica-induced sarcoidosis and silicosis.

Silica and silicates

Silicon (Si) and oxygen (O) are two dominant elements in the earth's crust. Silicon does not exist in a free state in nature, but as silica or silicates.[59] Although the chemical formula of silica is SiO_2 (silicon dioxide), it is composed of a three-dimensional network of silicon tetroxide (SiO_4)

tetrahedral units joined by common oxygen atoms, so that each crystal consists of a giant molecule with an average stoichiometric formula of SiO_2 (Figure 2). When silica is uncombined—i.e., when it is not bound to other elements—it is referred to as "free silica". Silicates are "combined" silica, in which SiO_2 exists in combination with several types of cations. Silicates are a diverse group of minerals including magnesium silicates—such as talc $[Mg_3Si_4O_{10}(OH)_2]$—and aluminium silicates—such as kaolin $[Al_2Si_2O_5(OH)_4]$.

Free silica (SiO_2) occurs in crystalline and amorphous (non-crystalline) forms (Figure 3).[10] Silica is considered crystalline when there is a regularly repeating pattern of SiO_4-tetrahedral units in three dimensions (Figure 3A). The major forms of crystalline silica are quartz, cristobalite and tridymite. Epidemiological evidence shows that occupational exposure to respirable crystalline silica is associated with silicosis, lung cancer, emphysema, autoimmune disorders and chronic kidney disease.[62]

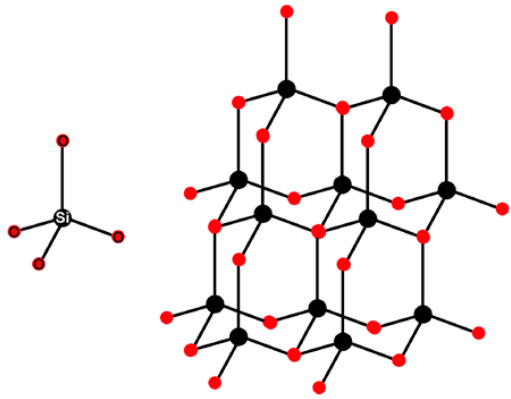

Figure 2—Quartz consists of a three-dimensional network of SiO_4 (silicate) tetrahedra, each adjacent silicon atom sharing its oxygen atoms with other silicon atoms, thereby creating a very strong covalently-bonded framework [figure reproduced from Mason J. Introducing Mineralogy. Dunedin Academic Press Ltd 2014][60]

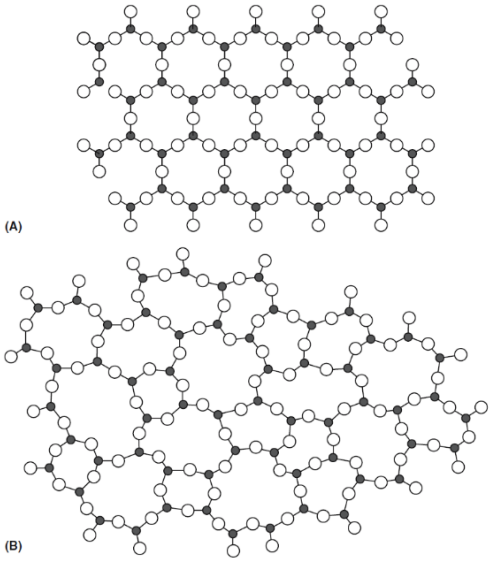

Figure 3—Simplified schematic two-dimensional representation of the atomic arrangement in (A) crystalline and (B) amorphous silica. While crystalline silica has a repeating pattern of arrangement of silicon (-●-) and oxygen (-O-) atoms over a long range, amorphous silica has very little order [figure reproduced from Carter CB, Norton MG. Ceramic Materials: Science and Engineering. 2nd ed. New York: Springer-Verlag 2013][61]

In amorphous silica the molecular arrangement is unstructured, and the units are randomly linked, forming no pattern (Figure 3B). Amorphous silica can be divided into naturally occurring amorphous silica—as found in diatomaceous earth—and synthetic amorphous silica—like colloidal silica, silica fume and fused silica. Fused silica is also called vitreous silica, fused glass or quartz glass, although the latter term is misleading as it is definitely not quartz.[63] Amorphous silica has been studied less than crystalline silica and is generally considered less toxic than crystalline silica.[64] However, the traditional paradigm confining adverse effects exclusively to crystalline silica has been challenged in recent years by experimental studies showing that toxic responses depended more on the surface activity of the particles than on the crystallinity *per se.*[65] Thus, Ghiazza *et al* demonstrated that amorphous fused silica particles obtained by grinding showed a remarkably similar behaviour as quartz in terms of reactivity and cellular responses elicited.[63]

Literature on silica and sarcoidosis

Sarcoidosis or sarcoid-like granulomatous lung disease have been associated with exposure to different forms of crystalline and amorphous silica in several case reports and population studies.[19,23,24,66–68] Solà *et al* reported a case suggesting an association between ingestion of (amorphous) colloidal silica—a vehicle for some oral drug formulations—and sarcoidosis.[67] Their patient clinically recovered after cessation of silica exposure and deteriorated after re-exposure.

In a cohort of 297,917 Swedish construction workers—in which exposure to silica dust was evaluated using a job–exposure matrix—an increase in risk for sarcoidosis was observed for workers with medium-high exposure, while adjusting for age and smoking (relative risk [RR] 1.83, 95% confidence interval [CI] 1.14-2.95, n=18 cases). Ever-smokers with medium-high exposure had a RR of 2.44 (95%CI 1.37–4.33).[19]

A cohort study in iron foundry workers suggested a dose-response relation between crystalline silica (quartz) exposure and incidence of sarcoidosis. The incidence rate of sarcoidosis was significantly higher among individuals with yearly average silica exposure > 0.048 mg/m³ compared to those with lower or no exposure (standardised incidence ratio = 3.94; 95%CI 1.07 to 10.08; based on 7 cases in the high exposure group).[24] The authors did, however, not provide an association with *cumulative* silica exposure (i.e., average exposure level × exposure duration).

Using the Swedish national outpatient care registry, Graff *et al* conducted a population-based case-control study.[66] Using a job-exposure matrix to estimate exposure to respirable crystalline silica they found that cases with sarcoidosis were more likely to be exposed than controls (OR 1.27, 95%CI 1.13-1.43). Notably, an increased sarcoidosis risk was even observed at low cumulative doses of <1 mg/m³-years (OR 1.27, 95%CI 1.12-1.44). Also, they did not find a dose-response relationship—higher cumulative doses of respirable crystalline silica led to similar odds ratios as lower cumulative doses.

An Icelandic case-referent study reported a strong association between sarcoidosis and working at a diatomaceous earth processing plant (OR = 13.2), where workers were exposed to (amorphous) diatomaceous earth and (crystalline) cristobalite.[23]

The ACCESS study showed a positive association of sarcoidosis with "dusty trades with crustal dust" in African Americans (OR 2.57, 95%CI 1.02–7.28).[22] No statistically significant association was found between silica exposure and sarcoidosis although the authors explicitly stated a priori not having enough power in the study to detect this association.[13] Of note, in the ACCESS study patients with silicosis had been carefully excluded.

Studies that have looked at the outcome "sarcoidosis on death certificate" did not find associations with silica exposure, which suggests that sarcoidosis in silica-exposed is not likely to be a direct cause of mortality.[56,69]

In animal experiments, silica exposure has been shown to cause the development of granulomas similar to those in human sarcoidosis patients. Continuous low dose silica exposure of Lewis rats can induce granuloma formation.[70,71]

World Trade Center responders and sarcoidosis

Additional support for a role of inorganic dust exposure is provided by epidemiological studies among World Trade Center (WTC) responders—showing an increased risk of sarcoidosis in those exposed to very high levels of irritant, inorganic dust generated by the collapse of the WTC in 2001.[21,72]

In New York City firefighters, the incidence of biopsy-confirmed sarcoid-like granulomatous pulmonary disease was significantly higher during the first 5 years following the WTC collapse compared to the 15 years preceding 9/11 (RR 2.36, 95%CI 1.17-4.78, p=0.017).[21] Between 9 September 2001, and 11 September 2006, 26 WTC dust-exposed rescue workers of the New York City Fire Department (FDNY) were found to have pathologic evidence of (non-infectious) granulomatous pulmonary disease: all 26 patients had intrathoracic adenopathy, 6 (23%) had extrathoracic disease. Thirteen

patients were identified during the first year after WTC dust exposure (incidence rate, 86/100,000), and 13 patients were identified during the next 4 years (average annual incidence rate, 22/100,000; as compared to 15/100,000 during the 15 years before the WTC disaster).[21] A major strength of this study is the fact that their screening methods were identical before and after the WTC disaster. Although the number of patients receiving chest radiographs did increase after the WTC disaster, especially in the first 12 months, they could avoid potential case-ascertainment bias by stratifying their analysis by whether a diagnostic evaluation for sarcoidosis was initiated by an abnormal screening chest radiograph or by the presence of symptoms. In a follow-up study of the same FDNY cohort (up until 9 September 2015), the increased incidence of sarcoidosis persisted at least until 2013.[73]

Additionally, among around 20,000 responders that have been examined through the World Trade Center Medical Monitoring and Treatment Program in the 6 years following the WTC collapse, 38 cases of biopsy-confirmed sarcoid-like granulomatous disease have been found, which was higher compared with other published background rates.[72] However, in this study—unlike the study in the FDNY—there is a high risk of selection bias due to the monitoring program, possibly contributing to more cases being diagnosed, or being diagnosed earlier than if no monitoring program had existed.

"Markers" of exposure—Particles in bronchoalveolar lavage or tissue

In addition to occupational histories or job-exposure matrices, also "markers" of exposure could be used to retrospectively assess exposure—for example by demonstrating silica or other inorganic particles in bronchoalveolar lavage or tissue—based on the notion that inhaled silica and other inorganic particles tend to accumulate in intrathoracic lymph nodes and lung tissue.[74,75]

Many case reports/series have demonstrated birefringent particles—suggestive of the presence of silica or silicates such as talc or mica—in tissue of sarcoidosis patients.[17,76] Silica particles are weakly birefringent under polarised light, while silicates such as mica and talc tend to be strongly

birefringent.[59] Additionally, techniques for elemental analysis—such as scanning electron microscopy (SEM) combined with energy-dispersive X-ray spectroscopy (EDX)—can demonstrate the precise composition of particles in bronchoalveolar lavage or tissue.

For example, Catinon *et al* examined the mineralogical content of bronchoalveolar lavage of 20 patients with biopsy-proven sarcoidosis and 20 controls. Stainless steel particle load was higher in cases than in controls ($p=0.029$). Silica particle load was higher in sarcoidosis patients, but not statistically significantly, possibly due to the very small sample size. Nevertheless, 6 out of the 20 sarcoidosis patients had higher silica load than all control subjects.[77]

A recent study collected BAL and bronchial washing samples from patients with sarcoidosis and other interstitial lung diseases. After size fractionation—to separate microparticles (>1 µm), submicron particles (ranging from 100 nm to 1 µm) and nanoparticles and ions (particles < 100 nm)—the silicon-content of the different size fractions was measured using inductively coupled plasma atomic emission spectroscopy (ICP-AES). Interestingly, the authors found that the mean concentration of *submicron* silicon-containing particles was significantly higher in the BAL and bronchial washing samples from patients with sarcoidosis than those from patients suffering from other interstitial lung diseases (501 vs. 246 ng/mL for BAL and 564 vs. 292 ng/mL for bronchial washing, respectively).[78] Of note, this association was observed only for the particles in the submicron size range but not for the bigger (i.e. micron-sized) particles. Silicon-containing submicron particles were detectable in bronchial washing of 12/14 (86%) sarcoidosis patients against only 43/81 (53%) controls. Because, strictly speaking, they assessed the silicon content of the BAL and bronchial washing samples (using ICP-AES), this does not necessarily mean that these particles are (free) silica.

These findings suggest the probable importance of particle size on the pathogenesis of sarcoidosis. Future studies should therefore consider separating differently sized particles instead of performing elemental analysis on whole samples. Also, because submicron particles are not visible by

regular light microscopy (with or without polarized light) these findings suggest that “simple” microscopy might not be sufficient when assessing past exposures in sarcoidosis cases.

Studies on skin sarcoidosis offer additional insights. In a study of 14 consecutive patients with cutaneous sarcoidosis, Colboc *et al* identified crystalline silica inside granulomas in biopsies of 3 patients.[79] Furthermore, whereas traumatic skin exposure to silica induces an initial foreign body granulomatous reaction—with a predominantly macrophage response and rapid resolution—in all individuals, several case reports have described that in some susceptible individuals, after a latent interval of years, a delayed hypersensitivity-type granulomatous response occurs—with a histological picture identical to that of sarcoidosis.[80–82]

In addition, anecdotal evidence suggests that other minerals such as talc, mica, glass fibres, and man-made mineral fibres can induce sarcoid-like granulomatous disease.[17,18,83,84] Farber *et al* published a case series of 6 men with sarcoid-like granulomatous disease showing birefringent crystals consistent with talc in BAL or lung tissue of all patients—presumably after intravenous injection of crushed talc-containing pentazocine tablets.[17] Thomeer *et al* reported on an amateur magician with sarcoid-like lung disease due to talc. The patient blew up about 150,000 balloons per year, in which the presence of talc powder was confirmed using energy-dispersive X-ray spectroscopy (EDX).[83] Drent and colleagues described a case of sarcoid-like skin granulomas after applying talc-containing black and blue make up.[85]

Mica is a group of phyllosilicates or sheet silicates (aluminium or magnesium silicates). Hulo *et al* described 4 cases of sarcoid-like disease who were exposed to high concentration of pure mica dust in a muscovite milling unit.[84] Pimentel reported cases with sarcoid-like liver granulomas containing cement or mica dust (confirmed by EDX).[86]

Drent *et al* found that 14 of 50 patients recalled a history of exposure to either glass fibres or rock wool.[18] Drent and colleagues also attributed a case

of sarcoidosis to cat litter—most probably containing a silicate clay.[87] Crummy *et al* reported on an office worker with sarcoid-like lung disease employed at an office located in a limestone quarry, with limestone particles (consisting predominantly of calcium carbonate with only a limited amount of silica) confirmed by EDX.[88]

Denisova and colleagues performed elemental analysis—using neutron activation analysis—of lung tissue of 76 sarcoidosis patients and 30 controls. They found elevated concentrations of several metals in lung tissue of sarcoidosis patients: iron, chromium, cobalt, cesium, europium, lutetium, hafnium, gold, thorium, and uranium. However, they did not measure the element silicon.[89]

Lymphocyte proliferation testing

As previously discussed, exposure alone does not suffice to develop sarcoidosis. In other words, finding particles in tissue does not prove that these are causing the disease. Probably because of a genetic susceptibility, individuals develop an immune response to an (unknown) antigen, which can eventually lead to a granulomatous inflammation.

These two stages have been well described in the development of chronic beryllium disease. Initially, beryllium-exposed individuals may develop beryllium sensitization—while still being asymptomatic and without evidence of lung function or chest radiographic abnormalities—which can be demonstrated by a positive beryllium lymphocyte proliferation test. Beryllium sensitized individuals may subsequently progress to chronic beryllium disease, in which both beryllium sensitization and granulomatous inflammation are present. Longitudinal studies have shown that 1.0 to 16.2% of beryllium-exposed workers developed beryllium sensitization over time, and 0.0 to 11.0% developed CBD.[27]

The delayed-type hypersensitivity induced by beryllium is considered as a model for immunologically driven granulomatous lung disease.[90] This paradigm has been applied to other metallic agents. The LPT has been found to be useful to detect sensitization to metals such as zirconium, aluminium,

chrome, titanium or cobalt, in patients with sarcoid-like lung disease, however, with much less evidence than for beryllium.[20,26,32,33] Of note, LPT is also used to document type IV hypersensitivity to drugs and to identify culprit allergens in allergic contact dermatitis.[91,92]

LPT with silicates have also been performed.[32,33,93,94] Fireman *et al* found silicon-containing particles—using SEM/EDX—in 11 out of 13 patients with sarcoidosis.[95] In those 11, they performed a MELISA (memory lymphocyte immuno-stimulation assay) test—a modified LPT. In 2 cases (a teacher and a dental technician) they found a positive LPT to soluble sodium silicate (Na_2SiO_3), however, without specifying the reasons for the choice of this testing agent.

In a Dutch study by Beijer *et al*, the MELISA test was done on samples of 26 metal- and/or silica-exposed sarcoidosis patients (with exposures assessed using a job-exposure matrix), 7 unexposed sarcoidosis patients, and 19 controls with obstructive sleep apnoea.[33] Only sarcoidosis patients had positive LPTs to at least one of the compounds tested (n=7, p=0.039). Two of those patients had a positive LPT to "silica" (presumably also soluble sodium silicate).[33]

Subsequently, Beijer *et al* performed MELISA testing with metals and silica in 105 sarcoidosis patients and 24 obstructive sleep apnoea controls, which confirmed earlier findings: positive LPTs were shown in 27.6% of sarcoidosis patients and only 4.2% of controls (p=0.014). LPT with silica was positive in 12 sarcoidosis patients (11.4%) compared to only 1 control (4.2%).[94] Moreover, they showed that positive LPTs were associated with the development of fibrotic sarcoidosis 5 years after diagnosis.

In one of our reported cases (see next part of this chapter) a positive LPT was found with two types of nano-silica particles (*NanoComposix 20 nm Non-Functionalized NanoXact™ Silica; Ludox colloidal silica*). This finding could be of relevance as it shows that the LPT can also be performed with water-insoluble particles, which better resembles a real-life occupational dust exposure than water-soluble salts.

In summary, although some groups have shown positive LPTs with silica (in soluble or particle form), evidence is still lacking about whether silica can act as an antigen. Further experimental and clinical studies are necessary to confirm these findings and to clarify their implications.

Sarcoidosis can be induced by relatively low and short exposures

Case reports from CBD patients suggest that "low" exposures can be sufficient to induce CBD in susceptible individuals. One report by Newman and Kreiss describes CBD in a woman whose husband was a beryllium production worker.[96] Kelleher and colleagues showed increased risk of Be sensitization and CBD in workers exposed to mean respirable beryllium concentrations < 2 µg/m³ (with CBD occurring after a widely variable latency period of 3 to 20 years), but found no cases at concentrations below 0.02 µg/m³.[97] Frye and colleagues described a cluster of 5 beryllium-sensitized construction workers, that was identified incidentally after one of their co-workers had been diagnosed with CBD. They did not work with beryllium directly but were exposed to concrete dust from a nearby concrete factory. The dust contained high amounts of beryllium (up to 6-fold higher compared to control samples from other metropolitan regions).[98] Of note, the cluster was discovered because the possibility of an occupational trigger was raised by the index patient himself, who had noted a relationship between the onset of his symptoms and an increase in aerosolized dust from the local cement factory.[98,99]

A population-based case-control study using the Swedish national outpatient care registry[66] found that exposure to crystalline silica was associated with an increased sarcoidosis risk, even at low cumulative doses of <1 mg/m³-years (OR 1.27, 95%CI 1.12-1.44). Also, they did not find a dose-response relationship—higher cumulative doses of respirable crystalline silica led to similar odds ratios as lower cumulative doses. These findings indicate a very different dose-response relation than chronic silicosis—which is unlikely to occur at these low cumulative doses. Also, these results support the importance of individual susceptibility to the occurrence of the disease. As

sarcoidosis is hypothesized to be a hypersensitivity reaction, we could expect that the disease can occur after long but also after relatively short (and low) exposures—unlike the "classic" pneumoconioses in which relatively high cumulative exposures are required to lead to disease.

Also, in the recent study by Beijer *et al* occupational exposure to metal/silica determined by a job exposure matrix (JEM) was not predictive for a positive LPT.[94] Because most inorganic dust JEMs used for epidemiological studies are designed to be very specific (to avoid false-positives which would attenuate statistical associations), they are possibly not capturing low and/or infrequently occurring exposures.

In summary, the literature suggests that sarcoidosis can be induced by relatively low and brief exposures. This implies that when assessing exposure in sarcoidosis patients, instruments that are sufficiently sensitive to detect low/rare exposures should be used.

Latency period between exposure and occurrence of sarcoidosis

Beyond the nature and amount of exposure, several factors complicate studying the temporal relationship between exposure and the occurrence of sarcoidosis. Firstly, assessment of the exposure is generally done retrospectively, which makes a precise reconstruction of (relatively low) exposures difficult. Secondly, the time of onset of the disease is generally unclear. The time between disease onset and the diagnosis of the disease can depend on many factors: what type of symptoms are present, whether the patient was diagnosed because of symptoms or 'fortuitously' (e.g., because of a chest X-ray done for reasons not related to the disease), what organs are involved, etc. Thirdly, from chronic beryllium disease we know that it is a 2-stage process—initially a sensitization occurs, which can progress to CBD. Although there is no evidence that the same process occurs in other types of 'sarcoidosis', this is likely.

Case studies reporting on patients exposed to silica and silicates—including mica and talc—suggest latency periods from 6 months up to 40 years between exposure and onset of symptoms.[67,76,84,100] Some have described

clinical improvement after cessation of the exposure,[76] while others have described persisting or worsening clinical symptoms after cessation of exposure.[84] Webber *et al* found, in the FDNY cohort of WTC first responders, an increased incidence of sarcoidosis at least until 2013, with a peak incidence 7-9 years after the WTC collapse.[73]

Also, in the development of beryllium sensitization and, subsequently, CBD the latency periods vary widely. A (limited) number of longitudinal studies with baseline testing have shown incidence of beryllium sensitization between 0.7 and 1.9 / 1,000 person-months in beryllium-exposed workers.[27] Newman *et al* found that CBD developed in 17 out of 55 beryllium sensitized individuals (31%) within an average follow-up period of 3.8 years (range, 1.0-9.5 years). It is unclear if all beryllium-sensitized workers will eventually develop CBD if exposure continues. Genetic susceptibility probably contributes to the time of development of beryllium sensitization and progression to CBD. Moreover, CBD may even emerge many years after cessation of exposure to beryllium.[27]

In summary, the wide variation in reported exposure and latency periods suggests an important role for individual susceptibility factors in determining the effects of exposure. Probably also the nature of the causative compound influences the minimal dose needed. Also, bio-persistence might play a role in disease progression or even occurrence years after exposure stop. Nevertheless, there are no studies comparing these factors between different compounds.

Genetic susceptibility, silica exposure, and sarcoidosis

Significant associations of several loci of the human leukocyte antigen gene (HLA) have been established with the development of sarcoidosis, protection from developing sarcoidosis, and specific phenotypes of the disease.[101,102] In addition to HLA, other genes with apoptotic, enzymatic, regulatory, immune and inflammatory functions have been implicated as candidate loci in sarcoidosis.[103]

It is hypothesized that HLA gene polymorphisms result in conformational changes in the antigen binding pockets of HLA molecules.[102] Most evidence for this hypothesis comes from CBD, which has been linked to HLA-DP alleles that contain a glutamic acid at amino acid position 69 (βGlu69).[34] HLA-DP molecules expressing βGlu69, but not HLA-DP molecules with a lysine at that position, have been shown *in vitro* to bind beryllium with high affinity.[35]

However, there is no evidence that patients with sarcoidosis that have been exposed to silica have a particular genetic background. Cleven *et al* did a case-control study in 55 cases of WTC-related sarcoidosis in NYC firefighters and 100 controls among WTC-exposed firefighters. Matching was done on race, age, smoking, and detailed WTC exposure history. They found 17 allele variants of human leukocyte antigen (HLA) and non-HLA genes to be associated with sarcoidosis—all were within chromosomes 1 and 6. However, these genetic variants were similar to those reported in studies of sarcoidosis without known environmental exposures.[104]

In the ACCESS study, occupational insecticide exposure was found to interact with HLA DRB1*1101 ($p = 0.074$) and with HLA DRB1*1501 ($p = 0.124$); exposure to molds or musty odors interacted with HLA DRB1*1101 ($p = 0.135$). No interactions were found with silica exposure.[7] Also, Beijer *et al* did not observe any associations of HLA-DRB1*0301 or HLA-DRB1*1501 with LPT results with metals/silica in sarcoidosis patients.[94]

In summary, there are strong indications for a role for genetic susceptibility in the development of sarcoidosis. What genetic background would make individuals exposed to inorganic dust prone to develop the disease is, however, unknown.

Inorganic dust exposure and sarcoidosis phenotype

Exposure to organic and inorganic dust, such as metal or silica dust, has been shown to be associated with pulmonary-only sarcoidosis.[21,52] In the ACCESS study, patients exposed to wood burning (in blacks, OR 0.36; 95%CI 0.23–0.59) were less likely to have extrapulmonary involvement.[52] World Trade Center (WTC) rescue workers with sarcoidosis—who had been exposed to high levels of inorganic dust resulting from the WTC collapse in 2001—also had less extrapulmonary involvement than expected.[21] Also, patients with chronic beryllium disease have fewer extrapulmonary manifestations: hepatic, splenic and cardiac involvement are rare, and ocular and neurological impairment have not been reported.[27]

A possible explanation for the association between dust exposure and sarcoidosis that is limited to the lungs is that inhaled dust particles do not readily disseminate systemically. Small inhaled particles that deposit in the deep lung can—when not removed by the mucociliary escalator—be transported via the lymphatic system to regional lymph nodes.[74,75] Particles accumulate in lymph nodes but can—to a limited extent—gradually translocate into the systemic circulation where they are filtered from the blood in liver and spleen.[74] Small fractions can be taken up by other organs such as the brain or the heart.[105] The probability and speed of systemic dissemination depends on particle characteristics such as size, surface properties, chemical composition and solubility.[74] This might explain why extrapulmonary involvement in dust-exposed patients is less common, but not impossible.

Differentiating between silicosis and sarcoidosis

Differentiating between silicosis and sarcoidosis poses several problems. The clinical, radiological and histological presentation of sarcoidosis and silicosis can be similar. Although the silicotic nodule is regarded as the typical silicotic lesion, this is actually the end-stage of a dynamic silica-induced pathologic process. Early silicotic lesions appear as cellular nodules of dust-laden macrophages which are much more difficult to differentiate

from sarcoid-like granulomas. Only in later stages do these lesions evolve to relatively acellular silicotic nodules with concentric fibrosis in the centre and peripheral dust-laden macrophages.[62,106]

The complexity of distinguishing both diseases goes beyond "technical" issues, but is also related to disease *definitions*. Especially the definition of sarcoidosis as a diagnosis "of exclusion" is problematic. Because silicotic nodules are specific for established silicosis, cases exposed to silica in whom histologically both sarcoid-like granulomas and silicotic nodules are encountered, are classified as "silicosis".[107] Nevertheless, the presence of sarcoid-like granulomas in patients with pneumoconiosis does not seem to be rare—although it is probably rarely mentioned by pathologists, possibly because it is not considered to be relevant. Two studies from the 1970s found sarcoid-like granulomas in 9 out of 52 patients with proven pneumoconiosis,[108] and in 7 out of 41 patients with pneumoconiosis (silicosis, mixed-dust pneumoconiosis or asbestosis),[109] respectively. Quero *et al* retrospectively investigated all patients that had visited their hospital during a 30-year period who had a histological diagnosis of sarcoidosis *and* an exposure history of silica. By reexamining the biopsies, they found concurrent silicotic lesions and sarcoid granulomas in 6 out of 7 cases. Moreover, in 4 cases they found birefringent material under polarized light.[110]

Also, numerous reports mention cases clinically compatible with sarcoidosis—including features such as iritis, erythema nodosum, etc.— with concurrent sarcoid-like granulomas and silicotic nodules,[111-114] by some referred to as "sarcoido-silicosis".[115] For example, Nakajima *et al* describe a case with bilateral hilar lymphadenopathy on chest X-ray, uveitis and sarcoid-like granulomas on a lymph node biopsy. After steroid therapy, the bilateral hilar lymphadenopathy and uveitis disappeared. On autopsy, silicotic nodules were found near the sarcoid granulomas.[116] Some case reports re-classify "sarcoidosis" cases as silicosis—even without finding silicotic nodules—merely because of the presence of birefringent particles in the sarcoid granulomas.[117] Also in the dermatology literature, some authors

suggest using polarized light microscopy to distinguish “silica granulomas” from “sarcoidosis”.[82]

Finding extrapulmonary lesions is considered an argument in favor of sarcoidosis—which is regarded as a systemic disease. In contrast, silicosis is generally regarded as a disease of lungs and thoracic lymph nodes. Nevertheless, silicotic nodules have been described in liver, spleen, bone marrow, and extrathoracic lymph nodes.[106,118,119] Barbazza *et al* reexamined 300 autopsies of patients affected by pulmonary anthracosilicosis and showed a correlation between the severity of pulmonary anthracosilicosis and hepatic involvement.[119] However, in another autopsy study Slavin *et al* showed that the typical silicotic (sclerohyaline) nodule occurred infrequently in the spleen and liver, but that loose cellular nodules of dust-laden macrophages—i.e., early stage silicotic lesions—occurred more commonly in extrapulmonary locations.[106]

Conclusion

In conclusion, the available limited evidence suggests some association between the occurrence of sarcoidosis and exposure to respirable silica. In addition, anecdotal evidence suggests that other minerals such as talc, mica, glass fibres, and man-made mineral fibres can induce sarcoid-like illness.

Relatively low and short exposures seem to be able to induce the disease. Also, published latency periods between exposure and disease occurrence range from month to decades, all suggesting an important contribution of immunological mechanisms. However, no genetic factors, such as HLA types, are yet known to increase the risk of sarcoidosis in individuals exposed to mineral dust.

In sarcoidosis, epithelioid granulomas are presumably an immunological response to persistent antigens, possibly combined with an adjuvant signal triggering an innate immune response [25]. Dust particles might be the target of this immune response, although it is uncertain if they act as antigens, as adjuvants or as nidus.[25]

1.1.3. Aims and outline of the chapter

In the first part of this chapter (1.2), I describe two cases of sarcoid-like granulomatous lung disease that occurred among employees in a small production unit of about 30 workers making metal-halide lamps, who were exposed to fused silica dust originating from the lamp tubes. The combination of epidemiological arguments, exposure evidence, and the clinical course in these patients, made a strong case for an occupational etiology of their disease.

In the second part of this chapter (1.3), I present a retrospective clinical study on the associations between occupational and environmental exposures and organ involvement in sarcoidosis. Given, the diverse clinical manifestations and the wide range of exposures that have been associated with the disease, we sought to find the answer to a hitherto barely tested question: do different exposures lead to different phenotypes of sarcoidosis? Our aim in this retrospective study was to study how occupational and environmental exposures—such as inorganic dust, organic dust and infectious agents—relate to organ involvements in sarcoidosis patients.

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1.2. Granulomatous lung disease in two workers making light bulbs [Case report]

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Abstract

Associations between sarcoidosis or sarcoid-like granulomatous lung disease and exposure to silica and other inorganic agents have been suggested in several studies. We describe granulomatous lung disease in two workers of a small production unit making metal-halide lamps. Initially, both were diagnosed with sarcoidosis. However, in both men birefringent particles were observed in lung or mediastinal lymph node biopsies. Clipping of glass tubes led to moderate exposure to dust, consisting mainly of amorphous fused silica, with some cristobalite. After removal from exposure, both subjects improved clinically, radiologically and functionally. The present cases support the hypothesis that silica might be a trigger for sarcoid-like granulomatous lung disease. Sarcoidosis should be considered a diagnosis of exclusion and clinicians should carefully collect occupational and environmental exposure histories to identify workplace triggers.

Here, we report two cases of granulomatous lung disease that occurred among employees in a small production unit of about 30 workers making metal-halide lamps, where they were exposed to amorphous fused silica dust originating from the lamp tubes. Various arguments suggest a role for silica dust exposure in triggering their disease.

Case report

A 27-year-old man (case A) with an unremarkable medical history presented to a pulmonologist in January 2013 with fatigue, cough and dyspnea on exertion. He had a 7-pack-year smoking history but had quit smoking with the onset of dyspnea in 2011. He reported no fever, night sweats or weight loss. He had no familial history of lung disease. Chest auscultation revealed no abnormal findings, and there was no evidence for skin eruption, cervical or supraclavicular lymphadenopathies, arthralgia or uveitis.

Except for an elevated serum angiotensin converting enzyme (ACE) of 107 U/L (normal values 20-70 U/L), laboratory investigations showed no abnormalities (including autoantibodies). Pulmonary function tests revealed a mildly restricted pattern with a forced expiratory volume in 1 second (FEV_1) of 3.55 L (81% of predicted value), a forced vital capacity (FVC) of 4.13 L (80% pred), and a total lung capacity (TLC) of 5.80 L (81% pred). Diffusing capacity of the lung for carbon monoxide (DL_{CO}) was mildly reduced (74% pred). Chest high-resolution computed tomography (HRCT) showed multiple nodular lesions with lymphatic distribution and enlarged mediastinal lymph nodes (Figure 1a-b). Bronchoalveolar lavage fluid revealed an increased lymphocyte percentage (42%) with a normal $CD4^+/CD8^+$ ratio of 1.4, and absence of infectious agents. Histology of mediastinal lymph node tissue (obtained by mediastinoscopy) revealed noncaseating granulomas consisting of epithelioid and giant cells, compatible with sarcoidosis (Figure 2a). Cardiac and ophthalmologic evaluations were unremarkable. There were no signs of neurologic involvement. Based on these findings, he was diagnosed with stage II sarcoidosis and treated with corticosteroids.

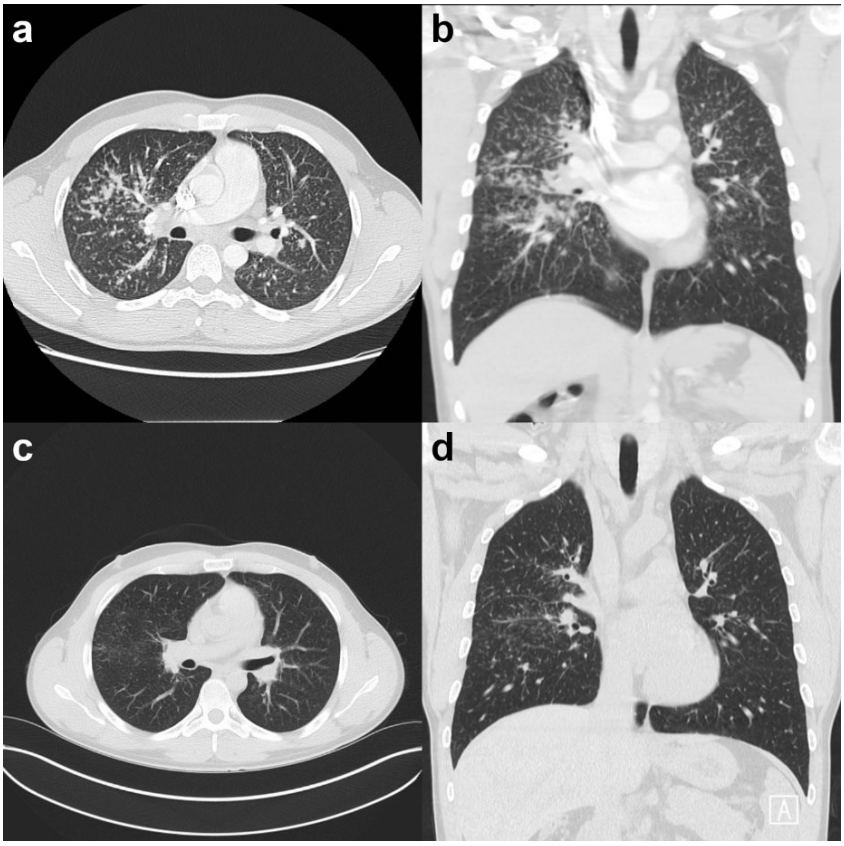

FIGURE 1. **Case A**: (a - b) High-resolution computed tomography (HRCT) from January 2013 showing multiple nodular lesions with a lymphatic distribution and enlarged mediastinal lymph nodes. (c - d) In January 2014, one year after removal from exposure, a HRCT scan showed regression of the nodular lesions.

The patient was puzzled by the fact that one of his co-workers also had sarcoidosis. This 33-year-old man (case B) had been diagnosed 5 years earlier (in 2008), because of exertional dyspnea, restrictive-obstructive impairment (FEV_1 1.71L, 39% pred; FVC 3.10L, 59% pred; TLC 67% pred; DL_{CO} 45% pred), abnormal chest radiography and an open lung biopsy showing epithelioid granulomas (Figure 2c). He was an active smoker (10 pack-years). He had been treated with oral corticosteroids and azathioprine, which were stopped in June 2011. Initially, he had improved, but in June 2013, he relapsed, and corticosteroids were restarted.

Occupational exposure

Both men had worked, since 2005, as operators in a production unit of about thirty workers making metal-halide lamps. This unit was part of a large factory employing more than 700 workers. According to the technical data sheet the lamps were composed of a tube made of fused silica. To shape the tubes, they were heated and clipped. Inside the tubes a tungsten wire filament was placed, doped with thorium. The tubes were filled, in a closed system, with mercury vapor and a metal halide, and were coated by immersion in a zirconium oxide-containing liquid. No beryllium was used.

Both workers described the workplace as ‘very dusty’ as most of the time dust was generated by several processes. They mentioned that the heating and clipping of the tubes (one tube being clipped every five seconds), and especially the cleaning of the machinery produced substantial amounts of dust. Because the molten glass tended to stick to the machinery, they had to chip it off for approximately 5 minutes every two hours. Additionally, a so-called ‘preventive’ maintenance was done each week, taking 4 hours, to clear all the glass dust from the machines using compressed air. The workers did not use respiratory protection. A dust measurement was ordered by the company only after the second case was diagnosed. A personal breathing zone sample collected during the maintenance of the clipping machine—as this was supposed to be the activity with the highest dust exposure—revealed a respirable dust concentration of 5.99 mg/m³ in 1 hour. No measurements were done covering the whole 8-hour shift. No respirable crystalline silica dust was detected (NIOSH method No.7602). Electron Probe MicroAnalysis and X-ray powder diffraction revealed that settled dust samples from the workplace consisted mainly of amorphous silica and some (crystalline) cristobalite, which corresponded to lamp tube material (see supplement). No tungsten, thorium, mercury or zirconium were detected in the dust. Although this single measurement cannot be extrapolated to the entire working day, it indicates—in combination with the qualitative description of the workplace by the workers—that the exposure to respirable fused silica dust was substantial, considering that the German MAK

(Maximum Workplace Concentration) for fused silica is 0.3 mg/m³ (respirable fraction, 8-hour time-weighted average).[1]

Subsequent re-examination of mediastinal lymph node (Case A; Figure 2b) and lung tissue (Case B; Figure 2d) under polarized light revealed small birefringent crystals. No silicotic nodules were observed. Lymphocyte proliferation tests (LPT) with beryllium and zirconium were negative. Interestingly, LPT with nano-silica particles was positive in case A, but negative in case B, who was under corticosteroid therapy.

A tentative diagnose of granulomatous lung disease caused by exposure to fused silica was made in both subjects and removal from exposure was advised.

Follow-up

In January 2013, shortly after diagnosis, case A left the factory and had no further exposure. His cough and dyspnea gradually disappeared. Corticosteroids were gradually tapered and stopped over a 1-year period. In January 2014 an HRCT showed regression of the nodular lesions (Figure 1c-d). Pulmonary function continued to improve until August 2016 (FEV_1 4.01L, 94% pred; FVC 4.74L, 93% pred; TLC 80% pred; DL_{CO} 81% pred) and was still stable in January 2018. No relapses have occurred during the 5-year follow-up period after cessation of exposure.

In January 2014, more than five years after initial diagnosis and continued exposure, Case B moved to another job in the same factory where he was no longer exposed. Two years later, he had improved clinically and radiologically but still had severe obstructive impairment (FEV_1 1.77L, 42% pred; FVC 3.82L, 75% pred; TLC 95% pred; DL_{CO} 65% pred) and used inhalers and low-dose oral corticosteroids.

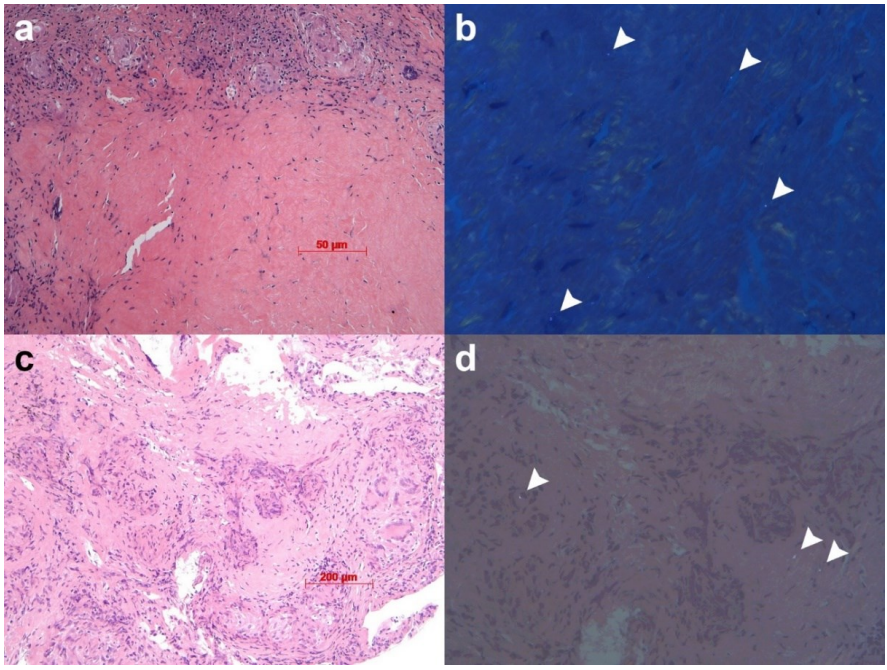

FIGURE 2. **Case A:** (a) Mediastinal lymph node tissue showing noncaseating granulomas consisting of epithelioid cells and giant cells (hematoxylin and eosin). (b) Occasional small birefringent crystals visible under polarized light (*arrowheads*). **Case B:** (c) Pulmonary parenchyma showing noncaseating granulomas consisting of epithelioid cells and giant cells (hematoxylin and eosin). (d) Occasional small birefringent crystals under polarized light (*arrowheads*).

Discussion

We report two workers who developed granulomatous lung disease after three to six years of occupational exposure to amorphous fused silica dust. Several arguments suggest that this exposure triggered their disease. First, sarcoidosis is a rare disorder with a prevalence of about 4.7–64 per 100,000 persons, and a yearly incidence of 1.0–35.5 per 100,000 persons.[2] Therefore, the probability to encounter two cases in a relatively short time period in a group of about 30 workers is very low. Interestingly, this "epidemiological" argument was brought up by one of the patients, which

triggered the present investigation. Second, in both men, birefringent particles were observed in lung or mediastinal lymph node tissue. Finding dust particles in biopsies does not prove causality, but at least confirms exposure that is enough to be considered as abnormal. Furthermore, analysis of settled dust samples from the workplace showed the presence of amorphous fused silica and some cristobalite (exposure argument). Third, both cases—case A more than case B—improved after removal from exposure (clinical argument). Although the clinical improvement in our patients could be attributed to their corticosteroid treatment or could have occurred spontaneously, we believe that the combination of the epidemiological argument, the exposure evidence, and the clinical course, makes a strong case for an occupational etiology.

Silica (SiO_2) occurs in crystalline and amorphous (i.e. non-crystalline) forms.[10] The major forms of crystalline silica are quartz, cristobalite and tridymite. Occupational exposure to respirable crystalline silica is associated with silicosis, lung cancer, emphysema, autoimmune disorders and chronic kidney disease.[3] Amorphous silica can be divided into naturally occurring amorphous silica—as found in diatomaceous earth—and synthetic amorphous silica—like colloidal silica, silica fume and fused silica. Fused silica is also called vitreous silica, fused glass or quartz glass, although the latter term is misleading as it is definitely not quartz.[4] Amorphous silica has been studied less than crystalline silica and is generally considered less toxic than crystalline silica.[5] However, the traditional paradigm confining adverse effects exclusively to crystalline silica has been challenged in recent years by experimental studies showing that toxic responses depended more on the surface activity of the particles than on the crystallinity *per se.*[6] Thus, Ghiazza et al. demonstrated that amorphous fused silica particles obtained by grinding, possibly akin to the particles to which our workers were exposed, showed a remarkably similar behavior as quartz in terms of reactivity and cellular responses elicited.[4]

Sarcoidosis or sarcoid-like granulomatous lung disease have been associated with exposure to different forms of amorphous and crystalline

silica in several case reports and some population studies. Solà et al. reported a case suggesting an association between ingestion of (amorphous) colloidal silica, a vehicle for some oral drug formulations, and sarcoidosis.[7] Their patient clinically recovered after cessation of silica exposure and deteriorated after re-exposure. An Icelandic case-referent study reported a strong association between sarcoidosis and working at a diatomaceous earth processing plant (OR = 13.2), where workers were exposed to (amorphous) diatomaceous earth and (crystalline) cristobalite.[8] A cohort study in iron foundry workers suggested a dose-response relation between crystalline silica (quartz) exposure and incidence of sarcoidosis. The incidence rate of sarcoidosis was significantly higher among individuals in the highest quartile of silica exposure (SIR = 3.92).[9] In addition, anecdotal evidence suggests that other minerals such as talc, mica, glass fibers, and man-made mineral fibers can induce sarcoid-like illness.[10–13] Additional support for the role of inorganic dust exposure is provided by epidemiological studies showing increased sarcoidosis incidence among responders to the World Trade Center collapse.[14,15]

Also, some dermatology reports provide complementary insights. In a recent study on 14 consecutive patients with cutaneous sarcoidosis, Colboc et al identified crystalline silica inside granulomas in biopsies of 3 patients.[16] Furthermore, whereas traumatic skin exposure to silica induces an initial foreign body granulomatous reaction—with a predominantly macrophage response and rapid resolution—in all individuals, several case reports have described that in some susceptible individuals, after a latent interval of years, a delayed hypersensitivity-type granulomatous response occurs—with a histological picture identical to that of sarcoidosis.[17–19]

The question then remains what is the exact mechanism that leads silica to induce these sarcoid-like granulomas. Some authors hypothesize that two things need to be present: a persistent antigen and an adjuvant signal triggering an immune response.[20,21] Silica or other inorganic dusts could thus play a role as a "second hit" in addition to the "first hit" given by an exposure to microbial or other antigens. Although we did not identify any known

antigens in the workplace of our patients, this might still be a possible etiological mechanism in our cases. Others have suggested that silica can act as an antigen in itself, an hypothesis that could be supported by our positive LPT with nano-silica particles.[7,18,22] However, as this test still needs validation, it is difficult to draw conclusions on its result. Nevertheless, our LPT at least confirms that silica nanoparticles can enhance lymphocyte proliferative responses.[23]

In conclusion, the present cases support the hypothesis that silica might be a trigger for sarcoid-like granulomatous lung disease and emphasizes the fact that sarcoidosis should be considered as a diagnosis of exclusion. Clinicians should always evaluate the possibility of exogenous causes in patients with granulomatous lung disease and thoroughly exclude known infectious agents (such as mycobacteria), organic antigens (such as fungi which can induce hypersensitivity pneumonitis) and inorganic agents (such as beryllium, other metals and silica).[20,24]

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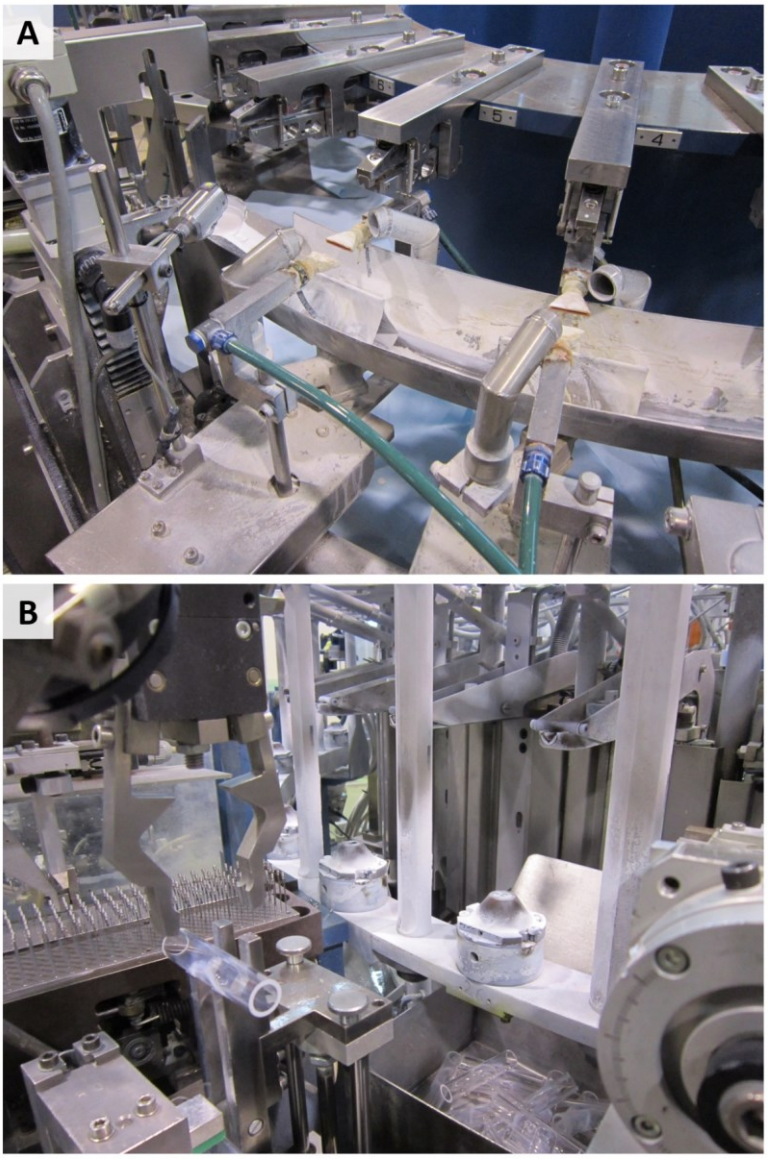
Supplement (unpublished)

1) Pictures of the workplace

FIGURE S1: Coating (A) and clipping machines (B). On both machine a layer of white dust can be noticed. The dust is generated by the mechanical operations on the light bulbs.



2) Settled dust samples from the workplace (courtesy of prof. R. Swennen)

Settled dust was collected from the workplace (i.e., the white dust seen in Figure S1). A light microscopic image is shown in Figure S2; an image of the dust obtained by Scanning Electron Microscopy (SEM) is shown in Figure S3. Electron Probe MicroAnalysis (EPMA) revealed that the dust consisted mainly of silica and some copper and zinc oxide (Figure S4). X-ray powder diffraction, used to determine the precise form of silica, demonstrated mainly amorphous silica, with possibly some cristobalite, but no quartz (Figure S5). Thus, the settled dust seemed to consist mainly of amorphous fused silica originating from the lamp tubes.

FIGURE S2: Light microscopy pictures of settled dust from the light bulb factory (i.e., the white dust seen in Figure S1).

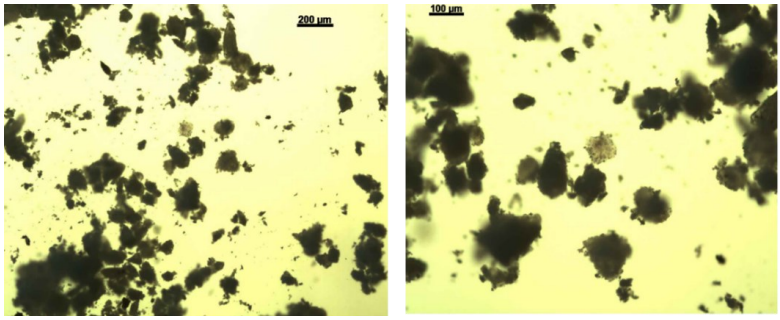


FIGURE S3: Scanning Electron Microscopy (SEM) picture of settled dust from the light bulb factory at a magnification of ×450.

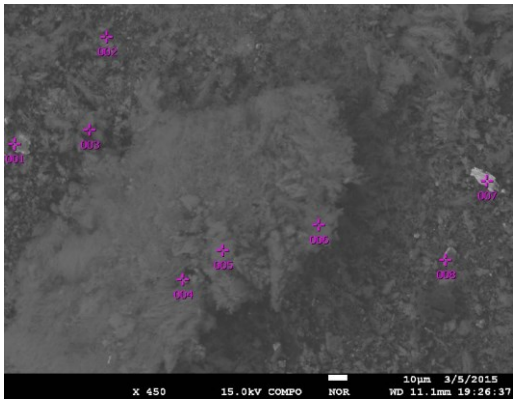


FIGURE S4: Energy-dispersive X-ray spectrum analysis at 8 different points in the dust (indicated in figure S3) using a Field Emission Gun Electron Probe MicroAnalyser (FEG-EPMA) revealing that the dust consisted mainly of silica and some copper and zinc oxide

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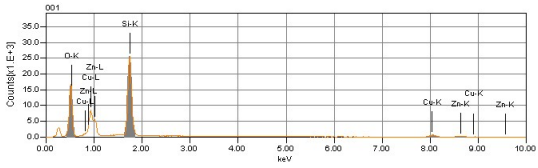

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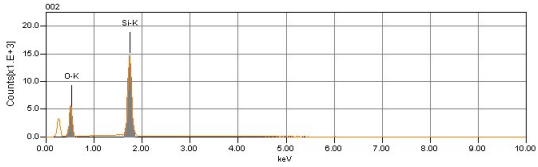

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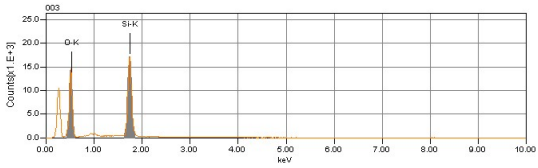

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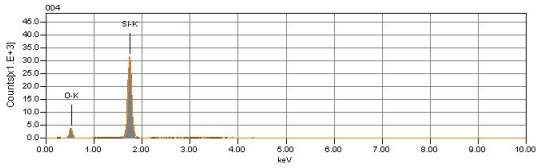

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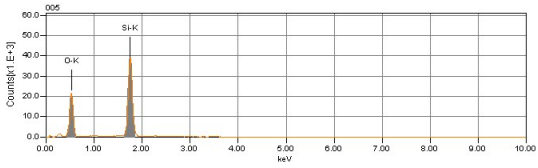

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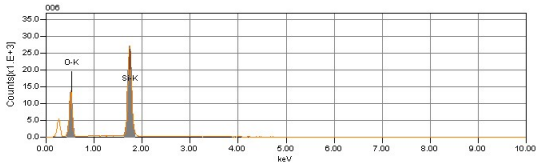

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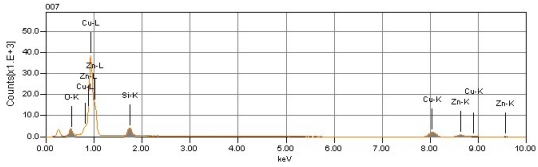

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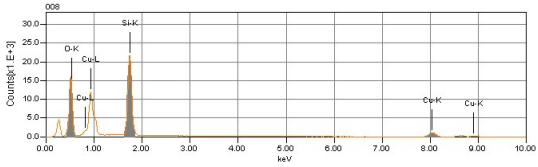
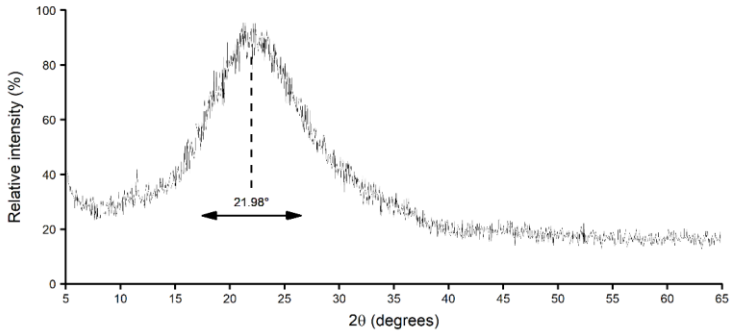


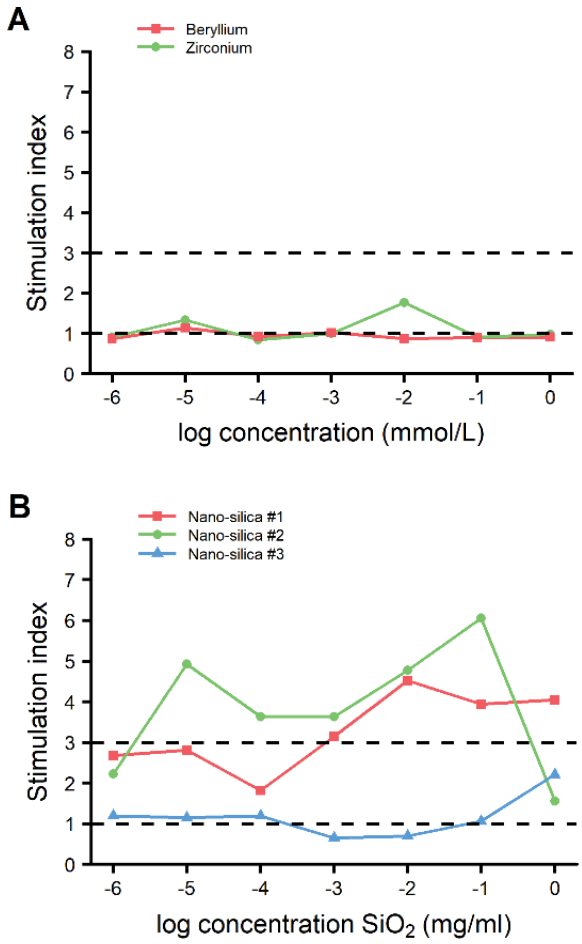
FIGURE S5: X-ray powder diffraction, used to determine the precise form of silica, demonstrated mainly amorphous silica. The X-ray powder diffraction pattern of the settled dust showed a broad peak at 2θ = 21.98°, indicating weak crystallinity.,



3) Lymphocyte proliferation tests

To perform the lymphocyte proliferation tests (LPT) peripheral blood mononuclear cells from the patients were placed in culture for seven days in the presence of a test agent (stimulus) in a range of concentrations (Figure S6). Lymphocyte proliferation was measured by the incorporation of tritiated thymidine into dividing cells. In case A, the LPT was negative with beryllium and zirconium, but convincingly positive with two out of three types of nano-silica (while not taking any medication) (Figure S6). In case B, who was under corticosteroid therapy, LPT was negative with both beryllium and nano-silica (data not shown). As a negative control, the LPT with nano-silica was negative in another co-worker with the same occupational exposure for 9 years, who had COPD, but no evidence of granulomatous lung disease, and who was not taking any medication (data not shown).

FIGURE S6: (A) Negative results of the Blood Lymphocyte Proliferation Test (LPT) for beryllium (Be) and zirconium (Zr) in case A. Results are expressed as a 'stimulation index' (SI) which is the ratio of the amount of tritiated thymidine in the simulated cells divided by the counts for the unstimulated cells on the same culture day (day 6).
(B) Results of the LPT for three types of nano-silica. With the first nano-silica 4 out of 7 SIs were above 3.0. With the second nano-silica 5 out of 7 SIs were above 3.0. *Nano-silica #1 = NanoComposix 20 nm Non-Functionalized NanoXact™ Silica;* Nano-silica #2 = *Ludox colloidal silica;* Nano-silica #3 = *precipitated silica JRCNM02002a.*



1.3. Associations between occupational and environmental exposures and organ involvement in sarcoidosis: a retrospective case-case analysis [Research article]

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Abstract

Background: Sarcoidosis most commonly affects lungs and intrathoracic lymph nodes, but any other organ can be involved. In epidemiological studies, many occupational and environmental exposures have been linked to sarcoidosis but their relationship with the disease phenotype has barely been studied.

Objective: To investigate how occupational and environmental exposures prior to diagnosis relate to organ involvement in patients with sarcoidosis

Methods: We retrospectively studied patients seen at a sarcoidosis clinic between 2017 and 2020. Patients were included if they had a clinical presentation consistent with sarcoidosis and histologically confirmed epithelioid granulomas or had Löfgren syndrome. In a case–case analysis using multivariable logistic regression we calculated odds ratios (OR) of prespecified exposure categories (based on expert ascertainment) for cases with a given organ involvement versus cases without this organ involvement.

Results: We included 238 sarcoidosis patients. Sarcoidosis limited to pulmonary involvement was associated with exposure to inorganic dust prior to diagnosis (OR 2.11; 95% confidence interval [CI] 1.11 - 4.17). Patients with liver involvement had higher odds of contact with livestock (OR 3.68; 95%CI 0.91 - 12.7) or having jobs with close human contact (OR 4.33; 95%CI 1.57 - 11.3) than patients without liver involvement. Similar associations were found for splenic involvement (livestock: OR 4.94, 95%CI 1.46 - 16.1; close human contact: OR 3.78; 95%CI 1.47 - 9.46). Cardiac sarcoidosis was associated with exposure to reactive chemicals (OR 5.08; 95%CI 1.28 - 19.2) or livestock (OR 9.86; 95%CI 1.95 - 49.0). Active smokers had more ocular sarcoidosis (OR 3.26; 95%CI 1.33 - 7.79).

Conclusions: Our study indicates that, in sarcoidosis patients, different exposures might be related to different organ involvements—hereby providing support for the hypothesis that sarcoidosis has more than one cause, each of which may promote a different disease phenotype.

Introduction

Sarcoidosis most commonly affects the lungs and intrathoracic lymph nodes, but any organ can be involved [1, 2]. Several lines of evidence support the idea that sarcoidosis results from exposure of susceptible individuals to one or several antigen(s), leading to the activation of macrophages and T-cell immunity against these antigens. In epidemiological studies, many occupational and environmental exposures have been linked to sarcoidosis, such as organic dust [3–5], inorganic dust (including metals and minerals) [6, 7], and infectious agents (including mycobacteria and *Cutibacterium acnes*) [8]. It is unclear whether these exposures are truly 'causing' the disease, whether they render the immune system more susceptible to the development of sarcoidosis, or whether they exacerbate subclinical cases.

The diverse clinical manifestations and the wide range of associated exposures fuel the hypothesis that sarcoidosis has more than one cause, each of which may promote a different disease phenotype [9]. However, the relationship between exposure and disease phenotype has barely been studied. Indirect support for this hypothesis comes from studies demonstrating distinct patterns of organ involvement in men and women—who have different occupational exposures [10–12]. Also, studies have shown that sarcoidosis patients with respiratory exposure to inorganic or organic dust are less likely to have extrapulmonary involvement than unexposed patients [6, 12, 13].

In this study, we selected a range of occupational/environmental exposures previously associated with sarcoidosis [3–8] and assessed the relationship between these exposures (prior to diagnosis) and organ involvements in patients visiting a sarcoidosis clinic.

Material and methods

We retrospectively studied sarcoidosis patients that had visited the outpatient sarcoidosis clinic at the Department of Respiratory Diseases in the University Hospitals Leuven (Belgium) between January 1, 2017 and November 1, 2020 (n=321) [14]. The clinic is a WASOG Sarcoidosis Centre

of Excellence which means that the assessment of patients with sarcoidosis can involve the expertise of pulmonologists, cardiologists, dermatologists, ophthalmologists, rheumatologists and neurologists. All patients were subjected to history taking, clinical examination, laboratory work-up including urinalysis, chest imaging, eye examination, electrocardiography, and lung function testing. Pathological confirmation was sought except in patients presenting with the Löfgren syndrome. Further testing was based on clinical symptoms, signs or abnormalities detected by baseline screening tests in accordance with current guidelines [15].

Patients were included in our study if they had a clinical presentation consistent with sarcoidosis and histologically confirmed epithelioid granulomas (with negative cultures and stains for acid fast bacilli) or had Löfgren syndrome (n=304) [15]. Patients under the age of 18 (n=3), with a previous history of malignancy (n=44), and with missing data on job history (n=19) were excluded. The study was approved by the Ethics Committee Research UZ/KU Leuven (S64710).

Outcomes. An organ was considered affected when involvement was "highly probable" or "probable" according to the WASOG Sarcoidosis Organ Assessment Instrument [16]. Skin involvement was divided into "specific" lesions—resulting from the presence of granulomas in the skin—and erythema nodosum. Pulmonary-only sarcoidosis was defined as lung or intrathoracic lymph node involvement, without any evidence of other internal organ involvement (liver, spleen, heart, bone marrow, parotid/salivary gland or neurological system).

Exposures. Exposure categories were selected based on previously demonstrated associations with sarcoidosis [3–8]. Two experts in occupational and environmental medicine independently estimated how likely patients had been ever exposed prior to diagnosis (unlikely, probable or possible) based on information on jobs, hobbies and housing conditions extracted from the medical records. The following exposures were assessed: 1) respiratory exposure to reactive chemicals (such as isocyanates, methacrylates, epoxy resins), 2) inorganic dust (including metals and silica)

or 3) organic dust (plant, animal, or microbial antigens), if they had 4) close contact with livestock (such as cows, sheep, goats or horses), 5) jobs with close human contact (such as health care professionals, educators, and child or elderly care workers), or 6) administrative jobs. A patient was considered exposed when both experts estimated that there had been at least 'possible' exposure, and at least one expert estimated that the exposure was 'probable'. Multiple exposures could be assigned to one patient. Given the retrospective nature of the study, level and duration of exposure and latency period could not be reliably estimated. The experts were blinded for any demographic or clinical information.

Covariates. Covariates were chosen based on assumptions regarding their role in influencing the association between exposures and outcomes. Included covariates were potential confounders (age and sex—which could be regarded as a proxy for unmeasured exposures), potential effect modifiers (such as a family history of sarcoidosis, autoimmune or autoinflammatory disorders) as well as other potential risk factors of the outcomes (but not associated with exposure, i.e., non-confounding factors, such as having metal prostheses or silicone implants)—because adjustment for such factors could increase the precision of the estimates of the effects of the exposures of interest by reducing residual variation. The following covariates were extracted from the medical records: sex, race, age at diagnosis, presence of autoimmune or autoinflammatory diseases (such as Sjögren syndrome, rheumatoid arthritis, psoriasis, inflammatory bowel disease, diabetes mellitus type 1, alopecia areata, vitiligo, etc.), genetic disorders (such as autosomal dominant polycystic kidney disease), a family history of sarcoidosis, a family history of autoimmune or autoinflammatory disease, having metal prostheses or silicone implants, or taking medication (before diagnosis) that could have potentially triggered sarcoidosis (e.g. anti-TNF).

Statistical analysis. We did a case–case analysis to examine the association between the studied exposures and organ involvements. A case-case analysis is a special form of a case-control analysis in which cases with

different subtypes of the same illness are compared instead of including disease-free controls. This approach can reduce selection and recall bias relative to other case–control formats by ensuring that both case and "control" subjects have all been affected by (a different phenotype of) the same disease and thus underwent a similar selection process. First, univariable logistic regression was performed between each organ involvement and each exposure. Subsequently, for each organ involvement a separate multivariable logistic regression model was constructed to investigate statistical associations with the various exposures. The selection of exposures included in the final model for each organ involvement was done using an automated model selection procedure, implemented by the R package *glmulti* [17]. The best-fit models were selected based on their AIC ranking (Akaike Information Criterion) among all possible models—considering all possible subsets of exposure variables and other covariates (sex, age, presence of a systemic or organ-specific autoimmune disease, presence of genetic disorders, family history of sarcoidosis, family history of autoimmune or autoinflammatory diseases, having metal prostheses or silicone implants and taking medication that could have potentially triggered sarcoidosis). Additionally, tests for interaction were performed using interaction terms in the logistic regression models.

Results were expressed as odds ratios (ORs) with 95% confidence intervals (CI). The OR from this analysis represent the odds of having been exposed for cases with a given organ involvement divided by the odds for all other cases without this organ involvement [18].

Sensitivity Analysis. The case-case analysis does remain vulnerable to selection bias. Because smoking and respiratory exposures to reactive chemicals, inorganic or organic dust might lead to respiratory health effects independently of the presence of sarcoidosis, exposed patients could potentially seek medical care earlier than unexposed. Respiratory symptoms might therefore be potentially confounding the association between exposure and organ involvement. To assess this potential confounding, we

performed a sensitivity analysis by adjusting for the different lung function parameters (at diagnosis) in the regression models.

All statistical analyses were performed in statistical computing language R [19]. The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guideline was followed for reporting the study [20].

Results

We included 238 sarcoidosis patients—84 women and 154 men—who were predominantly Caucasian (4 were African, 1 Asian). Median age was 45 years (interquartile range 37 - 52y) for women and 41 years (IQR 35-47y) for men (Table 1). Sarcoidosis limited to lung and/or lymph nodes was present in 164 patients (69%). The most common extrapulmonary organ involvements were spleen (16%), eye (12%), liver (9.7%), and heart (7.1%) (Table 2). Chest CT findings and lung function parameters of the included patients are shown in Table 1. Comorbidities and other covariates are presented in the Additional file 1:Table S1.

The majority of the patients had never smoked (62%), and only 18% was an active smoker. Twenty-six patients (11%) had been exposed to reactive chemicals (such as isocyanates, methacrylates, epoxy resins) prior to diagnosis, mostly while having jobs in building industry (working with reactive adhesives or epoxy resins) or in chemical industry (for example in a paint factory, plastics/polymers production, or a chemical laboratory). Seventy-four patients (31%) had been exposed to inorganic dust, which included patients with jobs in which they were exposed to metal dust and/or fumes (such as metal workers and welders) or jobs with silica exposure (such as road and building construction workers or plumbers). Sixty-three patients (26%) had had organic dust exposure (plant, animal, or microbial antigens), which included mostly patients working in food production (bakers, cooks, butchers), wood workers, gardeners, farmers and pigeon breeders. Fifteen patients (6.3%) had close contact with mammalian livestock (cows, sheep, goats, or horses), mainly as animal farmers. Thirty-one patients (13%) had jobs with close human contact, such as health care professionals, educators,

and child or elderly care workers. Forty-four patients (18%) had only had administrative jobs. Men were more likely to have had inorganic dust exposure (46% of men versus 3.6% of women), while women were more likely to have jobs with close human contact or administrative jobs (Table 1).

Associations between organ involvements and exposures

Table 2 shows the distribution of organ involvements for patients in each exposure category. Results of the univariable logistic regression analysis (without adjustment for other exposures or covariates) of the associations between organ involvements and exposures are shown in the Additional file 1: Table S2.

For each organ involvement a multivariable logistic regression model was constructed to investigate statistical associations with the various exposures (Table 3). The selection of exposures included in the final model for each organ involvement was done using an automated model selection procedure, based on AIC ranking, among all possible models—considering all possible subsets of exposure variables and other covariates such as sex and age (see Material and methods). In the final multivariable models, isolated pulmonary sarcoidosis was associated with inorganic dust exposure (OR 2.11; 95% confidence interval [CI] 1.11 - 4.17) and tended to be associated with organic dust exposure (OR 1.86; 95%CI 0.95 - 3.82). Sarcoidosis patients with liver involvement had higher odds of having contact with livestock (OR 3.68; 95%CI 0.91 - 12.7) and having jobs with close human contact (OR 4.33; 95%CI 1.57 - 11.3) than patients without liver involvement. Splenic involvement was associated with contact with livestock (OR 4.94; 95%CI 1.46 - 16.1), jobs with close human contact (OR 3.78; 95%CI 1.47 - 9.46), and with administrative jobs (OR 2.52; 95%CI 0.99 - 6.16). Cardiac sarcoidosis was associated with exposure to reactive chemicals (OR 5.08; 95%CI 1.28 - 19.2) and contact with livestock (OR 9.86; 95%CI 1.95 - 49.0).

Table 1. Demographic and clinical data of the included sarcoidosis patients according to exposure category

			Exposure						
		Overall (n = 238)	**Reactive chemicals** (n = 26)	**Inorganic dust** (n = 74)	**Organic dust** (n = 63)	**Contact with livestock** (n = 15)	**Close human contact** (n = 31)	**Admin work only** (n = 42)	**Active smoker** (n = 43)
Demographics									
Gender	*Women*	84 (35%)	5 (19%)§	3 (4.1%)*	22 (35%)	6 (40%)	25 (81%)*	22 (52%)*	9 (21%)*
	Men	154 (65%)	21 (81%)§	71 (96%)*	41 (65%)	9 (60%)	6 (19%)*	20 (48%)*	34 (79%)*
Age at diagnosis		42 (35-50)	37 (34-49)	41 (35-48)	39 (34-48)§	47 (38-52)	44 (39-50)	42 (36-46)	38 (30-46)*
Smoking									
Never smoker		148 (62%)	14 (54%)	40 (54%)§	43 (68%)	14 (93%)*	21 (68%)	30 (71%)	0 (0%)
Past smoker		47 (20%)	6 (23%)	17 (23%)	13 (21%)	1 (6.7%)	5 (16%)	6 (14%)	0 (0%)
Active smoker		43 (18%)	6 (23%)	17 (23%)	7 (11%)§	0 (0%)§	5 (16%)	6 (14%)	43 (100%)
Packyears (for past or active smokers)		10 (5-20)	7.5 (5-20)	10 (5-20)	12 (5-20)	45	5 (5-14)	10 (9-15)	10 (6-20)
Chest CT at diagnosis									
Enlarged hilar/mediastinal lymph nodes		235 (99%)	25 (96%)	73 (99%)	63 (100%)	15 (100%)	31 (100%)	40 (95%)§	43 (100%)
(Micro)nodules		183 (77%)	21 (81%)	55 (74%)	51 (81%)	10 (67%)	22 (71%)	35 (83%)	36 (84%)
Fibrotic changes		13 (5.5%)	2 (7.7%)	4 (5.4%)	2 (3.2%)	0 (0%)	2 (6.5%)	5 (12%)§	4 (9.3%)
Airway abnormalities		44 (18%)	7 (27%)	20 (27%)*	9 (14%)	1 (6.7%)	3 (9.7%)	8 (19%)	10 (23%)
Lung function at diagnosis									
FVC %pred		94 (85-105)	91 (77-102)	94 (81-103)	90 (78-98)*	94 (91-103)	99 (86-108)	94 (90-108)§	94 (81-106)
FEV_1 %pred		89 (76-102)	84 (70-98)	89 (75-104)	82 (71-92)*	92 (87-98)	90 (77-102)	94 (80-106)	81 (70-99)§
FEV_1/FVC%		78 (73-83)	76 (62-82)§	77 (74-82)	76 (70-80)*	80 (77-82)	81 (71-85)	80 (76-83)§	78 (67-83)
TLC %pred		92 (83-100)	88 (80-99)	89 (80-98)§	86 (80-98)§	91 (86-97)	94 (89-102)	96 (88-100)§	86 (80-101)
T_{LCO} %pred		80 (68-92)	74 (64-93)	81 (67-95)	80 (68-88)	84 (74-96)	81 (68-87)	79 (69-90)	73 (62-89)*

Table 1 (continuation)

		Exposure						
	Overall (n = 238)	**Reactive chemicals** (n = 26)	**Inorganic dust** (n = 74)	**Organic dust** (n = 63)	**Contact with livestock** (n = 15)	**Close human contact** (n = 31)	**Admin work only** (n = 42)	**Active smoker** (n = 43)
Broncho-alveolar lavage								
% Lymphocytes	17 (10-25)	19 (14-25)	15 (10-21)	15 (10-23)	13 (7-33)	18 (11-32)	15 (7-25)	14 (7-21)
Not available	125 (53%)	13 (50%)	34 (46%)	27 (43%)	9 (60%)	20 (65%)	24 (57%)	21 (49%)
Treatment								
Treated within first year after diagnosis	118 (50%)	10 (38%)	41 (55%)	33 (52%)	5 (33%)	16 (52%)	21 (50%)	26 (60%)
Oral corticosteroids	116 (49%)	10 (38%)	41 (55%)	33 (52%)	5 (33%)	16 (52%)	19 (45%)	26 (60%)§
Methotrexate	46 (19%)	5 (19%)	17 (23%)	14 (22%)	0 (0%)§	5 (16%)	7 (17%)	16 (37%)*
Azathioprine	47 (20%)	6 (23%)	17 (23%)	15 (24%)	1 (6.7%)	5 (16%)	10 (24%)	14 (33%)*
Chloroquine	27 (11%)	4 (15%)	12 (16%)	8 (13%)	0 (0%)	3 (9.7%)	4 (9.5%)	10 (23%)*

Statistics presented: median (25%-75%), n (%); Statistical tests performed, comparing exposed to non-exposed: Wilcoxon rank sum test, Fisher's exact test or Pearson's Chi-squared test; * when $p<0.05$, § $p<0.10$

Table 2. Organ involvements of the included sarcoidosis patients according to exposure category

		Exposure						
	Overall (n = 238)	**Reactive chemicals** (n = 26)	**Inorganic dust** (n = 74)	**Organic dust** (n = 63)	**Contact with livestock** (n = 15)	**Close human contact** (n = 31)	**Admin work only** (n = 42)	**Active smoker** (n = 43)
Organ involvement								
Pulmonary involvement only	164 (69%)	17 (65%)	**58 (78%)***	47 (75%)	**6 (40%)***	**16 (52%)***	27 (64%)	32 (74%)
Intrathoracic lymph node	235 (99%)	25 (96%)	73 (99%)	63 (100%)	15 (100%)	31 (100%)	40 (95%)§	43 (100%)
Lung	191 (80%)	22 (85%)	59 (80%)	53 (84%)	11 (73%)	24 (77%)	34 (81%)	38 (88%)
Liver	23 (9.7%)	1 (3.8%)	**3 (4.1%)***	8 (13%)	**4 (27%)***	**8 (26%)***	4 (9.5%)	3 (7.0%)
Spleen	37 (16%)	3 (12%)	**6 (8.1%)***	7 (11%)	**6 (40%)***	**10 (32%)***	9 (21%)	4 (9.3%)
Cardiac	17 (7.1%)	**5 (19%)***	3 (4.1%)	2 (3.2%)	**4 (27%)***	2 (6.5%)	4 (9.5%)	3 (7.0%)
Eye	29 (12%)	2 (7.7%)	7 (9.5%)	4 (6.3%)§	0 (0%)	6 (19%)	5 (12%)	**11 (26%)***
Skin (excluding erythema nodosum)	23 (9.7%)	2 (7.7%)	6 (8.1%)	8 (13%)	1 (6.7%)	2 (6.5%)	3 (7.1%)	7 (16%)
Erythema nodosum	30 (13%)	5 (19%)	11 (15%)	9 (14%)	0 (0%)	3 (9.7%)	5 (12%)	4 (9.3%)
Neurologic	9 (3.8%)	1 (3.8%)	2 (2.7%)	1 (1.6%)	0 (0%)	2 (6.5%)	1 (2.4%)	2 (4.7%)
Parotid/salivary gland	8 (3.4%)	0 (0%)	1 (1.4%)	3 (4.8%)	2 (13%)§	2 (6.5%)	2 (4.8%)	0 (0%)
Bone marrow	9 (3.8%)	0 (0%)	2 (2.7%)	3 (4.8%)	1 (6.7%)	3 (9.7%)§	1 (2.4%)	3 (7.0%)
Löfgren syndrome	30 (13%)	3 (12%)	9 (12%)	6 (10%)	1 (7%)	3 (10%)	6 (14%)	3 (7%)

Statistics presented: n (%); Statistical tests performed, comparing exposed to non-exposed: Fisher's exact test or Pearson's Chi-squared test; * when $p<0.05$, § $p<0.10$

Table 3. Final multivariable logistic regression models for six organ involvements showing associations with occupational and environmental exposures in patients with sarcoidosis

	Pulmonary only (n = 164)			Liver involvement (n = 23)			Splenic involvement (n = 37)			Cardiac involvement (n = 17)			Eye involvement (n = 29)			Skin granulomas (n = 23)		
Exposure	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**
Reactive chemicals (n = 26)		—			—			—		5.08*	1.28 - 19.2	0.016		—			—	
Inorganic dust (n = 74)	2.11*	1.11 - 4.17	0.026		—			—		0.21*	0.04 - 0.76	0.029		—			—	
Organic dust (n = 63)	1.86	0.95 - 3.82	0.079		—			—		0.22	0.03 - 0.91	0.066		—			—	
Contact with livestock (n = 15)	0.23*	0.07 - 0.71	0.012	3.68*	0.91 - 12.7	0.047	4.94*	1.46 - 16.1	0.008	9.86*	1.95 - 49.0	0.004	0.00		>0.99		—	
Close human contact (n= 31)		—		4.33*	1.57 - 11.3	0.003	3.78*	1.47 - 9.46	0.005		—			—			—	
Administrative work only (n = 42)		—			—		2.52*	0.99 - 6.16	0.046		—			—			—	
Active smoker (n = 43)		—			—			—			—		3.26*	1.33 - 7.79	0.008	2.50	0.89 - 6.54	0.069

*For each organ involvement a separate multivariable logistic regression model was constructed. Odd ratios shown result from the best-fit multivariable logistic regression models, using Akaike information criterion (AIC) for model selection. OR = Odds Ratio for having been exposed (cases with a given organ involvement versus all other cases) while adjusting for other exposures and covariates retained in the final models (See Material and methods). CI = Confidence Interval; p = p-value; * when statistically significant (p < 0.05)*

Active smokers had more ocular sarcoidosis (OR 3.26; 95%CI 1.33 - 7.79) and were possibly more likely to have skin granulomas (OR 2.50; 95%CI 0.89 - 6.54). No statistically significant associations were found between erythema nodosum and any exposure (model not shown). A sensitivity analysis including adjustment for lung function at diagnosis yielded similar effect size estimates (see Table S3).

Discussion

Our study suggests that various occupational/environmental exposures prior to diagnosis are related to organ involvement in sarcoidosis patients. The main novelty of our study is that unlike previous studies searching for associations between exposure and sarcoidosis occurrence, we investigated the associations between exposure and *organ involvement* in sarcoidosis—hereby aiming to provide support for the hypothesis that each "cause" of sarcoidosis might promote a different disease phenotype [9].

We selected a range of exposures which had been previously associated with sarcoidosis [3–8]. Due to the wide range of exposures described in the literature, we categorized them in 5 categories: inorganic dust, organic dust, reactive chemicals, contact with (mammalian) livestock, and close human contact. We speculated that the last two categories entailed an increased risk of exposure to infectious agents. A sixth category—"administrative work only"—was used for patients without any of the above-mentioned exposures.

Dust exposure

We found a significant association between exposure to inorganic dust, such as metal or silica dust, and sarcoidosis limited to lungs and/or intrathoracic lymph nodes (OR 2.11; 95%CI 1.11 - 4.17). Also, organic dust exposure—including exposure to plant, animal, or microbial antigens—tended to be related to pulmonary-only sarcoidosis (OR 1.86; 95%CI 0.95 - 3.82).

In the ACCESS (A Case Control Etiologic Study of Sarcoidosis) study, patients exposed to agricultural organic dust (in whites, OR 0.33; 95%CI 0.16–0.71) and wood burning (in blacks, OR 0.36; 95%CI 0.23–0.59) were

less likely to have extrapulmonary involvement [12]. World Trade Center (WTC) rescue workers with sarcoidosis—who had been exposed to high levels of inorganic dust resulting from the WTC collapse in 2001—also had less extrapulmonary involvement than expected [6]. Patients with chronic beryllium disease, a disorder clinically, radiologically and histopathologically almost indistinguishable from sarcoidosis—but known to be caused by a cell-mediated immune response to beryllium—have fewer extrapulmonary manifestations: hepatic, splenic and cardiac involvement are rare, and ocular and neurological impairment have not been reported [21].

In sarcoidosis, epithelioid granulomas are presumably an immunological response to persistent antigens, possibly combined with an adjuvant signal triggering an innate immune response [9]. Dust particles might be the target of this immune response, although it is uncertain if they act as antigens, as adjuvants or as nidus [9].

A possible explanation for the association between dust exposure and sarcoidosis which is limited to the lungs is that inhaled dust particles do not readily disseminate systemically. Small inhaled particles that deposit in the deep lung can—when not removed by the mucociliary escalator—be transported via the lymphatic system to regional lymph nodes [22, 23]. Particles accumulate in lymph nodes but can—to a limited extent—gradually translocate into the systemic circulation where they are filtered from the blood in liver and spleen [22]. Small fractions can be taken up by other organs such as the brain or the heart [24]. The probability and speed of systemic dissemination depends on particle characteristics such as size, surface properties, chemical composition and solubility [22]. This might explain why extrapulmonary involvement in patients exposed to dust is less common, but not impossible.

Reactive chemicals

We found that respiratory exposure to reactive chemicals—including isocyanates, methacrylates, or epoxy resins—was associated with the presence of cardiac sarcoidosis (OR 5.08; 95%CI 1.28 - 19.2). We should be

cautious in interpreting this result as it concerns a limited number of patients (exposure to reactive chemicals was present in 5 out of 17 patients [29%] with cardiac sarcoidosis, but only in 21/221 cases [9.5%] without cardiac involvement). As these chemicals are known to cause asthma (and occasionally hypersensitivity pneumonitis), we did not expect an association with any extrapulmonary involvement [25]. It is unclear what the underlying pathways and mechanisms could be. We found only one study (on the ACCESS dataset) reporting a similar association, finding that occupational insecticide exposure combined with HLA class II allele DRB1*1101 was associated with cardiac sarcoidosis [3].

Infectious agents

Our analysis showed that contact with (mammalian) livestock (including cows, goats, sheep, horses) and jobs with close human contact (including health care workers, educators, child and elderly care workers) were independently associated with liver and spleen involvement (Table 3). Moreover, contact with livestock was related to cardiac involvement (OR 9.86; 95%CI 1.95 - 49.0). We speculate that such contacts entail an increased risk of exposure to infectious agents.

Infectious agents—such as mycobacteria and *Cutibacterium acnes*—have been suspected of being involved in the development of sarcoidosis in some patients [8]. This does not necessarily imply that sarcoidosis is an infection. Numerous researchers have unsuccessfully attempted to culture mycobacteria from sarcoid tissues [26]. Nevertheless, T-cell responses to mycobacterial antigens, such as mKatG, and heat-killed *C. acnes* have been demonstrated in peripheral blood mononuclear cells (PBMCs) and bronchoalveolar lavage fluid of some patients [27, 28].

Interestingly, Beijer et al. demonstrated that sarcoidosis patients whose PBMCs responded to mycobacterial antigens, had more cardiac involvement (3/5 patients) than unresponsive patients (34/196; p=0.044) [29]. Also, patients where C. acnes was present in histological samples—confirmed by immunohistochemistry—were more likely to have liver involvement (19%

compared to 4%; p=0.057) [30]. Although a systemically disseminated trigger could be suspected, we can only speculate on the agents to which our patients were exposed and the precise mechanisms leading to liver, spleen and/or heart involvement. Unlike in our study, no increase in extrapulmonary sarcoidosis was found in health care or childcare workers in the ACCESS study [12]. Indirect support for the association between close human contact and extrapulmonary sarcoidosis is suggested by studies showing more extrapulmonary sarcoidosis in women, who are more likely to have care jobs than men [10, 11].

We also found an association between administrative jobs and splenic involvement. Although associations between mould exposure in damp indoor environments and sarcoidosis have been reported [9], we could not assess if mould exposure was present in our patients with administrative jobs. In one outbreak of sarcoidosis in office workers in a water-damaged building, 3 out of 6 cases had “multiorgan” sarcoidosis (without further details reported) [31]. In contrast, in the ACCESS dataset, exposure to moulds or musty odours combined with HLA class II allele DRB1*1101 was associated with pulmonary-only sarcoidosis.

Smoking

In our study, smoking was associated with ocular sarcoidosis (OR 3.26; 95%CI 1.33 - 7.79) and skin granulomas—although not statistically significant (OR 2.50; 95%CI 0.89 - 6.54). While smokers are less likely to be diagnosed with sarcoidosis in general [32], smoking has been previously shown to be a risk factor for ocular sarcoidosis [33]. It is unclear whether this results from a local effect—with the eye as portal of entry of the disease trigger—or whether it represents a systemic effect.

We could not identify other studies investigating the relation between smoking and skin granulomas in sarcoidosis. Although it is possible that this relation is confounded by other unknown exposures, studies have shown that smoking leads to an increased prevalence of various cutaneous disorders characterized by defective permeability, such as eczema and psoriasis [34].

Smoking might therefore facilitate the penetration of unknown antigens triggering skin granulomas. No associations between the other studied exposures and skin granulomas were found, possibly because we did not specifically assess dermal exposures.

Strengths and limitations

A concern might be that some included patients represent misdiagnosed cases of hypersensitivity pneumonitis (in those exposed to organic dust or reactive chemicals), pneumoconiosis (in those exposed to inorganic dust), or infections. Nevertheless, all included patients had histologically confirmed sarcoid granulomas (with negative cultures and stains, and exclusion of silicotic nodules) or presented with a Löfgren syndrome—highly supportive for a diagnosis of sarcoidosis [15].

One could argue that because sarcoidosis is “by definition” a disease of unknown cause, finding a potential cause excludes the diagnosis of sarcoidosis and requires another disease label. For example, for sarcoidosis cases who had been exposed to WTC dust, Izbicki et al. proposed the term "sarcoid-like granulomatous pulmonary disease” since they rarely had extrapulmonary involvement [6]. However, as already argued by Scadding in 1960 [35], this approach is not helpful when investigating the etiology of sarcoidosis, because it would be unclear when the presence of an exposure—epidemiologically related to sarcoidosis—should lead to exclusion from the category "sarcoidosis" and when it should be ignored as incidental and unrelated.

Our study has several limitations. Since the exposure information available from the medical records was not standardized, exposure misclassification is possible. Nevertheless, thanks to the longstanding presence of an outpatient clinic for environmental and occupational disorders within the hospital’s Department of Respiratory Diseases, there is a tradition of routinely registering occupational and environmental histories in the medical records of new sarcoidosis patients [36]. The exposure assessment categories were rather broad because specific agents would have been difficult for experts to

assess and would have limited the power of the study. Therefore, our approach possibly obscured the effect of specific exposures, such as certain metals—included in the category “inorganic dust”. Nevertheless, we consider the blinded exposure assessment as a strength of the study.

Because the exposure assessment was done retrospectively, we were unable to reliably estimate the latency period between exposure and disease onset or the precise duration of the exposures. The time relationship between exposure and occurrence of sarcoidosis has barely been studied. Case studies reporting on patients exposed to silica/silicates suggest latency periods from 6 months up to 40 years between exposure and onset of symptoms [37–39]. In a cohort of WTC first responders, a peak incidence of sarcoidosis was found 7-9 years after the WTC collapse [40]. Also, studies looking at duration of exposure and occurrence of sarcoidosis are scarce, and do not show a clear minimally needed duration of exposure [41].

Our recruitment strategy led to selection of patients with pulmonary involvement. In the workup of patients visiting our clinic, screening for extrapulmonary involvement is routinely performed [15]. Although we cannot exclude that subclinical organ involvements were missed, we are confident that we detected clinically relevant involvements, as the distribution of organ involvements in our study was similar to the one found in the ACCESS study [42]. However, limited inclusion of some rare organ manifestations, such as neurological involvement, prevented inclusion in our statistical analysis. Also, because we do not have follow-up data, we were unable to describe the disease course of our patient.

Since smoking and exposure to reactive chemicals, inorganic or organic dust might lead to respiratory health effects independently of the presence of sarcoidosis, exposed patients conceivably seek medical care earlier than unexposed. To assess whether respiratory symptoms potentially confound the association between exposure and organ involvement, we performed a sensitivity analysis by adjusting for lung function parameters. This did not substantially alter the effect size estimates for the different exposures,

suggesting the absence of substantial confounding (see Additional file1: Table S3).

Conclusion

Our study indicates that, in susceptible individuals, different exposures might be related to different clinical presentations of sarcoidosis. As this association has hardly been investigated, confirmation in other populations is warranted, preferably including more patients with rare organ manifestations. Future longitudinal studies could clarify whether not only disease presentation but also prognosis is related to exposure and if stopping or reducing these exposures could alter the disease course [38].

Supplementary information: Table S1. Comorbidities and other covariates of the included sarcoidosis patients; Table S2: Results for the univariable analysis of the associations between each organ involvement and each exposure. Table S3. Sensitivity analysis to assess potential confounding by adjusting for different lung function parameters in the best-fit logistic regression models from Table 1.

Abbreviations

ACCESS = A Case Control Etiologic Study of Sarcoidosis; AIC = Akaike information criterion; CI = confidence interval; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; HLA = Human Leukocyte Antigen; OR = odds ratio; PBMCs = peripheral blood mononuclear cells; %pred. = percentage of the predicted value; TLC = total lung capacity; TLCO = transfer factor of the lung for carbon monoxide; TNF = tumor necrosis factor; WASOG = World Association of Sarcoidosis and other Granulomatous Disorders; WTC = World Trade Center

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Supplementary information

Table S1. Comorbidities and other covariates of the included sarcoidosis patients

		Exposure						
	Overall (n = 238)	**Reactive chemicals** (n = 26)	**Inorganic dust** (n = 74)	**Organic dust** (n = 63)	**Contact with livestock** (n = 15)	**Close human contact** (n = 31)	**Admin work only** (n = 42)	**Active smoker** (n = 43)
Systemic autoimmune disease	4 (1.7%)	1 (3.8%)	1 (1.4%)	1 (1.6%)	1 (6.7%)	0 (0%)	1 (2.4%)	1 (2.3%)
Organ-specific autoimmune disease	14 (5.9%)	1 (3.8%)	2 (2.7%)	4 (6.3%)	1 (6.7%)	1 (3.2%)	2 (4.8%)	4 (9.3%)
Taking medication (before diagnosis) that could have potentially triggered sarcoidosis	4 (1.7%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)	2 (4.8%)	1 (2.3%)
Silicone breast implant	3 (1.3%)	0 (0%)	0 (0%)	1 (1.6%)	0 (0%)	0 (0%)	1 (2.4%)	0 (0%)
Metal joint implant	2 (0.8%)	0 (0%)	1 (1.4%)	2 (3.2%)[§]	1 (6.7%)	0 (0%)	0 (0%)	0 (0%)
Familial history of sarcoidosis	14 (5.9%)	2 (7.7%)	5 (6.8%)	8 (13%)*	2 (13%)	0 (0%)	2 (4.8%)	1 (2.3%)
Familial history of autoimmune of autoinflammatory disease	18 (7.6%)	2 (7.7%)	1 (1.4%)*	5 (7.9%)	0 (0%)	3 (9.7%)	7 (17%)*	5 (12%)
Genetic disorder	4 (1.7%)	1 (3.8%)	1 (1.4%)	1 (1.6%)	1 (6.7%)	2 (6.5%)[§]	1 (2.4%)	1 (2.3%)

Statistics presented: n (%); Statistical tests performed, comparing exposed to non-exposed: Fisher's exact test or Pearson's Chi-squared test; * when $p<0.05$, [§] $p<0.10$

Table S2: Results for the univariable analysis of the associations between each organ involvement and each exposure, without adjustment for other exposures or covariates.

	Pulmonary only (n = 164)			Liver involvement (n = 23)			Splenic involvement (n = 37)			Cardiac involvement (n = 17)			Eye involvement (n = 29)			Skin granulomas (n = 23)		
Exposure	**OR***	**95% CI***	**p***	**OR***	**95% CI***	**p***	**OR***	**95% CI***	**p***	**OR***	**95% CI***	**p***	**OR***	**95% CI***	**p***	**OR***	**95% CI***	**p***
Reactive chemicals (n = 26)	0.84	0.36 - 2.05	0.68	0.35	0.02 - 1.76	0.31	0.68	0.16 - 2.11	0.55	3.97	1.17 - 11.9	**0.017**	0.57	0.09 - 2.08	0.46	0.76	0.12 - 2.81	0.72
Inorganic dust (n = 74)	1.98	1.06 - 3.85	**0.036**	0.30	0.07 - 0.92	0.061	0.38	0.14 - 0.89	**0.039**	0.45	0.10 - 1.44	0.22	0.67	0.26 - 1.59	0.39	0.76	0.27 - 1.93	0.59
Organic dust (n = 63)	1.46	0.77 - 2.85	0.26	1.55	0.60 - 3.78	0.34	0.60	0.23 - 1.38	0.26	0.35	0.05 - 1.29	0.17	0.41	0.12 - 1.10	0.11	1.55	0.60 - 3.78	0.34
Contact with livestock (n = 15)	0.27	0.09 - 0.79	**0.018**	3.90	1.01 - 12.7	**0.031**	4.13	1.31 - 12.3	**0.012**	5.87	1.47 - 20.0	**0.006**	0.00		0.99	0.65	0.04 - 3.49	0.69
Close human contact (n= 31)	0.43	0.20 - 0.92	**0.029**	4.45	1.64 - 11.5	**0.002**	3.17	1.31 - 7.36	**0.008**	0.88	0.13 - 3.35	0.87	1.92	0.66 - 4.93	0.20	0.61	0.09 - 2.24	0.52
Administrative work only (n = 42)	0.78	0.39 - 1.59	0.48	0.98	0.27 - 2.79	0.97	1.64	0.68 - 3.68	0.25	1.48	0.40 - 4.45	0.51	0.97	0.31 - 2.52	0.95	0.68	0.15 - 2.10	0.54
Active smoker (n = 43)	1.39	0.67 - 3.05	0.39	0.66	0.15 - 2.03	0.51	0.50	0.14 - 1.36	0.22	0.97	0.22 - 3.14	0.96	3.38	1.43 - 7.76	**0.004**	2.18	0.79 - 5.50	0.11

** OR = Odds Ratio for having been exposed (cases with a given organ involvement versus all other cases). CI = Confidence Interval;* p-value*; bold when p<0.05*

Table S3. Sensitivity analysis to assess potential confounding by adjusting for different lung function parameters in the best-fit logistic regression models from Table 1.

	Pulmonary only (n = 164)			**Liver involvement (n = 23)**			**Splenic involvement (n = 37)**			**Cardiac involvement (n = 17)**			**Eye involvement (n = 29)**			**Skin granulomas (n = 23)**		
Exposure	**OR***	**95% CI***	**p***	**OR***	**95% CI***	**p***	**OR***	**95% CI***	**p***	**OR***	**95% CI***	**p***	**OR***	**95% CI***	**p***	**OR***	**95% CI***	**p***
Reactive chemicals (n = 26)										4.13	0.96 - 16.5	**0.047**						
Inorganic dust (n = 74)	2.22	1.14 - 4.50	**0.022**							0.24	0.05 - 0.88	**0.045**						
Organic dust (n = 63)	1.95	0.96 - 4.17	0.074							0.15	0.02 - 0.69	**0.031**						
Contact with livestock (n = 15)	0.15	0.04 - 0.52	**0.004**	4.08	0.97 - 14.7	**0.038**	7.57	2.05 - 28.4	**0.002**	11.6	2.11 - 63.7	**0.004**	0.00		>0.99			
Close human contact (n= 31)				4.21	1.51 - 11.2	**0.004**	4.23	1.58 - 11.1	**0.003**									
Administrative work only (n = 42)							3.04	1.14 - 7.91	**0.023**									
Active smoker (n = 43)													2.39	0.90 - 6.08	0.071	2.05	0.66 - 5.76	0.2
FEV_1 %pred	1.01	0.99 - 1.0	0.4	1.00	0.97 - 1.03	>0.9	0.99	0.97 - 1.02	0.6	0.99	0.95 - 1.03	0.6	1.02	0.99 - 1.05	0.14	1.01	0.98 - 1.04	0.6
FEV_1/FVC %	1.00	0.96 - 1.0	0.8	1.02	0.97 - 1.09	0.4	1.01	0.96 - 1.06	0.8	0.98	0.91 - 1.05	0.5	0.97	0.92 - 1.03	0.3	0.98	0.92 - 1.05	0.6
T_{LCO} %pred	1.00	0.98 - 1.0	0.9	0.99	0.96 - 1.03	0.7	0.99	0.96 - 1.01	0.3	1.01	0.98 - 1.05	0.4	0.98	0.95 - 1.00	0.10	1.00	0.97 - 1.03	>0.9

** OR = Odds Ratio for having been exposed (cases with a given organ involvement versus all other cases) while adjusting for other exposures and covariates (see Study design and methods); For lung function parameters the OR is given per percent of the predicted value; CI = Confidence Interval; p-value; bold when statistically significant (p<0.05)*

1.4. Discussion

1.4.1. Summary of the main findings

Two workers with sarcoid-like disease exposed to amorphous (fused) silica

In the first part of this chapter, we reported on two workers who developed sarcoid-like lung disease after three to six years of occupational exposure to amorphous fused silica dust. Several arguments suggest that this exposure triggered their disease. First, sarcoidosis is a rare disorder with a prevalence of about 4.7–64 per 100,000 persons, and a yearly incidence of 1.0–35.5 per 100,000 persons.[1] Therefore, the probability to encounter two cases in a relatively short time period in a group of about 30 workers is very low. Interestingly, this "epidemiological" argument was brought up by one of the patients, which triggered the present investigation. Second, in both men, birefringent particles were observed in lung or mediastinal lymph node tissue. Finding dust particles in biopsies does not prove causality, but at least confirms exposure that is enough to be considered as abnormal. Furthermore, analysis of settled dust samples from the workplace showed the presence of amorphous fused silica and some cristobalite (exposure argument). Third, both cases improved after removal from exposure (clinical argument). Although improvement in sarcoidosis patients can occur spontaneously, we believe that the combination of the epidemiological argument, the exposure evidence, and the clinical course, makes a strong case for an occupational etiology.

Occupational and environmental exposures and sarcoidosis phenotype

The diverse clinical manifestations and the wide range of associated exposures fuel the hypothesis that sarcoidosis has more than one cause, each of which may promote a different disease phenotype.[2] In the main study in this chapter, we looked at associations between occupational and environmental exposures and organ involvement in sarcoidosis. We found a statistically significant association between inorganic dust exposure and

pulmonary-only sarcoidosis (OR 2.11; p=0.026). Also, organic dust exposure—which included exposure to moulds—was related to pulmonary-only sarcoidosis although this did not reach statistical significance (OR 1.86; p=0.079). Exposure to organic and inorganic dust, such as metal or silica dust, has been previously shown to be associated with pulmonary-only sarcoidosis.[3,4] Next, we found evidence that sarcoidosis patients with contact with livestock (including cows, goats, sheep, horses) and close human contact (including health care workers, educators, child and elderly care workers)—both presumably related to a higher risk of exposure to infectious agents—were associated with liver and spleen involvement. Moreover, contact with livestock was strongly associated with cardiac involvement. Infectious agents—such as mycobacteria, *Cutibacterium acnes* (previously Propionibacterium acnes) and moulds—have been suspected of being involved in the development of sarcoidosis in some patients.[5] Although close contact with livestock or close human contact could increase the risk of exposure to several infectious agents, we can only speculate on the type of agents our patients were exposed to and the precise mechanisms by which the liver, spleen and/or heart involvement were triggered.

1.4.2. Finding the cause(s) of sarcoidosis—Challenges and future perspectives

Nearly 150 years after it was first described by Hutchinson,[6] the etiology of sarcoidosis is still enigmatic. Although in recent decades our understanding of the disease has improved, many challenges remain in finding causative antigens. Several factors could explain the difficulties encountered in studying the cause(s) of this disease. A major factor is probably the different types of expertise needed to be able to understand the disease. Immunology, infectious diseases, occupational and environmental medicine, toxicology, pathology, genetics and clinical expertise matter in the pathophysiology of sarcoidosis. Moreover, as the disease does not fit well within one medical discipline, the clinical expertise is divided over several

medical specialties: internal medicine, pulmonology, ophthalmology, cardiology, neurology, etc.

Defining sarcoidosis as a disease of unknown cause

A major source of confusion are the criteria that define sarcoidosis. The histological hallmark of sarcoidosis is the non-necrotising granuloma. The central core of a sarcoid granuloma is made up of a number of mononuclear phagocytes and their progeny (epithelioid and multinucleated giant cells) and is surrounded by a rim of T-cells, consisting mostly of $CD4^+$ T-cells but also containing some $CD8^+$ T-cells, B-cells, and plasma cells.[1,7]

The American Thoracic Society (ATS) Clinical Practice Guideline from 2020 states that the diagnosis of sarcoidosis is based on three major criteria: 1) a compatible clinical presentation, 2) the finding of non-necrotizing granulomatous inflammation in one or more tissue samples, and 3) the exclusion of alternative causes of granulomatous disease.[8] However, there are no established objective measures to determine if each of these diagnostic criteria has been satisfied, and, therefore, the diagnosis of sarcoidosis is never fully secure. The presence of noncaseating granulomas is not pathognomonic, and no diagnostic tests have high sensitivity or specificity for sarcoidosis. Even the Kveim test, which has been used in the past in the diagnosis of sarcoidosis, showed to be negative in a considerable fraction of cases.[9]

Especially, the approach of excluding “known” causes of granulomatous disease is problematic when aiming to find causes of sarcoidosis. First, it is unclear when the presence of a certain exposure should lead to exclusion from the category "sarcoidosis" and when it should be ignored as incidental and unrelated. Second, finding a “known” causes depends largely on the knowledge of the physician that is visited by the patient, on how thoroughly a cause is sought and on the techniques that are available to the clinician.

Numerous examples in the literature illustrate these difficulties. For example, Forst and Abraham describe a case clinically compatible with sarcoidosis, including histologically proven well-formed non-necrotizing epithelioid

granulomas, which they later reclassify as “hypersensitivity pneumonitis” (only) because the patient was exposed to diisocyanates, and high concentrations of particles were found in the lung biopsy (using electron probe microanalysis).[10]

As discussed in the introduction of this chapter, similar problems arise in silica-exposed patients with sarcoid-like granulomas. As silicotic nodules are specific for established silicosis, cases exposed to silica in which both sarcoid-like granulomas and silicotic nodules are encountered, are classified as “silicosis”.[11] Nevertheless, the presence of sarcoid-like granulomas in patients with pneumoconiosis does not seem to be rare.[12–18] In some reports the authors re-classify “sarcoidosis” cases as silicosis—even without finding silicotic nodules—because of the presence of birefringent particles in the sarcoid granulomas.[19]

Needless to say, that cases in which infectious agents such as *Mycobacterium tuberculosis* or *Brucella* spp. are encountered are not regarded as sarcoidosis. Nevertheless, also in some of these cases histologically granulomas can be found which are indistinguishable from sarcoid granulomas.[20]

Chronic beryllium disease is only distinguished from sarcoidosis by a positive beryllium lymphocyte proliferation test.[21] Nevertheless, when no BeLPT is performed—or can be performed because it is unavailable—CBD cases would be classified as sarcoidosis.[22]

In summary, defining sarcoidosis as a disease of unknown cause leads to numerous difficulties: while in some instances sarcoid-like granulomas will not be considered to be sarcoidosis—in the presence of silicotic nodules, microbial agents, or in case of a positive BeLPT—in other instances it is unclear when the presence of certain exposures should lead to exclude a diagnosis of "sarcoidosis"—for example when birefringent particles or microbial antigens are found in tissue, or when specific exposures (diisocyanates, organic dust, WTC dust) are documented.

Scadding emphasized the importance of defining sarcoidosis in such a way as to allow for the possibility that the histological picture may be caused by more than one agent.[23] He proposed, instead of giving new disease labels to cases of sarcoidosis in which a causative agent was identified to restrict the definition of sarcoidosis to its essence—i.e. the presence of epithelioid-cell non-caseating granulomas—and then to add the putative causal agent to the disease name, for example, "beryllium sarcoidosis" or "sarcoidosis induced by beryllium" instead of CBD, and "tuberculous sarcoidosis" or "sarcoidosis induced by *Mycobacterium tuberculosis*" instead of indolent non-caseating tuberculosis. If other sarcoidosis cases, either individually or as a group, are found to be associated with a detectable causative agent, a term indicative of etiology could then be added to the term "sarcoidosis" to identify them precisely.[24]

For sarcoidosis cases who had been exposed to WTC dust, Izbicki *et al* initially proposed the term "sarcoid-like granulomatous pulmonary disease" since these patients rarely had extrapulmonary involvement.[3] However, a recent study showed that the genetic variants in sarcoidosis cases exposed to WTC dust were similar to those found in "sporadic" cases of sarcoidosis in the general population (i.e., presumably cases without an assessment of exposures). The authors concluded that the cases of "sarcoid-like granulomatous disease" could be more correctly described as "WTC-related sarcoidosis."[25]

Defining relevant phenotypes of sarcoidosis

The heterogeneous clinical presentation of sarcoidosis also complicates the search for causative antigens.[8] The diverse clinical manifestations of sarcoidosis and the wide range of exposures associated with the disease suggest that sarcoidosis has more than one cause, each of which may promote a different phenotype and disease course[2] or that a single agent can produce different effects based on host factors, such as genetics.[26] However, it is unclear what is the best way to define sarcoidosis phenotypes in studies investigating the causes of sarcoidosis. Phenotypic differences

may relate to variability in specific organ involvement of sarcoidosis, to the duration or severity of disease, as well as to response to treatment.[27] As the appropriate stratification of disease phenotypes is unknown, Judson proposes to partition the phenotypes in multiple ways, such as organ involvements, disease course and corticosteroid-responsiveness.

Ascertainment of cases and of affected organs

The differences in how cases are recruited and included in epidemiological studies on sarcoidosis can introduce selection bias. Also, the phenotype of included patients depends largely on the type of clinic where patients are recruited (medical specialties involved, academic hospital setting, etc.) and the extent of the work-up of these cases (especially the thoroughness of the screening for extrapulmonary involvement).[8]

Autopsy studies suggest that the number of cases of sarcoidosis may be 10 times higher than the number of cases that are clinically apparent.[28] Also, at autopsy, the involvement of several organs is more common than clinically diagnosed. For example, cardiac sarcoidosis is diagnosed in around 5% of patients, although autopsy studies have shown that cardiac involvement is present in up to 25% of autopsy specimens.

Assessment of exposure and specific immune responses

If we want to discover exposures that cause sarcoidosis, we should, in the first place, be able to detect these exposures. However, the tools for retrospectively detecting potentially relevant exposures *in vivo* are limited: microbial cultures and *in situ* staining for microbes/microbial antigens in tissue, mineral analysis of tissue, and immunological assays such as the beryllium lymphocyte proliferation test. In recent years, new approaches have been used, such as proteomics,[29] mineral analysis of bronchial washing/BAL fluid,[30] or LPTs with other agents—such as mycobacterial antigens,[31] vimentin,[32] or other metals and silica.[33]

Epidemiological studies can help determining certain environmental risk factors and hereby narrow the search for causes. However, they are unable

to determine if certain environmental risk factors are acting as antigens themselves, if they induce immune reactions against autoantigens or if they are confounders and are merely *associated* with unknown exposures that are the real causes.

Epidemiological studies have mainly used retrospective exposure assessments using job-exposure matrices,[33] or job history/exposure questionnaires.[34] When assessing potentially causal exposures, we obviously need to look at exposures that have occurred *before* the onset of the disease. However, as symptoms of sarcoidosis may occurs long after the disease process has started, the exact time of onset of the disease is generally unclear. The time between disease onset and the diagnosis of the disease can depend on many factors, such as the type of symptoms (respiratory, ocular, systemic, …), whether imaging has been performed for unrelated reasons (which could lead to an accidental diagnosis), what organs are involved, etc.

Additionally, we do not know the latency period between exposure to an inciting agent and the onset of sarcoidosis. Therefore, we do not know the exact time period for which we should be assessing the exposure. Case studies reporting on patients exposed to silica/silicates suggest latency periods from 6 months up to 40 years between exposure and onset of symptoms.[35-37] In a cohort of WTC first responders, a peak incidence of sarcoidosis was found 7-9 years after the WTC collapse.[38] Also, studies looking at duration of exposure and occurrence of sarcoidosis are scarce, and do not show a clear minimally needed duration of exposure.[39]

Perspectives for studying causes of sarcoidosis

Studying sarcoidosis in order to find causal exposures is complex. Given this complexity we should probably investigate the question of what causes sarcoidosis from different angles and triangulate the evidence from various types of studies—including case reports/series, epidemiological studies with various study designs and populations, immunological studies, and experimental studies (animal or *in vitro*).

An approach that has been successful in clarifying parts of the pathophysiology has been adopted by studies that have limited inclusion to a specific phenotype of sarcoidosis—according to HLA type, disease presentation (e.g., Löfgren), (rare) organ involvement, common exposure, or other types of clustering (geographical, familial, seasonal).[26] For example, the group of Grunewald has focused on HLA-DRB1*03^{+} sarcoidosis patients. They demonstrated an accumulation of large clonal populations of specific Vα2.3/Vβ22 T-cell receptor-expressing CD4^{+} T-cells in the lungs of HLA-DRB1*03^{+} sarcoidosis patients. They also discovered that a vimentin-derived peptide matched perfectly into both the HLA peptide-binding pocket and the TCR Vβ22 CDR3 loop.[40] Subsequently this group showed that the same vimentin peptide could induce strong proliferative responses from peripheral blood T-cells of these patients.[40] The group of Fontenot has focused on HLA-DP2–expressing chronic beryllium disease patients. They first found that the involved antigens were Be-modified chemokine-derived peptides. Then they discovered that these Be-modified self-peptides were derived from C-C motif ligand 4 (CCL4) and CCL3.[41] Given these interactions between genetic factors and exposure future studies should consider including information on genetic susceptibility, such as HLA typing,

The definition of sarcoidosis used in clinical practice complicates studying its etiology. The use of criteria such as “the exclusion of alternative causes of granulomatous disease”[8] inevitably introduces a selection bias. Therefore, Scadding proposed to limit the definition of sarcoidosis to its essential feature—i.e., the presence of non-necrotizing epithelioid granulomas.[24]

Next, based on the unknown time relation between exposure and disease onset in sarcoidosis, studies should consider using an exposure assessment that includes a complete occupational and environmental history, with a timeline that is as detailed as possible, complemented with environmental measurements (of dust or microbial content) when possible. Additionally, “markers” of exposure—for example using elemental analysis on tissue/BAL for mineral particles or proteomics—can add valuable information. Given the compartmentalization of the pulmonary immune response in sarcoidosis,

histological material such as lymph node tissue or BAL fluid should be preferred over blood.[42]

Immunological testing such as LPT—with metals, silica, microbial antigens or self-antigens—might add further information as it bridges the gap between exposure and sensitization/disease. Nevertheless, the LPT is a technically challenging assay.

When studying the relationship between exposure and sarcoidosis phenotypes, a standardized work-up to assess organ involvement and other clinical features is crucial to avoid bias. As Judson[27] has proposed, descriptions of sarcoidosis phenotypes should be as elaborate as possible and include organ involvement,[43] a longitudinal follow-up of the disease course,[44] and response to treatment.[27]

Field investigations of the home and work environment of individual cases of sarcoidosis, and of case clusters, may be useful. Newman *et al* have proposed to use a "sentinel event" outbreak investigative approach similar to that used in seeking the underlying causes of other granulomatous conditions such as hypersensitivity pneumonitis and infectious granulomatous disorders.[26,34]

In summary, future studies should try to combine a standardized job and exposure histories, "markers" of exposure, immunological testing, genetic information, and detailed descriptions of disease phenotypes. Additionally, given the many sources of complexity, triangulating results from studies with diverse types of designs should be considered.

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Chapter 2 —
Old hazards in new places: Silicosis in artificial stone workers

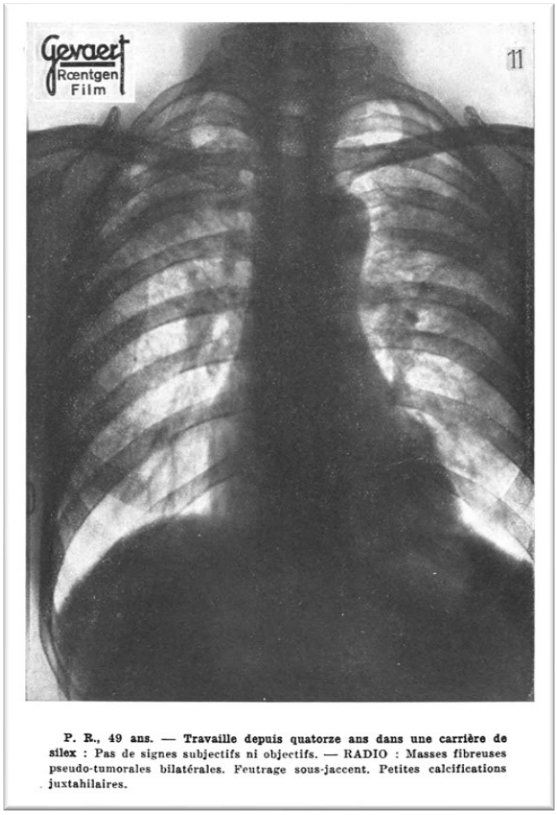

Figure 1—Because of the 1930 ILO Johannesburg Conference on Silicosis, silicosis became internationally recognized as an occupational disease. As there was barely anything known on the situation in Belgium, the labour inspection did, in 1935, a study to assess if silicosis also existed in Belgium ("La silicose existe-t-elle en Belgique?"). The answer was yes. This chest X-rays shows progressive massive fibrosis in a 49-year-old man having worked for 14 years at a silex quarry. Silex contains between 90 and 95% quartz. The caption mentions that he had "no subjective symptoms, nor objective signs" *[From: Langelez A. (1937), Enquête Organisée Par Le Service Médical Du Travail Au Sujet de La Silicose—Industries Autres Que Les Mines]*[1]

2.1. Introduction

"If It's Silica, It's Not Just Dust"

—Campaign to end silicosis, US Department of Labor, Occupational Safety and Health Administration (1996)

2.1.1. Background

Silicosis is a progressive and incurable lung disease, caused by long-term inhalation of respirable crystalline silica.[2] Silica is the most abundant mineral in the earth crust and its most hazardous form—crystalline silica—is present at varying concentrations in rocks such as sandstone, granite, slate and sand, but also in man-made materials like concrete and refractory bricks. However, as we have tragically learned from asbestos, it is not because it is a naturally occurring mineral that it is innocuous. Especially the very fine particles (smaller than 0.01 mm or 10 µm), generated by high-speed mechanical processes such as drilling, cutting, grinding, crushing, hammering or sandblasting, are most hazardous, because these particles are able to reach the alveoli. Mechanical processing of silica also alters particle surface activity, which probably makes the particles more hazardous.[3,4]

The disease can be classified into chronic, accelerated and acute silicosis. Chronic and accelerated silicosis are pathologically similar and are distinguished mainly by their time course. Chronic silicosis typically appears 10 or more years after initial exposure. Accelerated silicosis can occur within 2 years of onset.[5]

After long-term exposure to silica, small fibrotic nodules form in the lungs and lymph nodes that are, initially, not detectable through chest imaging.[6] When the disease progresses, the nodules become larger and visible on a high-resolution chest CT scan (figure 2B) and eventually on a chest X-ray. In some cases, the silicotic nodules merge into larger lesions that disrupt normal lung architecture, leading to a diagnosis of "progressive massive

fibrosis" (figure 2C). Acute silicosis is a rapidly occurring form of silicosis that occurs after very intense exposure. Nowadays, acute silicosis is rare.

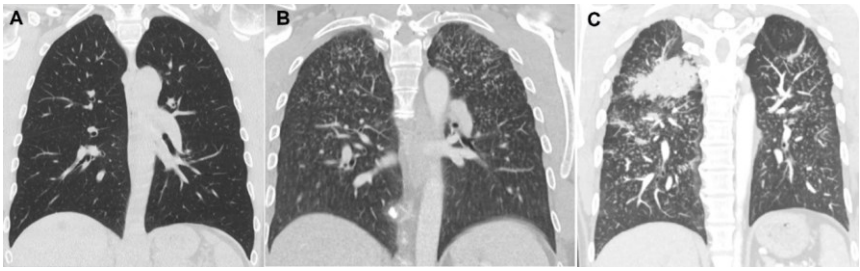

Figure 2—(A) Chest CT scan of a patient with normal lungs; (B) a patient with simple chronic silicosis; (C) a patient with progressive massive fibrosis [source: UZ Leuven patients].

Chronic and accelerated silicosis usually only give symptoms—such as chronic cough and shortness of breath—when the disease is already advanced. When respiratory symptoms have appeared, usually a lot of damage has already been done to the lungs. As dust accumulates in the lungs, the disease can progress after the exposure has stopped. At present there is no known treatment that will arrest the progression of the disease. Some workers may eventually need a lung transplant. Of note, the first patient who underwent a lung transplantation in Belgium in 1968 was a sandblaster with silicosis.[7,8]

Silicosis is not the only effect of silica exposure on workers' health. Respirable crystalline silica is associated with a range of other diseases: lung cancer (silica is an International Agency for Research on Cancer group 1 carcinogen), chronic obstructive pulmonary disease (COPD) or chronic bronchitis, an increased risk of tuberculosis, chronic sinusitis, chronic renal failure, sarcoidosis and several autoimmune disorders, such as systemic sclerosis, rheumatoid arthritis, dermatomyositis, polymyositis, systemic lupus erythematosus.[2,9,10]

Silicosis has never disappeared

In theory, silicosis is a perfectly preventable disease. However, it is still a global health problem, mainly in low- and middle-income countries. In the United Stated, Australia and Europe, the occurrence of silicosis has been declining in recent decades, due to improved prevention but to a large extent also because many hazardous industries, such as mining, were closed down or have moved to the global south (see Figure 3).

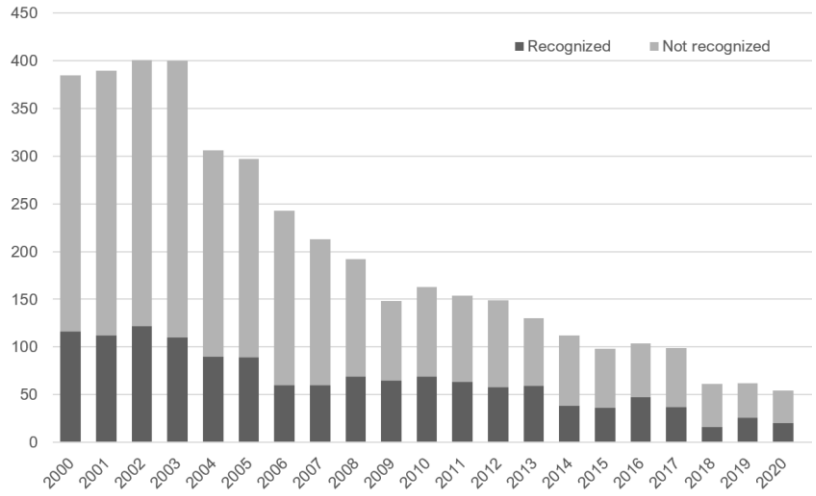

Figure 3—Number of applications for recognition of silicosis as an occupational disease in Belgium at the Federal Agency for Occupational Risks (FEDRIS) per year between 2000 and 2020. Both recognized and unrecognized cases are shown [source: Annual Statistical Reports, FEDRIS 2000-2020].

This made many in Europe think that silicosis was a disease ‘of the past’ and no longer needed attention. However, silicosis has never disappeared. It is estimated that in the EU 5 million workers are potentially exposed to respirable crystalline silica.[11] Workers in quarrying, mining, stonemasonry, building industry, road works, sandblasting, ceramics and foundries are most at risk.

Moreover, silicosis has re-emerged in new production processes or industries. One of the worst recent outbreaks occurred in Turkey in workers

sandblasting denim jeans to give them a 'worn-out' look.[12] Sandblasting was done mostly by young men in unregistered workplaces without any protection, leading to high exposures to fine silica dust and extremely high rates of silicosis, many leading to death. These findings have led to a Turkish ban on the process in 2009, after which the production—and the accompanying working conditions—moved to other countries such as China, Bangladesh, India and Pakistan.[13]

Re-emergence of silicosis in artificial stone workers

In recent years, outbreaks of silicosis in artificial stone workers have been reported around the globe.[14,15] Compared to most natural stones, artificial stones consist of a very high percentage of crystalline silica (70-95% quartz or cristobalite) bound together with synthetic resins. They are increasingly used to make kitchen or bathroom countertops. For the workers who process the stones, the risk of silicosis is particularly high, because the grinding and cutting of these stones generates high concentrations of respirable particles of crystalline silica.

Most silica-based artificial stone are produced using the "Bretonstone process". The Italian company Breton developed and patented this manufacturing process which is now used by manufacturers worldwide, such as Caesarstone, Cambria, Compac, Cosentino, Diresco, DuPont, Hyundai L&C, LG Hausys, Pokarna, Santa Margherita, Technistone and Vicostone. There are over 60 plants worldwide that now use the Breton technology and produce more than 20 million m² of artificial stone per year.[16]

In 2010, the first 3 artificial stone workers with silicosis were reported in Oviedo, Spain.[17] Other locations in Spain followed.[18,19] By 2016, at the University Hospital of Cádiz, 95 workers with silicosis had been reported.[20,21]

In Australia after 1 worker with silicosis was detected, a group of pulmonologists actively searched their medical records and found 7 more cases. Later, in a larger campaign in a number of companies in which 799 employees were screened over a number of months, 98 cases of silicosis were found.[22-25] Moreover, 15 of these men were diagnosed with progressive

massive fibrosis. In many reports the average age of the affected workers is around 40 years, with the disease having developed after only 10 to 15 years of work.

Artificial stone workers with silicosis have also been reported in Israel[9,26] and Italy.[27,28] In an Israeli case series, autoimmune disorders were found in 9 out of 40 artificial stone workers with silicosis.[9] Also, cases series described in the US and Australia included workers with autoimmune disorders.[29,30]

Studies have shown that artificial stone workers are exposed to silica concentrations far above the legal limit values. In one study[31] it was shown that dry grinding of artificial stone generated respirable crystalline silica concentrations of 44 mg/m³, wet grinding 5 mg/m³ and wet grinding with local extraction 0.6 mg/m³ (the Belgian limit value for quartz is 0.1 mg/m³ on an 8-hour time weighted average). The labour inspection of Queensland (Australia) audited 138 companies known to use artificial stone and issued 552 notices related to inappropriate prevention and absence of health surveillance for workers.[25] Queensland's minister of Industrial Relations prohibited unprotected dry cutting of the artificial stones on 18th September 2018.

Until now, we do not know the full extent of the problem and, we are possibly only seeing the tip of an iceberg. The market of artificial stones for kitchen countertops has been booming since 2000. Many customers prefer these stones as they are available in diverse colours and patterns and are indistinguishable from natural stone—but cheaper.

Many workers in the artificial stone industry have been exposed to hazardous concentrations of silica for years without appropriate protection. Only when workers started to have symptoms, did the problem become visible. Prevention has been failing at numerous levels. The manufacturers have a responsibility as initially production of the silica-containing artificial stone was started without risk assessment before marketing and without

providing adequate information to workers and small stonemason companies machining the stones, leading to insufficient preventive measures.[1]

The actors responsible for prevention at the workplace—such as occupational health services and labour inspection—have been unaware of these working conditions. Consequently, in many instances, no health surveillance was organized for the workers—even in countries where there is a legal obligation of health surveillance in silica-exposed workers.

2.1.2. Aims and outline of the chapter

The aim of this chapter is to describe Belgian cases of artificial stone-associated silicosis. Via the clinic for occupational and environmental medicine in the University Hospitals Leuven, we initially confirmed silicosis in two referred workers from a 2-man company in the province of Antwerp, Belgium. These cases were published in Occupational and Environmental Medicine and were the first reported in Belgium (see 2.2).

Next, in 2020, we five workers from a small company that employed 10 persons to produce artificial silica-based kerbstones were referred to our clinic. Four of these 5 workers had definite silicosis: the youngest being only 38 years old. In this chapter, I will provide a detailed description of this outbreak, including workplace exposure information and clinical data. I will discuss how the outbreak was initially missed, and how this could be prevented (see 2.3).

[1] A judgment of the Criminal Court of Bilbao (Spain), confirmed by the Provincial Court of Biscay in 2017 determined that Cosentino, a Spanish manufacturer of artificial stones, was co-responsible for the generation of the disease of several workers in the smaller workshops, because during many years it did not inform about any risk derived from handling their product.

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2.2. Artificial stone-associated silicosis in Belgium [Case report]

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We read with interest the article by Hoy *et al* reporting silicosis in seven Australian workers fabricating artificial stone countertops,[1] and the letter by Barber *et al* who could not identify cases in the UK.[2] We describe two cases of silicosis in workers employed in a two-man company producing and installing artificial stone kitchen countertops.

The first worker made the countertops by mixing epoxy resin, gravel, sand, pigment, and quartz flour (99.4% quartz; 10% of the particles <5µm, 50% <30µm, according to the technical data sheet). Approximately 200 kg of quartz flour were used weekly. After curing, the countertops were dry cut, ground and polished. No dust measurements were made. The worker occasionally used a dust mask. He underwent periodic occupational health examination, however, without chest X-ray. In earlier jobs, he had had no silica exposure. In 2015, at age 41, after 9.5 years of employment, he complained of dry cough without dyspnea. He had never smoked. Chest auscultation and pulmonary function tests (PFT) were normal—total lung capacity (TLC) was 6.1L (95%pred), diffusing capacity of the lung for carbon monoxide (D_{LCO}) was 94%pred. High-resolution computed

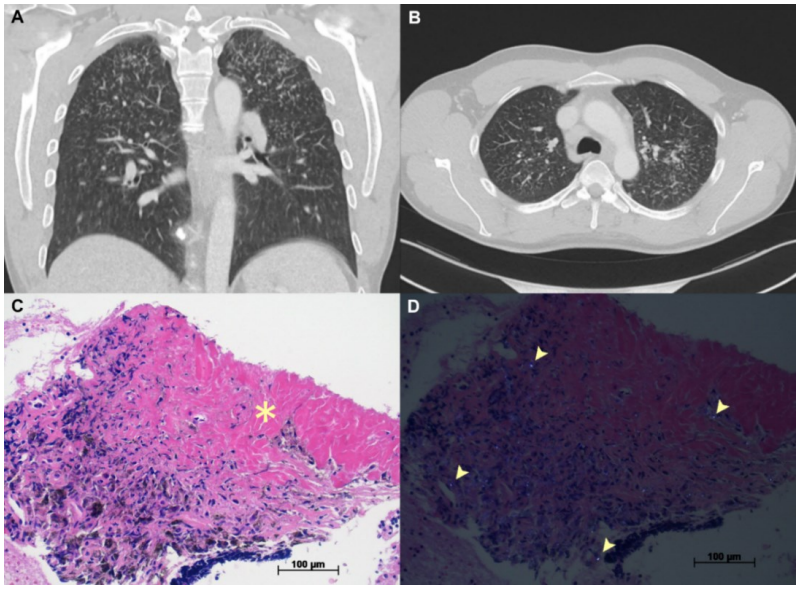
tomography (HRCT) showed bilateral diffuse micronodules with an upper lobe and posterior predominance and enlarged hilar and mediastinal lymph nodes (figure 1). Broncho-alveolar lavage revealed 38% lymphocytes (normal <20%). Mediastinal lymph node histopathology demonstrated silicotic nodules and birefringent particles (figure 1). After silicosis was diagnosed, he quit his job. Two years later, his cough had disappeared and PFT were unchanged.

The second worker installed the countertops at customers' homes, which involved stone grinding. Occasionally, he helped the first worker at the workshop. In his previous job, he had made concrete statues for 15 years. In 2012, at age 46, after 9 years of employment in the countertop company, this ex-smoker (<10 pack-years) started to have exertional dyspnea, cough and nocturnal wheezing. Chest auscultation and X-ray were considered normal. PFT were unremarkable (TLC 6.9L, 97%pred) except for a mildly decreased D_{LCO} (77.5%pred). Histamine bronchial challenge was positive (PD_{20}=0.25mg). Asthma was diagnosed, and inhaled corticosteroids/long-acting beta-agonist initially improved symptoms. Because of his occupational exposure, HRCT was performed 3 years later and showed bilateral centrilobular and subpleural micronodules with an upper lobe and posterior predominance and slightly enlarged hilar and mediastinal lymph nodes, some containing punctiform calcifications—compatible with silicosis. Five years after initial presentation and continued—but reduced—exposure, PFT remained unchanged.

Similarly to the cases described by Hoy *et al,*[1] the first worker developed respiratory symptoms after <10 years of making and processing high-silica content artificial stone. The second worker had silica exposure for nearly 25 years in his current and previous job, possibly both contributing to his lung disease. Outbreaks of artificial stone-associated silicosis have been described in Israel, Italy and Spain.[3–6] To our knowledge, no cases have been published in Belgium nor in its surrounding countries (UK, France, Germany, The Netherlands). Considering the increasing popularity of artificial stone

countertops, we expect more cases to be diagnosed. Industry-specific preventive strategies are needed, especially among small enterprises.

Figure 1—*First worker: (A, B) High-resolution computed tomography showing bilateral diffuse micronodules with an upper lobe and posterior predominance. (C) Light microscopic image of a mediastinal lymph node obtained by endobronchial ultrasound-guided fine-needle aspiration showing dense collagenous tissue containing fibroblasts, compatible with a silicotic nodule (*), adjacent to an area of dust accumulation. No granulomas were observed (hematoxylin-eosin; x200). (D) Polarized light microscopy demonstrating numerous birefringent particles (arrowheads) (x200).*



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2.3. Outbreak of silicosis in workers producing silica-based artificial kerbstones [Research article]

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Abstract

Background. Silicosis has recently re-emerged around the globe among workers producing, processing and/or installing artificial stone kitchen/bathroom countertops, especially in economically advanced countries. We report on an unusual outbreak in a plant producing novel applications of silica-based composites, which occurred in spite of periodic health surveillance.

Methods. Five workers from the same company were referred to our specialized clinic for occupational disease. Using past spirometry data from periodic health surveillance, we calculated individual yearly declines in FEV_1 and FVC (and 95%-confidence intervals, CI) using robust multivariable linear regressions including adjustment for smoking cessation. Respirable quartz was measured in the workplace after the first case had been diagnosed.

Findings. The five men (38 to 59 years) had been employed for 8 to 30 years at a Belgian company where about ten workers made silica-based artificial kerbstones for hygienic wall protection. All were former smokers. We diagnosed enlarged mediastinal/hilar lymph nodes without radiological lung involvement in one worker, simple silicosis in two workers (one also with emphysema), and progressive massive fibrosis in two workers. Annual spirometries—but no chest X-rays—had been performed since 8 to 10 years prior to diagnosis. The four men with silicosis proved to have undergone excessive declines in FEV_1 (between 98 and 221 mL/year) and FVC (17 to 220 mL/year). High respirable quartz concentrations (>0·1 mg/m³) were measured during various operations, especially during dry finishing of the cured kerbstones (1·080 mg/m³). No personal respiratory protection was used.

Interpretation. The discovery of rapidly progressive serious lung disease in workers producing silica-based artificial kerbstones shows that the hazards of artificial stone production/processing reach beyond the kitchen/bathroom countertop industry. Increasing awareness, improving prevention and establishing workers' health surveillance programmes—or improving the quality of existing programmes—are of paramount importance.

Research in context

Evidence before this study

Outbreaks of silicosis have been reported around the globe among workers producing, processing and/or installing artificial stone kitchen/bathroom countertops—even in young workers with relatively short duration of exposure.

Added value of this study

An outbreak of silicosis occurred in a company producing silica-based artificial kerbstones for hygienic wall protection, a novel application of silica-based composites. The outbreak is unusual as it occurred despite (legally obligatory) periodical workers' health surveillance. Annual spirometries had been performed since at least 8 to 10 years—but no chest X-rays. However, although the workers had undergone excessive lung function declines years before being diagnosed, this had not led to preventive actions. Therefore, the present data (unfortunately) reminds us of what happens to the lung function of workers exposed to continued high levels of crystalline silica. We show the wide range of clinical, radiological and histological presentations of silica-induced lung disease.

Implications of all the available evidence

Patients/workers can have high levels of silica exposure in unexpected industries, even in economically advanced countries. The present outbreak is the first to show that the hazards of artificial stone production/processing reach beyond the kitchen/bathroom countertop industry. If awareness of workers, companies, physicians and authorities is lacking, hazardous working conditions can persist for years, and are only discovered when irreversible damage to workers' health has occurred. Improving prevention and establishing workers' health surveillance programmes—or improving the quality of existing programmes—are crucial.

Introduction

In recent years, outbreaks of silicosis in artificial stone workers have been reported around the globe.[1,2] Artificial stones consist of a composite material of crystalline silica (70–95% quartz or cristobalite) bound with synthetic resins, and are increasingly used to make kitchen or bathroom countertops. For the workers who process the stones, the risk of silicosis is particularly high because the grinding and cutting of these stones generates high concentrations of respirable crystalline silica.[3] Artificial stone-associated silicosis has been described after unusually short exposures, thus affecting even young workers.[2]

Several reports have shown that if awareness of workers, companies, physicians and authorities is lacking, hazardous working conditions can persist for years, and are only discovered after irreversible damage to workers' health has occurred.[4] In Queensland Australia, a proactive screening campaign (using questionnaire, spirometry and chest X-ray) of 1,053 artificial stone workers—who had never received health surveillance—found 229 cases of silicosis, including 32 with progressive massive fibrosis.[5] Also in other economically developed countries, including Belgium, artificial stone-associated silicosis is probably an underestimated and underdetected problem.[6]

We report on five workers—of whom four had developed definite silicosis—referred in 2020 to a clinic for occupational and environmental medicine in an academic hospital in Belgium. Unlike previously reported cases in the kitchen and bathroom countertop industry, they worked at a small company producing silica-based artificial kerbstones for hygienic wall protection mainly to be used in the food industry. Beyond describing the disease, we tried to discover how such outbreak had occurred despite the legal obligation for companies to organize annual health surveillance for silica-exposed workers by an occupational health service.

Methods

The study group consisted of five men working at a company producing silica-based artificial kerbstones for hygienic wall protection in Belgium. Because of respiratory symptoms, they had all consulted a pneumologist (PG, VN), who referred them to the clinic for occupational and environmental medicine at the University Hospitals Leuven (Belgium) in 2020.

Clinical data at the time of diagnosis—including history, clinical examination, lung function, and chest computed tomography (CT)—were extracted from the electronic medical records. Available histological material was retrieved for reanalysis by a lung pathologist (BW). Slides made from formalin-fixed paraffin-embedded material were assessed for the presence of granulomas, silicotic nodules, black pigment, and birefringent particles under polarized light.

In Belgium, all salaried workers are affiliated with an occupational health service through their employer, regardless of the size of the company. So, we contacted the occupational physician to obtain past spirometry and exposure data. Spirometry data had been obtained since 8 to 10 years prior to diagnosis. Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were expressed in absolute values and as a percentage of the Global Lung Function Initiative predicted values.[7] Longitudinal evaluation of the spirometries was done by calculating, for each worker, the yearly decline of FEV_1 and FVC (and 95% confidence intervals, CI)[8] by fitting a robust multivariable linear regression including adjustment for smoking cessation—which has been shown to be potentially followed by a temporary improvement in lung function.[9] Because no spirometries were available from before or at the start of employment, comparisons with “baseline” values could not be made.[8]

Stationary sampling (Gilian GilAir Plus pumps, 2·2 L/min for 4-hour periods) of respirable dust (using a SKC cyclone with 25 mm plastic cassette) in relevant workplace locations was organized by the occupational health service in 2019, after the first case had been diagnosed. Respirable dust was quantified by gravimetric analysis (using the UK Health and Safety Executive

Method for the Determination of Hazardous Substances, MDHS 14/4) and respirable quartz was quantified by Fourier-transform infrared spectroscopy (using the National Institute for Occupational Safety and Health method, NIOSH 7602). Volatile organic compounds were also collected (pumps running at 0.1 L/min) using activated charcoal tubes (SKC 226-09) and analysed with gas chromatography–mass spectrometry.

All patients gave their informed consent for this publication, and approval was obtained from the Ethics Committee Research UZ/KU Leuven (S65659).

Results

The five referred men were between 38 and 59 years old when first diagnosed with lung disease (Figure 1 and supplementary material, Table S1 and Figure S1). Their respiratory symptoms—including exertional dyspnoea in all cases—had started after working for 7 to 27 years in the same company where about ten workers produced silica-based artificial kerbstones for hygienic wall protection, mainly to be used in the food industry. All men were former smokers with 5 to 40 pack-years of smoking history (Figure 1).

In all cases, chest high-resolution CTs had been ordered by the referring pneumologist (Figure 1; Table S1). All had enlarged mediastinal and hilar lymph nodes (containing small calcifications in three workers). Four had centrilobular/perilymphatic micronodular patterns, predominantly in the upper lobes. Of these four workers, one also had extensive emphysema and two had bilateral large mass-like conglomerates, typical for progressive massive fibrosis (PMF). Biopsies of lung and/or mediastinal lymph nodes had been obtained in the four workers with silicosis (Figure 2). Histological findings ranged from early reactions—such as dust-laden macrophages in a mediastinal lymph node (worker 4; Figure 2B) and granulomas containing dust-laden macrophages in the bronchial wall (worker 5; Figure 2D)—to typical chronic silicotic nodules in lymph nodes (workers 3 and 5; Figure 2A and 2C) or lung (worker 2). Birefringent particles were found in the histological material of three workers (Figure 2, panels E to H). Cultures for

mycobacteria, bacteria and fungi, PCR for mycobacteria and/or Mantoux test were negative in all cases (when performed). Serum angiotensin-converting enzyme (ACE) was elevated in two workers (92 and 105 U/L; normal 20–70)—but not tested in the other workers (Table S1).

We contacted the occupational physician to obtain relevant exposure and health data. No periodic chest X-rays had been done for health surveillance, but spirometries had been done annually. Based on data obtained since 8 to 10 years prior to diagnosis (Figure 1), the FEV_1 of the four workers with silicosis had been declining between 98 (95%CI 79 – 116) and 221 mL/year (95%CI 214 – 228) before diagnosis (Figure 1), i.e. considerably faster than the normal annual decline in FEV_1 of around 30 mL in a non-smoker.[10] FVC had declined between 17 (95%CI -149 – 183) and 220 mL/year (95%CI 167 – 274). Three workers had reached an FEV_1 below the lower limit of normal (LLN) several years before diagnosis.[7] Two workers had an FVC below the LLN. In three smokers, smoking cessation had been followed by a temporary improvement of FEV_1 between 250 and 562 mL, and of FVC between 98 and 492 mL (Figure 1).

The production process of the kerbstones consisted of various tasks that were performed alternately by the workers (see Table S1). The tasks and the associated exposure levels are described in the box. High respirable quartz concentrations (above the Belgian workplace 8-hour time-weighted average limit value of 0·1 mg/m³) were measured during the filling of moulds with the mineral-resin mixture (0·167 mg/m³), during cleaning of these moulds (0·329 mg/m³), and especially during dry finishing of the cured kerbstones with an angle grinder (1·080 mg/m³). Styrene concentrations were highest during the filling of the moulds (46 mg/m³) but did not exceed the workplace limit value (108 mg/m³). Personal respiratory protection was only introduced at the workplace after the first worker was diagnosed with silicosis and was rarely worn. All workers indicated that they were previously not aware of the hazards of silica dust.

Unfortunately, we had no access to information of other former or current employees of the company.

***Figure 1*—Data of five workers from a company producing silica-based artificial kerbstones**: surveillance spirometries from the years preceding diagnosis, chest CTs and pulmonary function tests at diagnosis

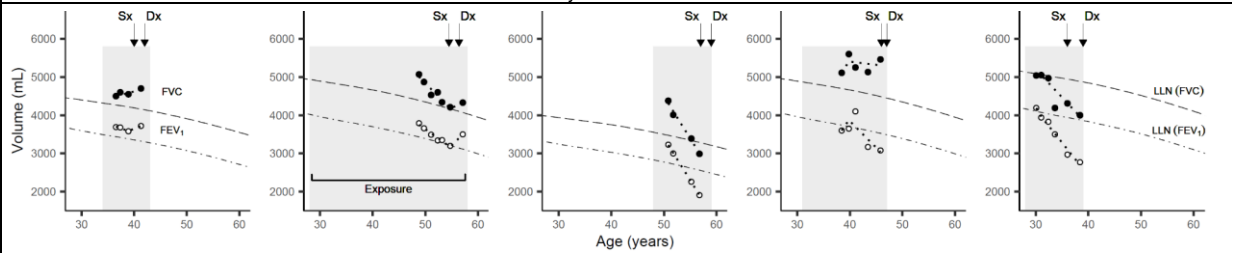
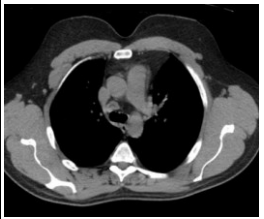
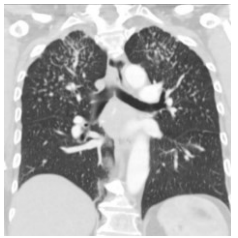
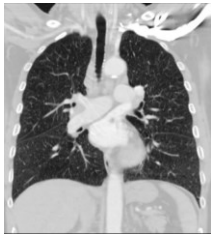
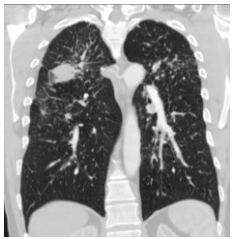
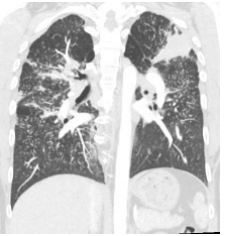
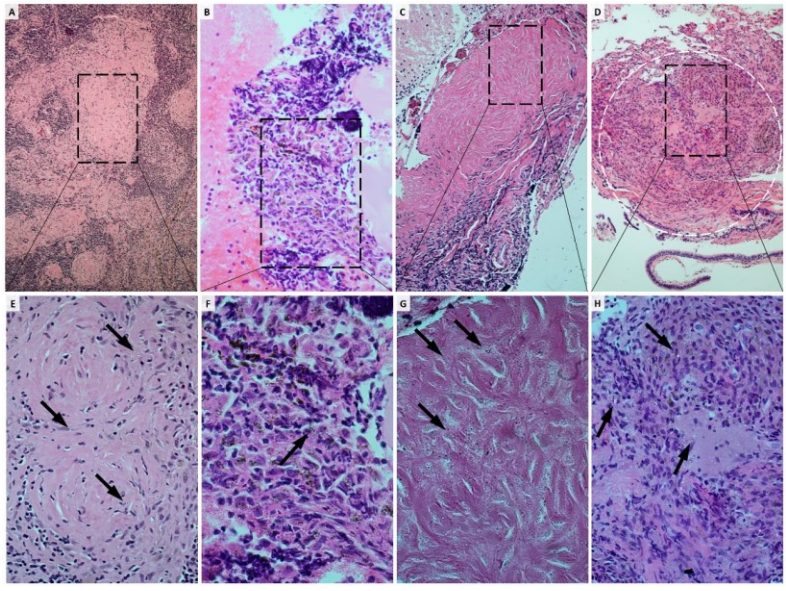
		Worker 1	Worker 2	Worker 3	Worker 4	Worker 5
Diagnosis		Enlarged lymph nodes	Simple silicosis	Simple silicosis and emphysema	Progressive massive fibrosis	Progressive massive fibrosis
Age at diagnosis		42 y	56 y	59 y	47 y	38 y
Smoking history		9 PY; stopped 3 y before dx	40 PY; stopped 1 y before dx	35 PY; stopped same year as dx	5 PY; stopped 7 y before dx	12 PY; stopped 8 y before dx
Spirometries before diagnosis						
Decline before diagnosis	FVC	-14 mL/year* (95%CI -218 – 190)	141 mL/year (95%CI 111 – 170)	220 mL/year (95%CI 167 – 274)	17 mL/year (95%CI -149 – 183)	147 mL/year (95%CI 121 – 173)
	FEV_1	49 mL/year (95%CI -21 – 118)	98 mL/year (95%CI 79 – 116)	221 mL/year (95%CI 214 – 228)	139 mL/year (95%CI -55 – 333)	172 mL/year (95%CI 128 – 217)

Figure 1 (continuation)

Chest CT at diagnosis						
Lung function at diagnosis	FVC	4410 mL (91%)	4470 mL (92%)	3800 mL (98%)	5580 mL (108%)	4290 mL (70%)
	FEV_1	3490 mL (88%)	3390 mL (89%)	1910 mL (62%)	3110 mL (74%)	3000 mL (61%)
	FEV_1/ FVC	0·79	0·76	0·50	0·56	0·70
	TLC	5860 mL (82%)	6720 mL (87%)	6870 mL (106%)	7710 mL (99%)	7280 mL (91%)
	D_{LCO}	9·08 mmol/min/Kpa (82%)	9·40 mmol/min/Kpa (87%)	2·23 mmol/min/Kpa (25%)	7·67 mmol/min/Kpa (66%)	7·43 mmol/min/Kpa (62%)

*Sx: start of symptoms; Dx: diagnosis; FVC (-●-): forced vital capacity; FEV_1 (-O-): forced expiratory volume in one second; Gray area: time period of employment at the company; Dashed lines represent the Lower Limit of Normal (LLN) for FVC and FEV_1 according to Global Lung Function Initiative (GLI); Dotted lines through the spirometric values represent robust linear regression lines including adjustment for smoking cessation (which resulted in improvements of FEV_1 between 250 and 562 mL and of FVC between 98 and 492 mL in workers 1, 2 and 4). The yearly decline of FVC and FEV_1 before diagnosis is represented by the regression coefficient (and 95% confidence interval, CI) of the robust multivariable linear regression analysis. * Worker 1 had a non-significant increase in FVC of 14 mL/y—and thus a "negative decline". PY: pack-years of cigarette smoking history. Lung function results at diagnosis are expressed in % predicted (GLI) in brackets. TLC: total lung capacity. D_{LCO}: diffusing capacity of the lung for carbon monoxide.*

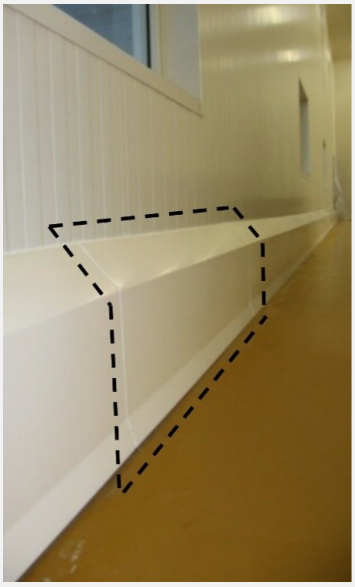
***Figure 2*—Histology of three workers with silicosis showing early reactions as well as typical chronic silicotic nodules.** Panels A to D: light microscopy (hematoxylin and eosin stain); Panels E to H represent the areas within the dashed lines in panels A to D at higher magnification and under polarized light. (A & E) Worker 3, lymph node 7 obtained by mediastinoscopy, showing multiple silicotic nodules (A) which include birefringent crystals under polarized light (arrows in E); (B & F) Worker 4, lymph node 7 obtained by endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), showing black pigment-laden histiocytes (B) and birefringent crystals (F; arrow) but no silicotic nodules; (C & G) Worker 5, lymph node 7 obtained by EBUS-TBNA, showing silicotic nodules (C), black pigment-laden histiocytes and birefringent crystals (G; arrows); (D & H) Also worker 5, bronchial biopsy (right upper lobe) showing a granuloma in the bronchial wall (D; white dashed circle) containing black pigment and birefringent crystals (H; arrows).



Box—Tasks performed by the workers and associated exposure levels

The production process of the silica-based artificial kerbstones consists of the following tasks:

- ***Mixing*.** First, a mixture is made of approximately 50% quartz powder, 22% quartz sand, 11% dolomite (calcium magnesium carbonate), polyester resin (dissolved in 33% styrene) and additives. Previously, the mixture was made manually in a concrete mixer. However, during the last eight years, mixing has been done in a closed system. Frequently, problems of wearing and breaking of rubber hoses had resulted in the spreading of quartz powder throughout the workshop, which then had to be cleaned with shovel and brush.
- ***Filling of the mould.*** The mineral-resin mixture is then poured into a stainless-steel mould. A hardener (liquid methylethylketone-peroxide) and an accelerator [liquid cobalt(II) 2-ethylhexanoate] are added to initiate the polymerisation of the polyester resin.
- ***Curing.*** During curing, the styrene—in which the resin is dissolved—further evaporates under an exhaust ventilation.
- ***Finishing*.** After curing, the kerbstone is removed from the mould, and is finished by dry grinding the edges (with a handheld angle grinder) and drilling. This task has only been done under an exhaust ventilation since 2020.
- ***Cleaning of the mould*.** Next, the empty moulds are cleaned with a scraper—to remove remaining pieces of composite material—and compressed air.
- ***Packing.*** The finalized kerbstones are packed before they leave the factory.



Figure—Finished and installed silica-based artificial kerbstones. Dashed line indicates one unit (for illustration)

- ***Workplace cleaning*** is generally done by dry sweeping or with compressed air—causing resuspension of settled dust.

Figure illustrates one of the kerbstone types as installed at another company.

Stationary sampling of respirable dust, respirable quartz, and styrene for four tasks (in 2019) showed the following results:

Task	Respirable dust (mg/m³)	Respirable quartz (mg/m³)	Styrene (mg/m³)
Limit value§	*3·00*	*0·100*	*108*
Mould filling	0·80	0·167	46·2 *
Finishing stone	3·70	1·080	0·741
Mould cleaning	3·40	0·329	12·7
Packing stones	0·11	0·033	0·144

§ The indicated limit values are the Belgian 8-hour time weighted average workplace limit values.
** Calibration range was exceeded*

Discussion

We report on five men working at a company producing silica-based artificial kerbstones, of whom four had developed definite silicosis, the youngest being only 38 years old with merely ten years at the company. Hitherto, all cases of artificial stone-related silicosis described in the literature had worked in the production, processing and/or installation of kitchen or bathroom countertops.[1] The present outbreak demonstrates that the risk of silica-based artificial stones exists in other workplaces and with more applications than we had assumed.

Exposure to respirable crystalline silica at these workers' company exceeded the Belgian/European threshold limit value (8-hour time-weighted average) of 0·1 mg/m³ during the filling of the moulds with the mineral-resin mixture, during cleaning of the moulds and especially—by tenfold—during dry finishing of the stones (1·080 mg/m³). Workplace measurements had been done only *after* the first case had been diagnosed. Presumably, exposure

levels had been even higher, as the workers described worse working conditions in the past, including intermittent peak exposures (for example, during cleaning of spilled quartz powder). The lack of earlier measurements has likely contributed to the occurrence of this outbreak.

Recent reports on silicosis in artificial stone workers have shown unusually severe lung disease, even in young workers within relatively short durations of exposure.[1] Two of our cases had developed PMF, which has been previously demonstrated in 8·7 to 21% of the artificial stone workers with silicosis.[11–13] One worker—with a smoking history of 35 packyears—had combined simple silicosis and emphysema. Higher rates of emphysema have been found among silica exposed workers than in the general population, even when adjusting for smoking history—especially in workers with PMF but also in those with simple silicosis.[14] One worker had dyspnoea and enlarged hilar and mediastinal lymph nodes on chest CT but no detectable parenchymal abnormalities. Enlarged hilar and mediastinal lymph nodes—found in all five workers—have been shown to precede parenchymal silicosis.[15,16] Serum ACE was elevated in two workers, as has recently been reported in workers with artificial stone silicosis.[17,18]

The various histological findings in our cases illustrate well the various stages of the lung and lymph node lesions induced by silica exposure. Textbook descriptions of silicosis generally focus on the hyaline silicotic nodule, because pathological studies have been primarily based on observations of autopsy lungs from patients with well-established silicosis.[19] The silicotic nodule is actually the end-stage of a dynamic silica-induced pathologic process.[19,20] Early silicotic lesions appear as cellular aggregates of dust-laden macrophages which may be difficult to differentiate from sarcoid-like granulomas. Only in later stages, do these lesions evolve to typical silicotic nodules consisting of concentric fibrosis in a relatively acellular centre and peripheral dust-laden macrophages.[19,20]

A striking feature of this outbreak is that it occurred in spite of periodical health surveillance. In contrast to the context in which previous outbreaks of artificial stone-associated silicosis were described—such as in Queensland,

Australia—occupational health in Belgium is traditionally heavily focused on health surveillance by occupational physicians of all salaried workers, even in small plants.[21] The legally prescribed health surveillance of workers exposed to silica includes an annual spirometry and chest X-ray. However, while surveillance by spirometry is widespread, there is less compliance with the implementation of chest X-rays. Systematic radiological screening had been widely performed in the past to detect tuberculosis but was rightly abandoned for this purpose when tuberculosis became rare in Belgium.

Interestingly, even though no chest X-rays were done, our cases could have been detected years earlier, based on the periodically performed spirometries.[8] In retrospect, in the two workers with PMF, FEV_1 was already below the lower limit of normal eight years before diagnosis. Moreover, in all four workers who were eventually diagnosed with silicosis, FEV_1 had been excessively declining, at rates between 98 (95%CI 79 – 116) and 221 mL/year (95%CI 214 – 228), i.e., three to seven times faster than normal.[10]

Occupational exposure to mineral dust has been associated with accelerated lung function decline. Although epidemiological studies have also shown fast declines in the absence of radiological silicosis,[22] the rate of decline in FEV_1 and FVC has been generally correlated to the radiological severity of silicosis[23] and excessive decline is more likely in workers with chest X-rays classified as International Labour Office (ILO) categories ≥ 2, or with PMF.[23–25] For example, in active South-African gold miners, an annual loss of FEV_1 of 37 mL was noted in those without silicosis, 57 mL in those with a chest X-ray classified as ILO category 1, 100 mL in those with category 2, and 128 mL in the men with category 3. A similar pattern of loss was noted for the FVC.[26] Some studies have suggested that the loss of pulmonary function in silica-exposed workers could be attributed to emphysema—more than to the radiological category of silicosis.[25]

An (unfortunate) strength of the present data is that we were able to show excessive lung function decline in active artificial stone workers, with continued silica exposure. To our knowledge, no studies in artificial stone workers have reported spirometry data preceding the diagnosis of silicosis.

Previous studies did, however, demonstrate that workers with artificial stone-associated silicosis who were removed from exposure after diagnosis had a more rapid loss of lung function than generally expected in chronic silicosis.[27–29] For example, a Spanish study of workers with artificial stone-associated silicosis found that after a median follow-up of 4 years—without continued exposure—FEV_1 had declined on average 83·4 mL/year, with 25% of the patients declining ≥133 mL/year.[29]

Besides respirable crystalline silica, our workers were also exposed to chemicals evaporating from the mineral-resin mixture—mainly styrene but potentially also additives such as methylethylketone-peroxide (MEKPO). Obliterative bronchiolitis has been reported in workers in fiberglass-reinforced plastics industry, who were exposed to styrene and MEPKO—just like our cases—but not to silica.[30,31] Also, epidemiological studies in that industry have shown more obstructive spirometries in the workers with the highest styrene exposures.[32,33] Although styrene measurements in the artificial kerbstone plant that we describe were below the workplace limit value, an additional effect of styrene or resin additives on respiratory symptoms and/or lung function cannot be excluded.

Recent experimental studies have shown that the biological activity of quartz dust is determined mainly by the surface characteristics of the particles (and not necessarily by crystallinity *per se)*.[34] Interestingly, Pavan *et al* demonstrated that the *in vitro* toxicity of quartz particles is modified by resin residues on the surface.[35] These findings suggest that besides the high exposure levels, the modification of the surface reactivity of the quartz particles by other chemicals present in the artificial stones might contribute to the unusually rapid course and severity of artificial stone-associated silicosis.[35,36]

Improving prevention and health surveillance

Prevention at artificial stone companies should be improved. Enclosing processes, installing local exhaust and water suppression can reduce dust exposure. However, studies have shown that even a combination of local

exhaust and water suppression might not reduce concentrations of respirable crystalline silica to non-hazardous levels.[3] Therefore, Australia's National Dust Disease Taskforce has recently proposed to ban silica-based artificial stone, if enhancing prevention in the coming years proves to be ineffective.[5]

Next to primary prevention, workers exposed to respirable crystalline silica should undergo periodic health surveillance to detect early signs of dust-induced respiratory disease.[37] Health surveillance is not only aimed at secondary prevention to prevent further exposure and damage in individual workers, but also at identifying workplaces that have not been adequately protecting their workers. Finding such workplaces should lead to preventive actions.

There is an ongoing debate on what is appropriate health surveillance of workers who are/have been exposed to very high levels of silica, such as artificial stone workers.[38] Periodical chest X-rays are probably insensitive to detect beginning dust-induced lung disease, as has been shown for the earliest phases of rapidly developing artificial stone-associated silicosis.[11,39] A recent position statement from the Thoracic Society of Australia and New Zealand suggests using low-dose CT instead of plain chest X-ray, although evidence for this suggestion is currently lacking.[38] Moreover, this costly option will not be available everywhere.

Spirometry—when performed as part of workers' health surveillance—should be evaluated not only by comparing the obtained values to general population reference values[7] but also to the worker's *own* previous values.[8] The FEV_1 is the preferred measurement to assess longitudinal change, as it is decreased in both obstructive and restrictive impairment and it is less affected by technical factors than the FVC.[8] Excessive loss in FEV_1 over time can be evaluated using either a percentage decline compared to baseline values (e.g., 15% plus loss expected due to aging) or using longitudinal analysis software such as SPIROLA—developed by researchers at the US NIOSH for early identification of individuals with excessive lung function decline.[8,40] However, these methods for longitudinal evaluation of

spirometries have not been validated for the surveillance of workforces with high-level silica dust exposures and high incidence of rapidly developing silicosis. Periodic spirometry *without* imaging should, in any case, not be considered a proper health surveillance instrument, because simple silicosis—without the presence of emphysema or PMF—might, in early stages, have only limited effect on spirometric values.[41]

Because of the high levels of exposure to respirable crystalline silica and high incidence of rapidly progressive lung disease, some have recommended *active case-finding* in artificial stone workers using (once) conventional high-resolution chest CT, spirometry and D_{LCO}.[38]

In conclusion, this outbreak of silicosis demonstrates that silica-based artificial materials are made for more applications than we had assumed. Hence, efforts are needed to increase awareness among all stakeholders—employers, workers and unions, health and safety inspectors and occupational health practitioners, respiratory and other specialists—of the hazards of artificial stone production/processing beyond the kitchen or bathroom countertop industry. Also, establishing workers' health surveillance programmes—or improving the quality of existing programmes—is of paramount importance.

Contributors

SR drafted the manuscript. PG, NJ, VN, EV, SK, BW, PHMH, JAJV, WAW, JY, BN reviewed and edited the manuscript. SR, PG, NJ, VN, EV, SK, WAW, JY and BN took part in the clinical management of the patients. BW performed the histological evaluation. All authors read and approved the final manuscript.

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Competing interests

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Ethics approval

All patients gave their written and signed informed consent for this publication. Approval was obtained from the Ethics Committee Research UZ/KU Leuven (S65659).

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Supplementary material

Table S1. Data of 5 workers who had worked at the same company producing silica-based artificial kerbstones

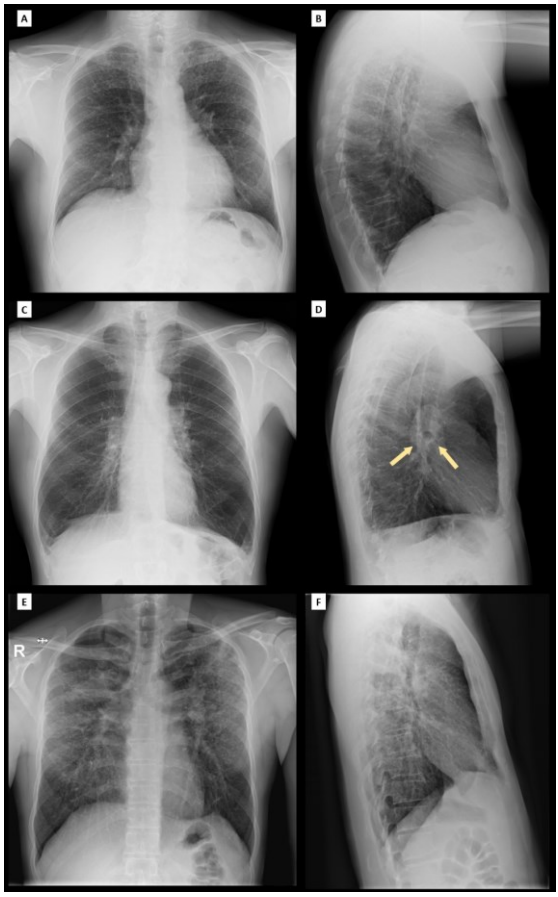
		Worker 1	Worker 2	Worker 3	Worker 4	Worker 5
Age at diagnosis		42	56	59	47	38
Symptoms		2 years before diagnosis: Dyspnoea, no cough	1 year before diagnosis: Dyspnoea, no cough, chest tightness, night sweats	2 years before diagnosis: Dyspnoea, cough, recurring bronchitis	1 year before diagnosis: Dyspnoea, no cough	3 years before diagnosis: Dyspnoea, cough, mucus production, night sweats, weight loss
Clinical examination at diagnosis		Normal breathing sounds	Normal breathing sounds	Decreased breathing sounds, discrete bilateral crackles, finger clubbing	Normal breathing sounds	Normal breathing sounds, discrete squeaks
Packyears (PY)		9 PY	40 PY	35 PY	5 PY	12 PY
Smoking cessation		3 years before diagnosis	1 year before diagnosis	Same year as diagnosis	7 years before diagnosis	8 years before diagnosis
Previous silica exposure		-	3 years brick production, 1 year asbestos cement (wet work)	-	-	-
Years of working at the company when diagnosed		8	30	11	16	10
Main tasks		Mixing/filling of moulds	Multiple tasks	Multiple tasks	Multiple tasks	Mainly finishing the kerbstones
Spirometry (before diagnosis)	FEV_1 decline [mL/year] (95%CI)*	49 (-21 – 118)	98 (79 – 116)	221 (214 – 228)	139 (-55 – 333)	172 (128 – 217)
	Improvement in FEV_1 after smoking cessation [mL]*	250 (29 – 471)	562 (444 – 681)	NA (cessation after last spirometry)	463 (-854 – 1779)	NA (cessation before first spirometry)
	FVC decline [mL/year] (95%CI)*	-14 (-218 – 190)	141 (111 – 170)	220 (167 – 274)	17 (-149 – 183)	147 (121 – 173)
	Improvement in FVC after smoking cessation [mL]*	98 (-553 – 749)	492 (323 – 661)	NA	320 (-474 – 1114)	NA
Lung function at diagnosis	FVC [mL] (% pred.)	4410 (91%)	4470 (92%)	3800 (98%)	5580 (108%)	4290 (70%)
	FEV_1 [mL] (% pred.)	3490 (88%)	3390 (89%)	1910 (62%)	3110 (74%)	3000 (61%)
	FEV_1/FVC	0·79	0·76	0·50	0·56	0·70
	TLC [mL] (% pred.)	5860 (82%)	6720 (87%)	6870 (106%)	7710 (99%)	7280 (91%)
	DL_{CO} [mmol/min/Kpa] (% pred.)	9·08 (82%)	9·40 (87%)	2·23 (25%)	7·67 (66%)	7·43 (62%)

Chest CT at diagnosis	Micronodules	-	+	+	+	+	
	PMF	-	-	-	+	+	
	Enlarged lymph nodes	+	+	+	+	+	
	Calcified lymph nodes	-	-	+	+	+	
	Emphysema	-	-	+	-	-	
Lab results at diagnosis	RF	-	-	-	-	n.d.	
	Anti-CCP	-	-	-	-	-	
	ANA	+ (homogeneous 1:160)	+ (speckled 1:80, homogeneous 1:160)	+ (speckled 1:320, cytoplasmatic 1:80)	+ (speckled nucleolar 1:80)	-	
	Anti-dsDNA	-	-	-	-	n.d.	
	CTD screen	n.d.	n.d.	+	n.d.	n.d.	
	ENA	-	-	-	-	n.d.	
	ANCA	Screen + p-ANCA - c-ANCA -	Screen + p-ANCA - c-ANCA -	Screen +; p-ANCA + 1/40; c-ANCA -; PR3 -; MPO -	-	-	
	ACE (nl. 20-70 U/L)	n.d.	92	n.d.	n.d.	105	
BAL	Lymphocytes (%)	17%	55%	n.d.	n.d.	10%	
Histology	Type	n.d.	Transbronchial biopsy	Mediastinoscopy	EBUS-TBNA	EBUS - TBNA	Bronchial biopsy
	Location	n.d.	RUL	LN 7	LN 7	LN 7	RUL
	Granulomas	n.d.	+	-	-	-	+
	Silicotic nodules	n.d.	+	+	-	+	-
	Birefringent particles	n.d.	-	+	+	+	+
	Black pigment	n.d.	+	-	+	+	+

** Calculated values (and 95% confidence interval, CI) by fitting robust multivariable linear regressions (for each individual) including adjustment for smoking cessation.*

PY: pack-years of cigarette smoking history; FVC: forced vital capacity; FEV1: forced expiratory volume in one second; TLC: total lung capacity. DLCO: diffusing capacity of the lung for carbon monoxide; Lung function results at diagnosis are expressed in % predicted (according to Global Lung Function Initiative) in brackets. PMF: progressive massive fibrosis; RF: rheumatoid factor; anti-CCP: anti-citrullinated protein antibodies; ANA: screening for anti-nuclear antibodies by manual Indirect Immunofluorescence; dsDNA: ELISA for anti-double stranded DNA antibodies; CTD screen: EliA™ connective tissue disease screen (Thermo-Fisher, Freiburg, Germany), solid phase fluorescence enzyme immunoassay (FEIA) detecting antibodies to a mixture of 17 autoantigens (U1RNP (RNP70, A, C), SSA/Ro (60 kDa, 52 kDa), SS-B/La, Centromere B, Scl-70, Jo-1, Fibrillarin, RNA Pol III, Rib-P, PM-Scl, PCNA, Mi-2- proteins, Sm-proteins, dsDNA); ENA: Extractable Nuclear Antigens to U1-RNP, RNP-70, Ro60, SSB/La, Scl-70, Jo-1, SmD; ANCA: anti-neutrophil cytoplasmic antibodies; ACE: angiotensin-converting enzyme; BAL: bronchoalveolar lavage; RUL: right upper lobe; LN: lymph node, EBUS-TBNA: endobronchial ultrasound-guided transbronchial needle aspiration; n.d.: not done

Figure S1. Chest radiographs at diagnosis for worker 2, 3 and 5 (not performed for the other workers)



(A, B) Worker 2: Posteroanterior (A) and lateral (B) chest radiographs showing bilateral micronodules predominantly in the upper lung zones, consistent with simple silicosis. (C, D) Worker 3: Posteroanterior chest radiograph (C) showing hyperinflation of the lungs and hyperlucency of the upper lung zones. Relative paucity of the vascular markings contrasts with the prominent hila. No micronodular opacities are evident. Lateral chest radiograph (D) showing flattening of the diaphragms, an increased anteroposterior diameter of the chest, and enlargement of the retrosternal space consistent with emphysema. Mediastinal and hilar lymphadenopathy creates a "doughnut sign" seemingly surrounding the left upper lobe bronchus (arrows). (E, F) Worker 5: Posteroanterior (E) and lateral (F) chest radiographs showing bilateral micronodules predominantly in the upper and middle lung zones. Mass-like opacities in both upper lung zones cause loss of volume with upward retraction of the hila, consistent with progressive massive fibrosis as observed on chest CT (Figure 1).

2.4. Discussion

Silicosis is a social disease, with medical aspects

—Irving J. Selikoff[1]

2.4.1. Summary of the main findings

We are witnessing outbreaks of silicosis around the globe in workers fabricating and installing artificial stone kitchen and bathroom countertops. In this chapter, I have described Belgian cases of artificial stone-associated silicosis that have visited our clinic at the University Hospitals Leuven. Initially, we found 2 employees with silicosis in a 2-man company in the province of Antwerp, Belgium.

Next, I describe an outbreak at a company producing artificial silica-based kerbstones. Five workers from a plant manufacturing kerbstone were referred to our specialized clinic for occupational disease. The five men (38 to 59 years) had been employed for 8 to 30 years at a Belgian company where about 10 workers made silica-based artificial kerbstones for hygienic wall protection. We diagnosed enlarged mediastinal/hilar lymph nodes without radiological lung involvement in one worker, simple silicosis in two workers (one also with emphysema) and progressive massive fibrosis in two workers. High respirable quartz concentrations (>0.1 mg/m³) were measured during various operations, especially during dry finishing of the cured kerbstones (1.080 mg/m³). Adequate prevention was lacking. Annual spirometries—but no chest X-rays—had been performed since 8 to 10 years prior to diagnosis. The four men with silicosis proved to have undergone an excessively rapid FEV_1 decline [between 98 (95%CI 79–116) and 221 mL/year (95%CI 214–228)].

The discovery of rapidly progressive serious lung disease in half the workforce of a company producing novel applications of silica-based composites shows that the hazards of artificial stone production/processing reach beyond the kitchen/bathroom countertop industry. Appropriate workers' health surveillance programs must be implemented.

2.4.2. Improving prevention of silicosis in artificial stone workers

Based on our observations, we estimate that in Belgian artificial stone workers, silicosis has been probably underdetected by occupational health physicians, pulmonologists, and general practitioners. The initial symptoms of silicosis are non-specific, many physicians have little experience in assessing occupational exposure, and—given the declining incidence of silicosis in recent decades—the awareness of most clinicians of this condition is limited. Moreover, occupational health surveillance as it is practiced in this sector is currently not appropriate for the detection of silicosis. A periodic chest X-ray is rarely taken. Moreover, longitudinal assessment of spirometry is often lacking. Also, workers and employers in this sector seem unaware of the risks, thus leading to insufficient preventive measures.

We need to improve prevention, workers' health surveillance and diagnosis. Based on our current understanding of the workers mostly affected, priority should be given to 1) workers in (large and small) companies producing artificial stones: kitchen or bathroom countertops, stairs, kerbstones, …; 2) workers finishing the stones, i.e., converting the 'semi-finished product' into a finished product (bearing in mind that also 'natural stone' companies are increasingly using artificial stones); 3) installers of kitchen and bathroom countertops, etc., who machine the stones during installation at the client's home.

1) <u>Improving prevention</u>

Improving prevention at these companies is crucial. Enclosing certain processes, local exhaust and water suppression can reduce dust exposure. However, studies have shown that even when combining local exhaust and water suppression concentrations of respirable crystalline silica could not be reduced to non-hazardous levels.[2] Therefore one could consider going a step further and ban high-silica content artificial stones.[3] Recently, Australia's National Dust Disease Taskforce—in their report to the Minister of Health—

proposed to ban the stone if improvements in preventive measures appear to be ineffective by mid-2024.[4]

Many alternatives are available—artificial stone made with other fillers such as recycled glass or natural stones with lower silica content, which we expect to be less hazardous. Nevertheless, also with these alternative types of stones appropriate dust control is needed.[3] A legal prohibition of dry cutting, as has been done in Queensland (Australia), can be quickly implemented and can support preventive action. In Belgium a similar prohibition exists for the use of silica sand for sandblasting. Respiratory personal protective equipment (PPE) should only have an auxiliary role. In a limited number of short-term tasks, the use of respirators could be considered. Obviously advising PPE as the sole preventive measure is inadequate.

The aim of prevention should be to reach respirable crystalline silica exposures that are "as low as reasonably possible". The current occupational exposure limit (OEL) of 100 µg/m³ (respirable crystalline silica (8-hour time-weighted limit) adopted in 2017 by the European Commission, does not sufficiently protect workers against silicosis, nor against lung cancer according to the current scientific understanding. US OSHA estimated that if 1000 workers are exposed to a concentration of 100 µg/m³ during their 45-year career, this would result in 33 extra lung cancer deaths (3.3%), 85 from other lung diseases—such as silicosis—and 39 from renal diseases.[5] This would add up to an excess death risk of 15%. In the US, the American Conference of Governmental Industrial Hygienists (ACGIH) recommends a four times lower TLV-TWA (25 µg/m³). The binding US OEL is 50 µg/m³. In 2003 already, the Scientific Committee on Occupational Exposure Limits (SCOEL)—until recently advising the European Commission—stated that based on scientific evidence a protective OEL should be below 50 µg/m³ (SCOEL/SUM/94 November 2003). However, unlike in the US, the European Commission estimated that the cost for lowering the OEL would be too high.[6]

2) Improving health surveillance

Besides prevention, it remains important that health surveillance is organized for workers that are potentially exposed to respirable crystalline silica to detect adverse health effects as early as possible. Especially, artificial stone workers that have already been exposed in the past years should be prioritized.

Health surveillance and screening are active processes, which means that workers-at-risk should be actively searched for. The Australian experience has shown that if no screening is done, the problem can remain hidden for many years and workers are only diagnosed in a late stage of the disease.[7]

What health effects to screen for?

What components to include in the health surveillance programme of silica-exposed workers depends on the health effects that the programme is aimed at detecting. Most recommendations state that health surveillance of workers exposed to silica should aim to detect early signs of silicosis and of chronic obstructive pulmonary disease (COPD)/chronic bronchitis.[8,9] Recently, it has been suggested to add autoimmune disorders to this list.[10]

Screening for silicosis is useful because 1) initially silicosis usually produces few symptoms, and 2) some studies suggest that the progression of silicosis can be slowed down by reducing or stopping exposure. Nevertheless, progression of the disease after stopping exposure is also possible. A recent study in Spanish artificial stone workers described 106 patients of whom 99 were considered to have simple silicosis (93.4%) and seven to have progressive massive fibrosis (PMF) (6.6%). After a mean follow-up of 4.0 (±2.1) years, disease had progressed two or more International Labour Organisation [ILO] subcategories in 56% of the patients, and the number of patients with PMF had increased to 40 (37.7%).[11] Previously, Akgun *et al* had followed up 74 former jeans sandblasters in Turkey. Over a 4-year period, the prevalence of silicosis had increased from 55.4% to 95.9%, and radiographic progression had occurred in 82% of the workers.[12]

Respirable crystalline silica is also a carcinogen.[13] However, cancer is a late health effect, and there are currently no studies showing that screening with the purpose of detecting lung cancer in workers exposed to silica would be beneficial. Currently the United States Preventive Services Task Force (USPSTF) recommends annual screening for lung cancer with low-dose CT (LDCT) in adults aged 50 to 80 years who have a 20 pack-year smoking history and currently smoke or have quit within the past 15 years.[14] These recommendations are largely based on the results of the US National Lung Cancer Screening Trial (NLST) and the Dutch-Belgian Randomized Lung Cancer Screening Trial (NELSON).[15] The NELSON trial showed that screening resulted in a lung cancer mortality reduction of 24% in men and 33% in women, but no reduction in all-cause mortality.[15] The USPSTF guidelines do not address occupational risks for lung cancer as a criterion of eligibility for lung cancer screening. However, the National Comprehensive Cancer Network (NCCN) and the American Society of Thoracic Surgeons have developed guidelines that do include additional risk factors such as occupational exposures to determine who should be screened.[16] This approach has been applied in the Building Trades National Medical Screening Program (BTMed), an occupational medical screening programme for construction trades workers that have been employed in US nuclear weapons facilities.[17] Studies from this programme show that if the number of pack-years required to be eligible for screening is reduced in whose having a history of > 5 years of occupational exposure to carcinogens, the lung cancer screening yield was similar to the large NLST and NELSON trials.[17,18] In summary, there is limited evidence that it can be useful to take into account occupational exposure to carcinogens when deciding on eligibility for lung cancer screening. However, in individuals that have been exposed to occupational carcinogens, no studies have yet shown the benefits of lung cancer screening on lung cancer mortality, nor on overall mortality.

Other possible health effects of silica exposure are: diffuse interstitial pulmonary fibrosis, cancer of the stomach and oesophagus, chronic renal

failure, and sarcoidosis[19,20]Also, for these health effects screening has not yet been shown to be useful.

Essential components of health surveillance

In general, health surveillance should contain 3 essential components:[9] a) Informing workers, b) Medical examination (at recruitment and, afterward periodically), and c) Reporting and improving prevention if necessary.

a) Informing workers

Next to improving prevention by control of the dust levels at the workplace, workers should be informed about the potential health risks of exposure to respirable crystalline silica, so that they understand why preventive measures are important, and what actions they can take individually.[9] In addition, workers should be informed about the reasons, content and benefits of health surveillance—i.e. both the benefits for the individual worker and the benefits for all workers at the workplace. Understanding its usefulness is crucial to successful health surveillance. The practical development of prevention and health surveillance should therefore be done through collaboration between workers/worker representatives, employers and occupational prevention services.

Prior to the health surveillance, it must be explicitly explained to the worker what will happen if deviating results are found and what information will and will not be communicated to the employer. Importantly, the findings of the health surveillance must be communicated to the worker.

Cigarette smoking is a leading cause of lung cancer and COPD. Quitting smoking reduces the risk of these conditions. Therefore—particularly in workers exposed to respirable crystalline silica—it is important to recommend smokers to stop smoking and to refer them to appropriate services that can support them.

b) Medical examination

The medical examination includes not only the practical organisation of medical tests but also the proper evaluation and interpretation of the information obtained with these tests.

In workers exposed to respirable crystalline silica, the World Health Organisation (WHO) recommended in 1996 screening for silicosis and COPD/chronic bronchitis, using 1) A questionnaire enquiring into work practices, exposure history, and symptoms, 2) chest X-ray with a systematic interpretation (e.g. using the ILO system), 3) spirometry, and 4) tuberculin skin-testing.[8] More recent recommendations generally include similar elements.[9] Given the relatively low prevalence of tuberculosis in Belgium within this population, tuberculin testing is probably no longer needed.

At recruitment, it is crucial to establish a "baseline" against which results from future periodic medical examinations can be compared. Health surveillance at recruitment should, therefore, include collecting a past medical history, a complete occupational history—with emphasis on past dust exposure—, and a smoking history. Also, a baseline symptom questionnaire, spirometry and chest X-ray (unless already available from the past 2 years) should be obtained.[8]

After recruitment, the medical examination should be repeated periodically. There is no consensus about the frequency of the medical examination. As the risk of silicosis is associated with the cumulative exposure (exposure level × duration), a general rule is that the frequency of the medical examination should depend on the level of exposure and the total duration during which the worker has been exposed (with higher exposure levels and longer duration leading to more frequent surveillance).

Lung function. A spirometry is recommended yearly.[8] Lung function testing beyond spirometry, including static lung volumes and diffusing capacity of the lung for carbon monoxide (D_{LCO}) has been proposed. D_{LCO} can be relevant for early detection of silicosis and emphysema. The equipment to

measure D_{LCO} has become increasingly portable, so it can easily be taken to the point of testing.[21]

Assessment of the spirometry should be done both in comparison to the general population (cross-sectional evaluation), as well as in comparison to the worker's own baseline values (longitudinal).

First, the absolute values of FEV_1, FVC and FEV_1/FVC should be compared with the predicted reference values of the Global Lung Function Initiative (GLI).[22] FEV_1 is considered abnormal when below the Lower Limit of Normal (LLN). The LLN is the 5th percentile of a healthy, non-smoking population taking into account age, gender, height and ethnicity. Spirometry in workers with silicosis can be normal, obstructive or restrictive. Spirometry alone cannot diagnose silicosis but it is useful in quantifying functional abnormalities.[8]

Next, a longitudinal evaluation is needed—but is often lacking. The primary measurement used to assess longitudinal change should be the FEV_1, as it is less affected by technical factors than the FVC.[23] Excessive loss in FEV_1 over time can be evaluated using either a percentage decline (15% plus loss expected due to aging) or using longitudinal analysis software such as SPIROLA, taking into consideration testing variability, worker exposures, symptoms, and other clinical information.[23] SPIROLA calculates several parameters to assess if there is an excessive decline. For most of these parameters a baseline value is required. When no baseline spirometric values (at the start of employment) are available, the sensitivity of its assessment probably decreases.[24] Additionally, SPIROLA does not allow to adjust for additional worker-specific factors such as smoking cessation.

Less evidence is available on how to perform longitudinal assessment of D_{LCO}. Some have proposed that workers with a change in D_{LCO} of more than 15% between screenings should be referred for high-resolution CT.[25]

Imaging. Regarding periodic chest imaging, the 1996 WHO recommendation on "Screening and surveillance of workers exposed to mineral dusts" states that a chest X-ray should be obtained at the start of employment (baseline),

then after 2 – 3 years of exposure. From then on chest X-ray is recommended every 2 – 5 years (for workers with <10 years since first exposure), every 1 – 2 years (for workers >10 years' exposure), or annually (for workers with >20 years since first exposure). Frequencies may be adjusted depending on the worker's age and intensity and duration of exposure.[8] The American College of Occupational and Environmental Medicine (ACOEM) recommends—in case of exposures equal to or greater than 0.05 mg/m³—a follow-up evaluation every 3 years (for a duration of exposure < 10 years), or every 2 years (for a duration of 10 or more years). The frequency of follow-up can be adapted based on questionnaire responses and documented exposure data. ACOEM also recommends conducting an exit evaluation when the worker leaves the job.[26] Because silicosis may not appear for many years after the exposure has stopped, it is important that health surveillance continues after ceasing employment because workers are still at risk in subsequent years.[21] Although, the Belgian law foresees the possibility of continued health surveillance, currently it is unclear how this should be applied practically in the Belgian context in workers with a history of silica exposure.

Currently, there is an ongoing debate on what is appropriate screening in workers who are/have been exposed to very high levels of silica, such as artificial stone workers. The periodic chest X-ray might be inadequate because it does not detect the earliest phases of the rapidly developing form of the disease that we are observing in artificial stone workers.[27,28] A recent position statement from the Thoracic Society of Australia and New Zealand suggests using low-dose CT instead of plain chest X-ray, although evidence for this suggestion is currently lacking.[21] This position statement also recommends *active case-finding* for artificial stone workers who have been previously exposed to high respirable crystalline silica levels using conventional high-resolution CT/spirometry/D_{LCO}.[21]

International guidelines for the interpretation of chest X-rays mostly use the ILO classification. Specific training of the radiologist is required for the use of this classification. However, in Belgium no such training exists, and this

classification is not used. Nevertheless, a standardized radiology report would be recommended.

c) Reporting and improving prevention if necessary.

Worker should receive a written report of their test results and advice should be given on the significance of any abnormal result.[8,9] In case of respiratory symptoms, abnormal clinical examination of the lungs, abnormal spirometry or abnormalities on imaging (including when there is diagnostic uncertainty), the worker should be referred to a pneumologist. Relevant respiratory symptoms are recurrent bronchitis or pneumonia, persistent exertional dyspnea, cough or wheezing (without evidence of infection). Wheezing or crackles on lung auscultation should also lead to referral.

In the presence of symptoms or clinical signs suggestive of an autoimmune disorder, the worker should be referred to a rheumatologist with expertise in autoimmune disorders. Relevant symptoms could be Raynaud's phenomenon, recurrent swelling and/or redness of joints (not including osteoarthritis or tendinopathies), sicca (dry eyes, dry mouth), etc.

If alternative diagnoses are suspected during the health surveillance—such as cardiac disorders—the worker should be referred to the general practitioner or relevant specialist.

When health effects due to exposure to silica are confirmed:

- Workers must be informed about all implications of their diagnosis, what information will be communicated to their employer, their predicted risk from continued exposure and where they can find additional information on their condition.
- All reasonable efforts must be made to allow work to continue in a dust-free environment or with reduced dust exposure.
- The occupational health physician and the pneumologist should assess the urgency of stopping or reducing silica exposure—depending on the observed abnormalities on imaging and lung function.

- If sufficient reduction of dust exposure is not possible, removal from the workplace is recommended. It should, however, be noted that removing a worker from the workplace and replacing him with a colleague without lowering exposure is obviously not an option.
- Confirmed health effects due to exposure at work should be reported to the relevant institutions. In Belgium, occupational diseases should be reported to the Federal Agency for Occupational Risks (FEDRIS) to be eligible for compensation. Currently only silicosis is 'recognised' as a health effect related to silica exposed, although FEDRIS is currently considering adding silica-induced systemic sclerosis to the list of recognizable occupational diseases. Other silica-related diseases can be reported but require the applicant to demonstrate "a definite causal link" between exposure and disease, which is very difficult to do.

Finding (possible) silica-related health effects in 1 or more workers in one workplace means that prevention has failed and that the risk analysis at this workplace should be reconsidered. Improving prevention is most probably needed and closer monitoring of exposure by organizing more frequent environmental measurements should be considered. Also, the health surveillance scheme of the colleagues of the ill worker should be adapted: workers with similar tasks or nearby workstations as the ill worker, including maintenance workers and temporary employees, should be regarded as high risk.

Additionally, a group-level summary of the health surveillance of all workers should be anonymously reported to the employer.

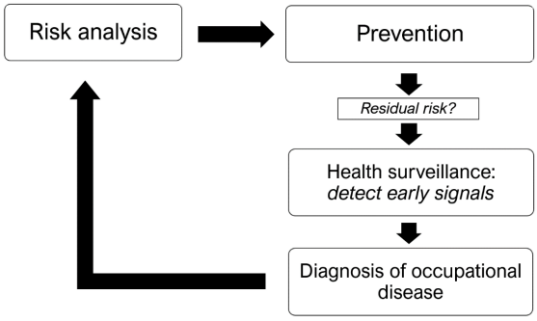


Figure 1—Finding an occupational disease in 1 or more workers in one workplace means that prevention has failed and that the risk analysis at this workplace should be reconsidered

3) <u>Improving diagnosis</u>

In addition to improving prevention and organizing health surveillance—which are tasks in which the occupational health service is involved—also improving diagnosis is crucial. There is presumably an underdetection of silicosis and other silica-induced health effects by general practitioners and pulmonologists. There are several reasons why physicians in the curative sector do not initially suspect silicosis in their patients, including artificial stone workers. The initial symptoms of silicosis are very non-specific, many doctors have little experience in taking an occupational history, and—given the declining incidence of silicosis in recent years—the experience of most pulmonologists and radiologists with this condition is limited, leading to misdiagnoses or delays in reaching a correct diagnosis in workers with silicosis.[29,30] Also, the fact that silica can cause not only silicosis but a wide spectrum of diseases is not well recognized.

In Belgium, many physicians consider that silicosis is a disease that only applies to former miners. We should inform general practitioners and pulmonologists about the current outbreak and make them aware that they should inquire their patients about their working conditions. Ideally, doctors should have easy access to (historical) exposure data from each individual worker that consults them.

2.4.3. Public outreach and future perspectives

To approach the problem of artificial stone-associated silicosis I believe 4 main steps should be taken in the short-term.

First, trying to raise awareness among the several actors involved in health and safety in the sector. I took the initiative to emphasize the need for prevention and improved surveillance to several audiences of actors involved in the world of 'health and work' in Belgium and abroad for the last 2 years. This included lectures for occupational physicians (at the Flemish and Dutch scientific societies of occupational medicine, at the association of Belgian external prevention services [CoPrev], at a European COST training school), for occupational hygienists, and for employers and trade unions in the building industry. I also published on the topic in non-scientific journals to reach the target audiences (magazine for health and safety professionals, magazine for building companies, magazine for trade unionists) (see full list of activities and publications in CV)

Second, we should—next to improving prevention and health surveillance—organize active case finding. As was shown in Queensland (Australia), using this approach workers with silicosis can be detected (in the short-term) and workplaces where exposure has been too high can be identified.

Third, as silicosis has become a rare disease in the last decades, the clinical experience of many physicians with the disease is limited. We lack updated guidelines on how to organize health surveillance (for occupational physicians), how to diagnose the silica-related diseases (for pulmonologists and other clinicians in the curative sector), and what to do when a patient with silica-related health effects is found (which referrals, work-up, treatments, advise for work, actions to be taken at the workplace, etc.). Developing a joint guideline (occupational physicians and curative sector) would be useful.

Fourth, there is a need for better evidence on several aspects: the optimal frequency of health surveillance, the role of CT scans and D_{LCO} in surveillance, cost-effectiveness of surveillance, and on how to best treat and follow-up patients.

2.4.3. References

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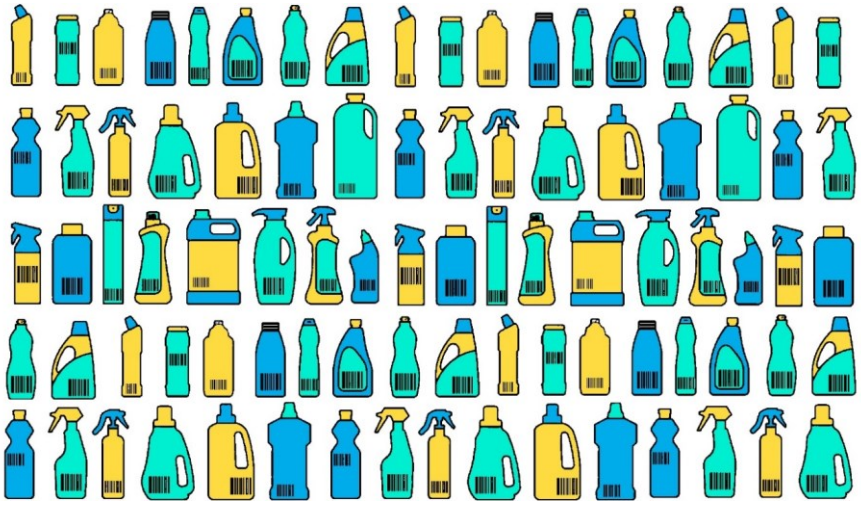
Chapter 3 —
Respiratory health effects of cleaning products in domestic cleaners



3.1. Introduction

3.1.1. Background

Studies indicate an increased risk of asthma and other respiratory symptoms among cleaners—especially among women employed in domestic cleaning. A number of studies have shown associations between the occurrence of asthma and certain types of products—most commonly sprays, bleach, ammonia and inhalation accidents due to mixing of incompatible products.[1–3] A recent Belgian study using census-linked mortality data found that smoking-adjusted Standardized Mortality Ratios (SMR) for all-cause mortality were higher among cleaners than among non-manual workers (men 1.25 ,95%CI 1.22–1.28; women 1.10, 95%CI 1.07–1.13).[4] Moreover, in cleaners significantly more deaths had occurred due to COPD (men 2.13, 95%CI 1.92–2.37; women 2.03, 95%CI 1.77–2.31) and due to lung cancer (men 1.31, 95%CI 1.22–1.39; women 1.21, 95%CI 1.11–1.32).[4] Little is known about the respiratory health of domestic cleaners in the service voucher sector.

In most countries, the work of domestic cleaners is "undeclared". Since 2004, in Belgium, domestic cleaning (and other paid domestic tasks) is organised in the so-called service voucher system, uniting around 150,000 workers. In this system, clients have a contract with a "service voucher company" that employs workers to provide domestic services. The system offers a regulated work environment.[5] The domestic cleaners have a number of fixed clients each week (which can range from one up to ten). This unique Belgian context provided an opportunity to set up a project with the long-term aim of improving the prevention of respiratory health of domestic cleaners.

Studying respiratory health effects of cleaning products in domestic cleaners is challenging. Firstly, cleaning products are complex chemical mixtures (containing a vast range of ingredients). Secondly, domestic cleaners use numerous cleaning products in every client's home, which complicates studying associations between exposures and health outcomes—and the

implementation of prevention strategies. Thirdly, domestic cleaners are a difficult to reach and socio-economically vulnerable population (mainly low-educated women with a high percentage of employees of foreign origin).

Work-related asthma

The term work-related asthma can refer to both pre-existing asthma *aggravated* by occupational exposure ("work-aggravated asthma") as well as asthma *caused* by occupational exposure ("occupational asthma"). Occupational asthma can be further divided into immunological occupational asthma—induced by a specific sensitizer—, and non-immunological occupational asthma—caused by inhalation of substances, gases or vapours with irritating or toxic properties ("irritant-induced asthma").[6] Asthma can be induced both by short exposure to high concentrations of irritants (inhalation accidents) and by long-term exposure to so-called 'low or moderate' concentrations of irritants.[7,8]

The main known sensitizers present in cleaning products are disinfectants—such as quaternary ammonium salts—, amines, aldehydes and fragrances.[9] Airborne irritants can be released when using cleaning products containing bleach (sodium hypochlorite), hydrogen chloride, ammonia and sodium hydroxide, especially when mixing incompatible products.[10] In addition, many cleaners have asthma-like complaints without meeting the (strict) diagnostic criteria for (occupational) asthma.

Asthma in cleaners is probably only in a minority of the cases induced by a sensitizer.[9] Most cases are probably predominantly caused by prolonged exposure to several irritants. This poses a problem with regard to the recognition of these cases as an occupational disease. In Belgium, the Federal Agency for Occupational Risks (FEDRIS) only considers immunological occupational asthma caused by a well-defined sensitizer to be eligible for compensation, while irritant-induced asthma is almost never considered. As a result, a large part of the work-related respiratory problems in this sector remains unrecognized and are therefore 'invisible' at the societal level.[11]

Prevention of respiratory health effects of cleaning products in domestic cleaners

Despite the increasing knowledge about the associations between cleaning products and respiratory health, there is little research into prevention.[12] Little attention has been paid to translating existing scientific insights into prevention at the workplace.[13] In the service voucher sector a combination of factors make prevention challenging. The sector is characterized by a high turnover and a vulnerable worker population.[14] Their precarious work situation may prevent them from expressing their health problems.[15,16] In addition, the working conditions are difficult to map and to influence (How can one intervene and implement workers' health and safety legislation in a work environment that is essentially a private environment?). Generally, their work is relatively isolated, and their precise exposures depend on the products that the clients provide.

There is probably also a lack of awareness about the seriousness of the problem among different actors in this sector. Cleaners are often unaware of the risks to which they are exposed or judge that these risks are 'part' of the job. Moreover, other health issues may be prioritized by the workers, such as musculoskeletal, skin and psychosocial problems.

Participatory approach

To overcome some of these barriers, we have set up a project with the Belgian service voucher sector ("dienstenchequesector"), in which our intention was to map the work-related respiratory health of domestic cleaners, to raise awareness about the work-related health problems in this sector among various social actors, to increase 'social visibility' of work-related health problems in the sector, and to elaborate a preventive intervention.

We apply a 'participatory action research' methodology, an approach in which there is a close interdependence between research, training/awareness raising and intervention (action).[17–20] Participatory action research is a collaborative approach to research that seeks an active

involvement of different partners at every stage of the research. In our project these partners are the cleaners/workers, employers and worker representatives, occupational health physicians, the sectoral training organisation and scientists—which all have their own specific expertise, knowledge, and strengths. Decisions on the research methods, the preventive actions to plan and the timing of the research are taken in consensus. In this way, both the process and the results become a shared responsibility. Through this *mutual ownership*, we try to increase support for the practical implementation of the project and guarantee the sustainability of future interventions. The researchers' role is to facilitate and coordinate this process.

In participatory action research, the explicit intention is to arrive at an intervention (action). Ideally, the intervention takes place at several levels (workplace, sector, society) and is aimed at the different actors: workers, worker representatives, employers, but also the clients. Possible preventive interventions could be: creating a database with alternatives to hazardous products that is easily accessible, raising awareness in clients to provide less hazardous cleaning products and strengthening workers' capacity to negotiate about their working conditions in the homes of the clients (*empowerment*).[21]

At the start of the project, we have set up a steering committee including various actors involved in the service vouchers sector. The members of the steering committee are: Peter Van de Veire (Service Voucher Training Fund/Sectoraal Vormingsfonds Dienstencheques), Hanne Pollet (employer representative Federgon), Hanne Sanders and Lisa Trogh (employee representatives General Labour Federation of Belgium [ABVV/FGTB]), Dries Vanheuverswyn and Ben Debognies (employee representatives Confederation of Christian Trade Unions [ACV/CSC]), Prof. Christophe Vanroelen (Interface Demography, Sociology Department, Vrije Universiteit Brussel), Dr. Katrien De Troeyer (master student epidemiology, UAntwerpen), Dr. Eline Vandebroek (occupational physician, Premed) and I.

The aim of the steering committee was to supervise and support the practical elaboration and implementation of the project.

Overview of the project

The above-described process is this still ongoing. The timing of the project and its practical implementation—such as the initial plan to organise focus groups—have substantially been adapted in the past 1.5 years due to the COVID-19 pandemic.

In this thesis, I describe the first part of this project, which took place in February/March 2020 ("pre-COVID-19"). In this first part, we did a questionnaire-based study in order to reach as many domestic cleaners as possible. In total, 1,586 cleaners participated. The results are described in this chapter (part 3.3).

In the second part of the study, we add a participatory component and improve the exposure assessment by asking the cleaners to use a smartphone app, with which they could scan the barcodes of the cleaning products they are using (over a 2-week period). We have developed this app based on a customisable barcode scanning app produced by the company CodeReadr.[22] The app was available for Android as well as Apple smartphones (see figure 1). In total, 538 cleaners have been using the smartphone app and all together they have scanned around 16,700 product barcodes (around 3,000 unique barcodes). The analysis of this data is currently ongoing.

In a third part of the study, we plan to further increase participation and ask a limited number of cleaners to use the smartphone app while using a peak flow meter 4 times a day to be able to correlate exposure and sequential peak flow measurements.

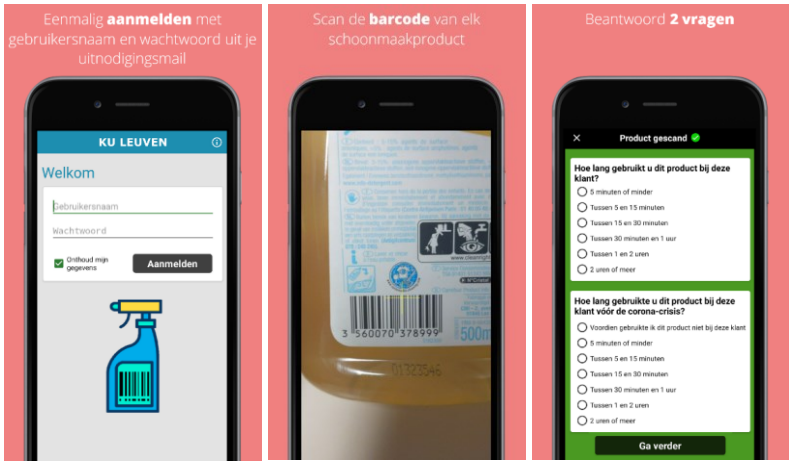


Figure 1: Screenshots of our smartphone app ProductScan. The app can be downloaded from https://play.google.com/store/apps/details?id=be.kuleuven.app.productscan (Android) or https://apps.apple.com/us/app/ku-leuven-productscan/id1541702026 (Apple) but can only be used with a participant login.

3.1.2. Aims and outline of the chapter

In this chapter, we first review the literature on the respiratory health effects of cleaning products, including epidemiological and toxicological studies (part 3.2). Then, the questionnaire-based study in domestic cleaners in the service vouchers sector is presented (part 3.3). The aim of this study was to investigate, among professional domestic cleaners, the associations of a range of respiratory outcomes with the use of specific categories of cleaning products at work and with the ability to choose their own products.

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3.2. Respiratory health effects of exposure to cleaning products [Review]

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ABSTRACT

There is consistent and growing evidence of an epidemic of 'asthma-like' symptoms among professional cleaners. Important questions remain unanswered: how big is this problem worldwide, which cleaning agents are dangerous, and how do they affect the lungs, is it really 'asthma'? This is an important public health issue because of the large and increasing number of professional cleaners (c.4 million in Europe only), many from 'vulnerable' categories, such as women, immigrants, and of low socio-economic status. In addition, there are potential implications for anybody exposed to cleaning products during routine domestic housekeeping, including children. In this chapter we will try to address these issues using the available evidence on this topic, from epidemiology to toxicology, to give a broad but concise overview on what we know so far and how we could prevent the cleaning-associated respiratory health public burden.

1. Introduction: why is this an important public health issue?

There is consistent and growing evidence of an epidemic of 'asthma-like' symptoms among professional cleaners. Important questions remain unanswered: how big is this problem worldwide? Which cleaning agents are dangerous, and how do they affect the lungs? Is it really 'asthma'?

This is an important public health issue because of the large and increasing number of professional cleaners (about 4 million just in Europe),[1] many from 'vulnerable' categories, such as women, immigrants, and of low socio-economic status. These figures are likely an underestimation given that many in this job sector are self-employed.

In these groups there are significant public health costs arising from: a) cleaners who leave work because of ill health, b) cleaners who develop chronic respiratory effects which persist even if they avoid further exposure. In addition, there are potentially important downstream implications for all end-users of cleaning products during domestic housekeeping. The public health impact could be higher still if there are effects from passive, 'bystander' exposure (including in vulnerable subjects such as children).

In this chapter we will address these issues using the available evidence on this topic, from epidemiology to toxicology, to give a broad but concise overview on what we know so far and how we could prevent the burden of cleaning-associated respiratory disorders.

2. Is there a global ‘asthma’ epidemic among professional cleaners?

Several studies worldwide have reported an increased prevalence and incidence of asthma-like symptoms among professional cleaners, mostly in the so-called developed countries (Europe, USA).[2,3] The issue has been reported mainly for female professional cleaners, with no specific age, or ethnical pattern. Neither atopy, nor smoking habit seem to be related to an increased risk. Most of the evidence comes from epidemiological population-based studies. This is not surprising, given the nature of cleaning sector, which is mostly based on part-time, and self-employed workers, thus making

it difficult to recruit and conduct traditional occupational 'cohort' studies. Most cohort studies were done among hospital nurses with cleaning tasks, whose findings are limited in their external generalizability because of the exposure to peculiar cleaning agents, used to disinfect or sterilize medical instruments or inpatients units. Also, the majority of the studies have a 'cross-sectional' design, so possibly affected by the known 'healthy worker survivor effect bias', that is the underestimation of the true prevalence of a health condition in a workforce due to the negative selection of the workers who become 'ill' or 'unfit' and so are forced to leave their job and, vice-versa, the retention of the 'healthiest' and 'fittest' ones.

Also, occupational exposure to cleaning agents is mostly retrospectively self-reported by cleaners, so possibly affected by the so called "recall bias" (i.e. systematic error in reporting past exposure or conditions); in particular, cleaners who are affected by significant respiratory symptoms or are ill are more likely than asymptomatic or healthy ones to report previous exposure to cleaning agents, especially to those with pungent odour, such as bleach, so possibly producing differential misclassification of exposure and spurious causal associations with these types of substances. None of the studies were able to measure quantitatively exposure to cleaning agents, and so evaluate dose-responses, which would strengthen the validity of the associations.

In relation to the health outcome definition, most of these studies defined asthma as self-reported by cleaners. Only a few used a spirometry-based definition, and so the possibility of a misclassification of the outcome, and an overestimation of the true asthma prevalence in this workforce, especially if based on self-reported symptoms instead of a doctor diagnosis, cannot be ruled out. On the other hand, the fact that this 'epidemic' has been reported only in this job category and not others, and consistently in time and space across several countries, supports the validity of these epidemiological findings. A further issue is related to the difficulty of defining true occupational asthma (i.e., adult new-onset asthma caused by respiratory hazards at work), and to differentiate it from work-exacerbated asthma (i.e., pre-existing asthma triggered or aggravated by respiratory hazards at work).

Of note, in a recent meta-analysis[4] (published as congress abstract only) the authors managed to pool 16 high quality epidemiological studies that similarly defined occupational asthma among cleaners and estimated a pooled increased relative risk (RR) of 51% (Figure 1).

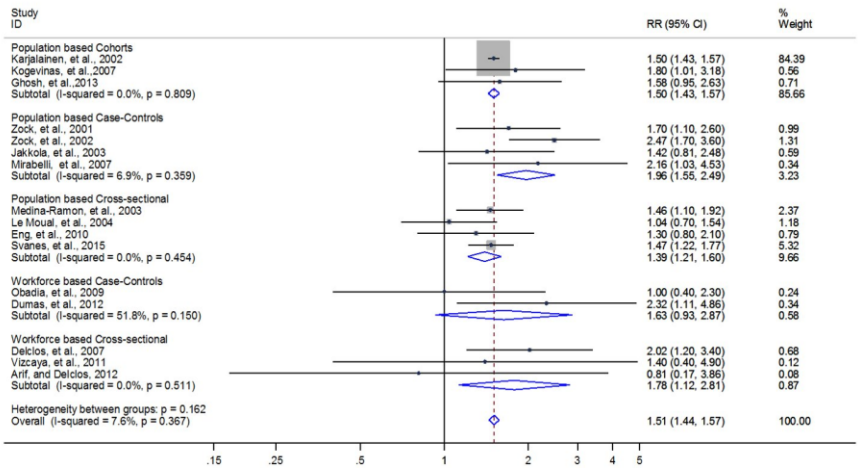

Figure 1. *Meta-analysis of 16 studies evaluating the association between professional cleaning exposure and asthma risk (relative risk [RR] and 95%confidence interval [CI]).*[4]

3. Is it really 'asthma'?

As reported above, the definition of occupational asthma among cleaners in most previous epidemiological studies is self-reported, and so potentially affected by disease misclassification. The agreed 'gold standard' for diagnosing sensitizer-induced allergic asthma (i.e. positive specific inhalation challenge test with the suspected causal cleaning agent) has been reported in a few case-report/series studies only.[5,6] This is not surprising given the complexity and the costs associated with this diagnostic test (that requires a sealed inhalation chamber, trained staff, and to admit the worker as hospital inpatient), which is rarely accessible or even feasible in most countries. Moreover, for irritant-induced asthma there is no such gold standard test,

making the attribution of asthma to irritant exposure difficult on an individual level.

In addition, the atypical presentation of asthma cases among cleaners (i.e. usually not associated to atopy, or inflammatory biomarkers and eosinophilia, and with scarce bronchial reversibility),[7] has generated scientific interest into evaluating a broader range of alternative cleaning-related respiratory health effects.

Among other respiratory outcomes presenting with 'asthma-like' symptoms, chronic obstructive lung disease (COPD) has been investigated by epidemiological studies. A significant association of working as a cleaner and having spirometrically-defined COPD (i.e., forced expiratory volume in one second, FEV_1/forced vital capacity, FVC < lower limit of normal, LLN) was found in a recent large population-based cross-sectional analysis of 228,614 people in the UK Biobank study. A 43% risk increase (prevalence ratio, PR=1.43;95%CI:1.28-1.59) was found for cleaning occupation, also confirmed in analyses restricted to never smokers, and non-asthmatics.[8] Also, a cross-sectional study of 13,499 Northern European cleaners reported an increased risk of self-reported COPD (OR=1.69; 95%CI: 1.29–2.20).[9] Of note, a recent US cohort study among hospital nurses found that regular use of chemical disinfectants increased COPD incidence with about 30%, with positive response trends for frequency and duration of exposure.[10] These findings support the hypothesis (that will be discussed in detail later in the potential underlying biological mechanisms section) that exposure to the noxious chemicals in the cleaning agents is able to produce not only acute but also chronic airways obstruction.

Also, a population-based cross-sectional study found a significant increase in phlegm and dyspnea prevalence suggestive for chronic bronchitis among cleaners compared to office workers used as controls, taking into account tobacco smoking as potential confounder.[11] However, another population-based case-control study found a similar result among domestic cleaners only when chronic bronchitis symptoms were combined with asthma symptoms as outcome.[12]

Of note, some authors have suggested, based on case-series, that upper airways conditions that mimic asthma symptoms such as vocal cord dysfunction (i.e. paradoxical laryngeal movement resulting in inappropriate adduction of the vocal cords) might be associated to exposure to cleaning agents and be mediated by irritative mechanisms.[13]

4. What are cleaning products?

Cleaning products are complex chemical mixtures used to facilitate dust and dirt removal (see Figure 2), to disinfect and to maintain surfaces. Household users and professional cleaners use a broad range of products: all-purpose cleaners, specialty cleaners (for floor, bathroom, oven, …), surface care products, decalcifiers, laundry products, dishwashing agents, drain cleaners, etc. There are large differences in the patterns of use of domestic cleaning products—such as sprays, household bleach and ammonia—across different countries.[14]

In healthcare settings also products are used for medical instruments cleaning (for example for endoscopes) and disinfection.[15] In other sectors special cleaning products may be used, such as in food preparation, agriculture and intensive animal farming, façade cleaning, graffiti removal or industrial cleaning. Disinfectants are included in a wide range of cleaning product groups—also in common household cleaning products—to destroy microbial life through different mechanisms—or combinations of mechanisms—such as damage to microbial cell walls, damage to microbial DNA or protein denaturation.[16] Commonly used disinfectants are chlorine-releasing compounds, such as hypochlorite (household bleach) and chloramine-T, alcohols (ethanol, isopropanol), aldehydes (formaldehyde, glutaraldehyde, ortho-phthalaldehyde), quaternary ammonium compounds (benzalkonium chloride), oxygen-releasing compounds (hydrogen peroxide, peracetic acid), biguanides (chlorhexidine) and enzymes.

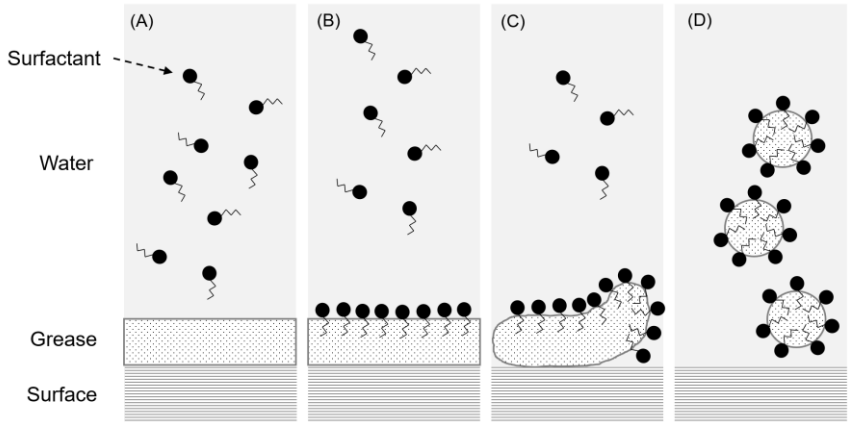

Figure 2. *Mechanism of action of soaps and detergents on dirt. (A) Detergent or soap dissolves in water. (B) Hydrophilic head and lipophilic tail of surfactant ions orientate themselves in water and grease. (C) Grease separated from surface. (D) Clean surface*

Cleaning products are an ever-changing technology. In the 1960s, proteolytic enzymes were introduced to improve the cleaning efficacy of washing powders, leading to high rates of asthma among exposed detergent production workers[17], and some evidence for IgE-associated allergy among domestic users.[18] Encapsulation of enzymes and engineering controls in the detergent factories led to reductions in the occurrence of asthma. In recent decades, many new enzymes (proteases, amylases, lipases, cellulases) were introduced in several types of cleaning products[19]—many now known to be potent respiratory sensitizers. More recently, cleaning product containing living microorganisms or spores—such as *Bacillus* spores[20]—as active ingredients have been introduced on the market. The respiratory health effects of these 'microbial-based cleaning products' (MBCPs) are poorly studied. Nevertheless, it is reasonable to consider them as possible respiratory sensitizers.[21]

5. Production and respiratory uptake of gases and particles

When using cleaning products several ingredients can become airborne in *gaseous* form (volatile compounds) or as an *aerosol* (volatile and non-volatile

compounds) which can be inhaled. The site where airborne compounds are deposited in the airways is an important determinant of whether—and where—respiratory health effects will occur.

Volatile constituents or reaction products of the cleaning products can enter the gas phase during or after use. Air concentrations of volatilized compounds depend on the cleaning task, amount of product used, boiling point, surface tension, size of the surface (air-liquid interface), concentration of the compound, water temperature, and size, humidity, temperature and ventilation of the room.[22] Even normal use—i.e. without mixing or using abnormally high amounts—of hypochlorite- and ammonia-containing products can produce air concentrations of chlorine and ammonia exceeding recommended occupational short-term exposure limits.[12,23]

A major concern associated with the use of hypochlorite (ClO^-) is that mixing with ammonia-based products—or even with urine—results in the formation of chloramines ($NH_2Cl \rightarrow NHCl_2 \rightarrow NCl_3$), whereas mixing with an acid–containing products creates chlorine gas (Cl_2). Mixing cleaning products has been associated with irritant-induced asthma in cleaners.[3] Even without mixing, commercially available hypochlorite-containing cleaning products can emit substantial concentrations of halogenated volatile compounds—mainly chloroform and carbon tetrachloride—due to the reaction of hypochlorite with organic molecules, such as surfactants and fragrances, contained in the product.[24]

The site where an inhaled gas is deposited in the respiratory tract is mainly determined by its water solubility.[25] Irritant gases that are highly water soluble, such as ammonia and hydrogen chloride, are generally deposited in the upper airways, causing an acute irritant effect here while sparing the lower respiratory tract. Less soluble gases, such as several solvents, penetrate deeper into the lower airway. They often cause no immediate symptoms but can cause irritant effects in the bronchi, terminal bronchioles, and alveoli. Gases of intermediate solubility, such as chlorine, may exert irritant effects widely throughout the respiratory tract.

Nonvolatile ingredients such as surfactants, acids and bases, quaternary ammonium compounds, preservatives, enzymes can become airborne when droplets are produced by using sprays and, to a lesser extent, by splashing or pouring of liquid products or by secondary resuspension of particles from surfaces. The concentration and droplet size distribution of the aerosol generated by spraying depend largely on the spray nozzle and dispersion mechanism used (pump vs propellant spray).[26] An experimental study showed that the use of a low-pressure nozzle could reduce the inhalable and thoracic fraction by up to 92%.[27]

6. Mechanisms of adverse respiratory effects

The wide range of compounds that can reach the airways at various sites, combined with the variable frequency and duration of exposure result in a broad spectrum of potential respiratory health effects.[28] Chemicals in cleaning products might be well-established sensitizers or irritants, chemicals with poorly characterized respiratory effects, or mixtures of all three.

Sensitizer-induced (allergic) rhinitis and asthma

Some cleaning agents can induce sensitization by an immunologic mechanism and cause allergic rhinitis or asthma. Positive bronchial and nasal provocation tests have been reported for chloramine-T[29,30], quaternary ammonium salts[31,32], triclosan[33], amines[34], glutaraldehyde[6], ortho-phthalaldehyde[35], fragrances[36] and enzymes[37,38]. An IgE-mediated mechanism has been suggested for very few compounds, such as chloramine-T[39], ortho-phthalaldehyde[40] and enzymes[37]. Most sensitizers in cleaning products probably act via immunologic non-IgE-mediated mechanisms. For ethylenediaminetetraacetic acid (EDTA), a pharmacologic mechanism—linked to its calcium-chelating activity—has been suggested by both experimental and clinical data.[41]

Interestingly, animal experiments have shown that the initial sensitization leading to the development of asthma does not *per se* occur at the level of

the airways but might also occur via the skin.[42,43] Låstbom showed in an experimental model that guinea pigs that were first skin-sensitized to 3-carene—a commonly used fragrance component and a potent skin-sensitizer—had an increased airway responsiveness after subsequent inhalation of 3-carene when compared to non-skin-sensitized animals.[44] This could be of interest for professional cleaners as their exposure is dermal as well as respiratory, and there is a high prevalence of contact dermatitis—both irritant and allergic—among cleaners. Allergic contact dermatitis and asthmatic symptoms have been shown to be associated in this population.[45]

Irritant-induced respiratory disorders

Many respiratory health effects of cleaning products are non-allergic, i.e. they do not involve a specific recognition by the adaptive immune system. In other words, they cause irritation by direct action on neurons or other cells. Such irritation can range from simple, transient discomfort to persistent irritant-induced conjunctivitis, rhinitis, sinusitis, pharyngitis, vocal cord dysfunction or inducible larynx obstruction[46], asthma, bronchitis, chronic obstructive pulmonary disease (COPD)[47] and (rarely) pneumonitis.[48,49] Irritants can induce new-onset asthma after a single, high-level exposure (known as “reactive airways dysfunction syndrome” [RADS]) as well as after chronic exposure to moderate levels of irritants. Also, pre-existing asthma can be exacerbated by irritant exposure (work-exacerbated asthma).[50] Cases of toxic pneumonitis have been reported due to waterproofing agents[48] and mixing of household ammonia and bleach.[49]

According to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) respiratory irritants are labelled with the hazard statement H335 (“May cause respiratory irritation”). The term respiratory tract irritation can be used to indicate either or both of two toxicological effects which are different but interlinked: sensory irritation and tissue irritation.[51]

Sensory irritation

Sensory irritation starts with interaction of a chemical agent with receptors of the nervous system (trigeminal or vagal nerve). In the afferent nerve endings in the airways, two key Transient Receptor Potential (TRP) channels are present: TRPV1 and TRPA1. These non-selective cation channels can be directly stimulated by a variety of inhaled irritants and mediate sensory irritation as part of a physiological response to make the subject aware of the presence of chemicals by inducing pain, nasal pungency, eye irritation, and defensive reflex responses, such as cough, sneezing, mucus hypersecretion, and bronchoconstriction.[52] Upon activation of the sensory nerves, various neuropeptides are released locally. These neuropeptides trigger an airway neurogenic inflammation[50] which reflects the transition from pure sensory, reversible effects to a general and inflammatory defense mechanisms.

Animal experiments have shown that TRPA1 is essential for irritant-induced airway responses.[53,54] Hox et al. demonstrated that also the induction of airway hyperreactivity by inhalation of hypochlorite depends on TRPA1 stimulation.[55] A rapid and concentration-dependent decline in respiratory rate in mice, is considered an important toxicological parameter, because the RD_{50}—the irritant concentration inducing a 50% decrease in respiratory rate in mice (known as the Alarie animal bioassay)—correlates well with subjective complaints of sensory irritation in humans.[56]

Thus, it has been proposed that chronic irritant stimulation of TRPA1 and TRPV1 can lead to long-lasting neurogenic inflammation, contributing to tissue damage and development of airway disease and to prolonged airway hyperreactivity to multiple irritants—clinically corresponding to irritant-induced asthma.[51,52] However, this remains to be proven in humans.

Tissue irritation

Tissue irritation is characterized by direct epithelial damage of the airways induced by an irritant agent.[57] There is no clear correlation between exposure concentrations leading to sensory irritation—as measured with the Alarie animal bioassay—and those inducing tissue irritation in the respiratory

tract after single or repeated exposure.[58] Some compounds may cause tissue irritation and injury without exhibiting much sensory warning (e.g. HF). However, the two mechanisms are interlinked, as injured epithelium can lead to exposure of nerve endings and induce neurogenic inflammation.[57] Also, damaged epithelial cells release signaling molecules, acting as warning signals to the nearby tissues, and initiating and modulating an inflammatory response, which in turn can modulate the sensitivity and expression of sensory neuronal TRP receptors.[52]

Human bronchial biopsies taken shortly after an acute exposure to chlorine showed considerable epithelial desquamation with an inflammatory exudate and swelling of the subepithelial space.[59] Experimental animal studies have confirmed the importance of the airway barrier damage in the context of irritant-induced asthma.[60] Studies looking at long-term pathologic consequences of acute high-level irritant exposures followed by asthmatic symptoms (RADS) showed significant neutrophilic and/or eosinophilic inflammatory changes in the bronchial wall and remodeling similar to allergic asthma in many aspects.[61]

Interactions between irritation and sensitization

Several sensitizers also have irritant properties, including disinfectants (glutaraldehyde, quaternary ammonium salts, chloramine-T, isothiazolinone), ethanolamine and enzymes. Moreover, exposure to irritants and enzymes can increase the risk of sensitization[62] and may increase specific bronchial responsiveness to an allergen to which the subject has been previously sensitized.[63] Irritants can also disrupt the epithelial barrier and facilitate the crossing of allergens.[62] Moreover, airway epithelial cells express pattern recognition receptors (PRRs) that detect irritants and damage-associated molecular patterns (DAMPs) released upon tissue damage. The activation of epithelial PRRs leads to the release of endogenous danger signals that attract and activate innate and adaptive immune cells.[64]

7. Future steps, and conclusions

Potential preventive strategies (cleaning agent types, formulations, and respiratory health surveillance)

In the Occupational Health field, prevention is hierarchically classified into primary, secondary, and tertiary. The best practice is primary prevention that aims to eliminate or at least minimise exposure to occupational hazards at workplace to avoid the consequent health effects among exposed workers. This is in line with the standard principle that the 'work' and not the 'worker' should be considered the true 'ill' and so appropriately treated. If this is unachievable (regrettably often for economic reasons), secondary prevention can be implemented via periodical occupational health surveillance programmes among exposed workers for early detection of any detrimental health effect or symptom, and so to prevent the subsequent disease onset. When these interventions fail, tertiary prevention can only aim to anticipate the diagnosis of any occupational disease that has already occurred and to manage and possibly treat the worker's disease. The last intervention should be considered a failure of an occupational health preventive strategy, not only for the associated costs for the individual (worker's disease and potential job loss), but also for society (occupational disease medical costs and compensation).

In relation to the prevention of cleaning-related respiratory health effects, a primary preventive approach would require the identification of all cleaning agents able to damage the respiratory system. This is unlikely to be achieved, primarily because manufacturers are protected by industrial trade secrets (i.e. not all ingredients must be disclosed in products labels), and also not all the agents reported in the cleaning products have been tested for potential respiratory health effects. This being said, under current international occupational health and safety regulations, manufacturers have to test (in vitro and in vivo) new developed agents for any potential health effects and for the existing ones on the market, GHS standard risk phrases (i.e. codes that identify agents hazardous for health) must be provided in the products' technical safety data sheets. In addition, occupational exposure to

those hazardous should be regulated or restricted by national occupational health and safety regulations. Sadly, in several countries, occupational exposure limits have been agreed only for some carcinogens, not for irritants or sensitising agents, so excluding the majority of the over 300 agents that have been reported as asthmagens or respiratory hazards.[65] So, according to primary prevention, cleaning products manufacturers should avoid these hazardous ingredients (e.g. quaternary ammonium compounds), or at least use less harmful formulations (e.g. less volatile ortho-phthalaldehyde instead of glutaraldehyde), and eliminate cleaning products in spray format. Actually, a growing number of so-called 'green' cleaning products are now available on the market, and a recent cross-sectional study performed in 329 custodians found a higher prevalence of upper and lower respiratory symptoms associated with high exposure to traditional cleaning products compared with high exposure to environmentally preferable cleaning products. Nevertheless, it was observed that these 'green' products are not totally safe if inhaled.[2]

Another important primary preventive intervention should be to inform cleaners about the potential risks of cleaning job tasks, and to train them to safely use cleaning products. Inhalation accidents in cleaners, such as mixing bleach and ammonia in a small, poorly ventilated area, have been associated with asthma symptoms, reactive airway dysfunction syndrome, irritant-induced occupational asthma and work-exacerbated asthma.[3] Moreover, specific job tasks, such as kitchen cleaning and furniture polishing, cleaning windows, washing dishes, mopping/waxing the floor, spot-cleaning carpets and cleaning tiles and grout, have been identified as causes or exacerbation of asthma.[12,66–68] Personal respiratory protective equipment should be always considered the last resort, and there is no evidence or agreement on a specific respirator type able to protect from all cleaning-related respiratory health effects.

In many countries, domestic cleaners are mostly employed in the informal sector and/or in conditions characterized by a precarious status, low wages, limited workers' organization and few legal protections. Many cleaners have

limited impact on the products they have to use. Therefore, preventive approaches based on participation and empowerment of workers are more likely to induce sustainable changes in product use.[69]

As secondary prevention, occupational respiratory health surveillance programs should be implemented among cleaners. For example, periodical questionnaires could be administered to cleaners as screening tool to early detect work-related respiratory symptoms, followed, when positive, by peak flow diaries to monitor any significant lung function declines. Avoidance at this stage of exposure to the suspected hazardous cleaning agent (ideally confirmed by specific inhalation challenge tests when applicable) could improve and even reverse any detected respiratory health effect, and so prevent a subsequent disease onset. Unfortunately, the high turnover and job instability of this type of workforce make the implementation of this intervention often quite challenging, combined also to the known reluctancy of workers to report any symptoms for fear of losing their job.

Finally, as tertiary prevention, any respiratory health condition suspected to be work-related among cleaners should be diagnosed as soon as possible to avoid further exposure to the potential causal agent at work and so likely slow down disease progression. In addition, the diagnosis should be reported to national compensation authorities and, for preventive and epidemiological purposes, also to national (voluntary) surveillance schemes for occupational diseases, such as MODERNET in Europe,[70] in order to estimate the public health burden and incidence trends, identify potential new causal agents, and characterize associated respiratory phenotypes.

In conclusion, cleaning-related respiratory health effects are preventable by using an integrated multi-step approach mainly focused on primary prevention for which it is pivotal to identify in cleaning products the specific underlying respiratory hazardous agents.

Research gaps to address

A collaborative effort with a multidisciplinary translational approach involving also cutting-edge molecular methods, such as -omics, could help overcome the limitations of previous research studies and fill the knowledge gap on this topic. Ideally, in a large prospective cohort of professional cleaners, quantitative exposure assessment using personal sensitive air monitors designed to identify known (and possibly unknown) specific agents in cleaning products should be performed. This would allow to evaluate dose-response relationships, not only to support causal associations, but also to possibly establish 'safe' occupational exposure limits currently lacking. Also, the range of the identified respiratory health effects should be clinically phenotyped by class of chemical(s) and host characteristics; and elucidate their underlying aetiopathogenetic mechanisms.

If we want to implement efficient focused preventive interventions among professional cleaners it is a requisite that we identify specific causal agents and/or exposures; and understand the underlying pathogenic mechanisms, in particular because irritant agents are likely to have a 'no adverse health effect' threshold that could be used to establish limit values to protect exposed workers.

Finally, because any respiratory heath effect in individual cleaners, if recognised early, could be potentially cured by avoidance of further exposure to the causal agents in the workplace; it is mandatory, for both public health and ethical reasons, that further research investigations finish the work of unpacking this challenging black box.[71]

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3.3. Identifying cleaning products associated with short-term work-related respiratory symptoms: a workforce-based study in domestic cleaners [Research article]

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Under review: De Troeyer K, De Man J, Vandebroek E, Vanoirbeek JAJ, Hoet PHM, Nemery B, Vanroelen C, Casas L*, Ronsmans S* (*shared last author). *Identifying cleaning products associated with short-term work-related respiratory symptoms: a workforce-based study in Belgian domestic cleaners*

Abstract

Domestic cleaners have an increased risk of asthma-like and other respiratory symptoms and conditions—repeatedly associated with the use of bleach, ammonia, disinfectants, and sprays. Uncertainty exists about which products are most hazardous. We aimed to investigate, among professional domestic cleaners, the associations of ocular/respiratory outcomes with using specific types of products at work and with the ability to choose their own products.

Among domestic cleaners employed by "service vouchers" companies in Belgium, we administered an online questionnaire on ocular/respiratory symptoms (frequency and time relation to workdays), frequency of use of 40 types of products, and ability to choose one's own products. Work-relatedness was defined as symptoms improving/disappearing on days off-work. We studied associations between frequency of product-use and work-related outcomes (eye irritation, rhinitis symptoms, sore throat, laryngeal symptoms, asthma symptoms, cough) and with chronic bronchitis, using multivariable logistic and elastic net regression. Adjusted odds ratios (OR) with 95%-confidence intervals were obtained *per product used per week*.

Among 1,586 domestic cleaners (99% women), the number of sprays used per week (median 12/week) was significantly associated with all outcomes (ORs between 1.016 and 1.038 per spray per week). Bleach/disinfectant-containing liquid products were associated with work-related eye symptoms (OR 1.100;1.017–1.190) and asthma (OR 1.104;1.008–1.208); ammonia with chronic bronchitis (OR 1.463;1.053–2.035). Cleaners able to choose their own products had fewer work-related eye symptoms (OR 0.758;0.576–0.996), rhinitis (OR 0.746;0.578–0.963) or cough (OR 0.697;0.539–0.901). Using elastic net regression, work-related rhinitis was most strongly associated with mould removal spray (OR 1.108;1.006–1.248), carpet/seat/curtain spray (OR 1.099;1.001–1.304) and ammonia (OR 1.081;1.002–1.372); work-related asthma with carpet/seat/curtain spray (OR

1.103;1.017–1.322), mould removal spray (OR 1.029;0.995–1.199) and drain cleaner (OR 1.023;0.979–1.302).

In a large group of domestic cleaners, we documented that cleaning products are associated with a range of adverse respiratory effects. Empowering cleaners to choose their products may reduce the burden of symptoms.

Key words cleaning products; work-related rhinitis; work-related asthma; occupational exposures; empowerment; service vouchers

Key messages

What is already known about this subject?

Cleaning products, especially sprays, have been associated with short-term and chronic respiratory symptoms in domestic cleaners.

What are the new findings?

In a large workforce-based questionnaire study among domestic cleaners, we showed associations between spray use and work-related eye symptoms, rhinitis, sore throat, laryngeal symptoms, asthma, cough, and chronic bronchitis. We showed that some sprays are more of concern than others. Cleaners that are able to choose their own products had fewer work-related eye symptoms, rhinitis or cough.

How might this impact on policy or clinical practice in the foreseeable future?

Results support the recommendation to limit the use of cleaning sprays among professional domestic cleaners. This requires empowerment of domestic cleaners and a regulatory role by their employment bodies.

1. Introduction

Domestic cleaners have an increased risk of asthma-like symptoms.[1] Other lower and upper respiratory tract symptoms and conditions—such as rhinitis and chronic obstructive pulmonary disease (COPD)—are also more common in cleaners, although this has been less studied than asthma.[1] Bleach, ammonia, disinfectants, sprays and mixing incompatible products have been repeatedly associated with these respiratory effects.[2,3] It is currently unclear which products—or ingredients—are most hazardous.[3] The form in which cleaning products are used is a major determinant of exposure: while users of liquid products can inhale volatile ingredients (such as ammonia) or reaction products, users of sprays can potentially inhale volatile *and* non-volatile ingredients, such as quaternary ammonium compounds (QACs).[4] As cleaning products are complex chemical mixtures, and domestic cleaners use a range of products for various durations in different homes, exposure assessment is challenging.

Since 2004, in Belgium, domestic cleaning and other paid domestic tasks are organized in a so-called service voucher system intended to offer a regulated work environment.[5] Currently, around 150,000 workers are employed by approximately 1,800 "service voucher companies" that employ workers to provide domestic services to private clients. The domestic cleaners work for one up to ten fixed clients each week. Salaries (currently 9 € per hour) and other administrative aspects are legally and contractually defined, but the working conditions—including psychosocial and physical demands—are essentially determined by the clients, who provide the cleaners with the cleaning products.

In this unique context, we have set up a project with the long-term aim to improve respiratory health through preventive actions. In this article, we report the results of the first part of this project—an internet-based questionnaire study investigating the associations of the use of cleaning products with short-term work-related ocular and respiratory outcomes and with chronic bronchitis. Associations were studied with cleaning products

categorized according to their potential for inhalation, as well as with individual products. Work-relatedness was defined as symptoms which improve or disappear on days off-work. We also assessed if the occurrence of work-related outcomes was associated with the cleaner's ability to choose their cleaning products.

2. Methods

We did a cross-sectional study using a self-administered online questionnaire. Between 24 February and 20 March 2020, domestic cleaners working in the Belgian service voucher sector were invited 1) via Facebook groups—maintained by trade union organizations—exclusively used by domestic cleaners (with approximately 73,000 "followers" in total) and 2) by 10 service voucher companies (covering around 12,000 cleaners) that agreed to email their workers. We were unable to ascertain how many workers actually received and/or read our invitation. In the first trimester of 2020, 150,498 workers were registered as employee of a service voucher company.[6]

The questionnaire included questions on socio-economic and demographic characteristics (sex, age, country of origin, level of education, years working as a cleaner, number of hours working per week), ocular, respiratory and skin symptoms (frequency and time relation to workdays), frequency of use of 40 categories of cleaning products, smoking status and ability to choose one's own products. The questionnaire was exclusively available online in five languages (Dutch, French, English, Polish, Spanish) on the Qualtrics platform. The study was approved by the Ethics Committee Research UZ/KU Leuven (S62943).

2.1. Respiratory outcomes

In the questionnaire, we collected information about the frequency of watery/itchy eyes, nasal congestion, rhinorrea, sneezing, nasal itching, sore throat, hoarseness, throat tightness, cough, dyspnea, wheezing, chest tightness, and mucus production in the last 12 months (i.e., daily, several

times a week, several times a month, several times a year, never). Additionally, we asked if these symptoms improved or disappeared during weekends or holidays. Symptoms were considered *work-related* when they were present at least several times per week and improved or disappeared during weekends or holidays.

Work-related eye symptoms, sore throat, and cough were defined based on one symptom, while work-related rhinitis, inducible laryngeal obstruction (formerly known as “vocal cord dysfunction”), and asthma as well as chronic bronchitis were based on combinations of symptoms.

Work-related rhinitis was defined as the presence of at least 2 work-related rhinitis symptoms (nasal congestion, rhinorrhoea, sneezing and/or nasal itching).[7] Work-related inducible laryngeal obstruction was defined as a positive (≥4 points) adapted Pittsburgh vocal cord dysfunction index[8] (throat tightness = 4 points, hoarseness = 2 points, absence of wheezing = 2 points) and presence of work-related hoarseness and/or throat tightness.

For asthma, we used the definition of the European Community Respiratory Health Survey (ECRHS),[9] i.e. an affirmative answer to at least one of the following questions: "Have you ever been woken by an attack of shortness of breath at any time in the last 12 months?"; "Have you had an attack of asthma in the last 12 months?"; "Are you currently taking any medicine (including inhalers, aerosols or tablets) for asthma?". Work-related asthma was defined as ECRHS-defined asthma with the presence of work-related cough, dyspnea, wheezing and/or chest tightness.

Chronic bronchitis was defined as a positive answer to both “Do you cough for as much as 3 months each year?” and “Do you usually bring up phlegm from your chest on most days for as much as 3 months each year?”.

2.2. Cleaning products

The questionnaire included questions about the use of 40 different types of cleaning products (Figure 1) and the number of client homes at which the product was used (between zero and all their clients) and the average

frequency of use at the client's home (used every time they work in the client's home, used at least monthly, or used less than once a month). Combining these answers allowed us to estimate the weekly number of times a product was used.

Products were classified into 4 categories based on their potential to be inhaled (Table S1): general liquid cleaning products with a low-volatility potential (a), liquid cleaning products containing ingredients with high volatility—bleach and/or disinfectants (b) or ammonia (c), and cleaning products in spray form (d). For each category, the total number of times a product of the category was used per week was calculated.

The questionnaire included a question on how often products were mixed (never, sometimes, often). "Mixing of products" was considered as occurring when reportedly done sometimes or often. Also, participants could describe in a free text field which products they mixed.

Participants also indicated in how many of their clients' homes they could choose themselves which products they used: ability to choose one's cleaning products was considered to be present for participants declaring to have a choice in ≥ 50% of their clients' homes.

2.3. Potential confounders

Potential confounders were smoking (number of years, cigarettes/day), years working as a cleaner, education (as a proxy for socioeconomic status), exposure to mouldy odour and/or visible mould in the workplace ≥1 day per week, number of hours working per week (considered to reflect workplace exposures that were not addressed, such as house dust mite).

2.4. Statistical analysis

Multivariable logistic regression models were constructed to study associations between each outcome and the four categories of products, while adjusting for potential confounders (see above). Odds ratios (OR) and 95% confidence intervals (95%CI) were calculated *per product used per*

week. To handle missing data (outcome variables were missing for 11% to 19% of the participants, product use in 20%, covariates in 2% to 31%) a multivariate imputation with chained equations with 30 imputations was done, under the missing at random assumption. Rubin's rules were used to pool the results across the different imputations.[10] In sensitivity analyses we first excluded cleaners currently on sick leave, and secondly, those having worked as cleaners for 2 years or less. In a third sensitivity analysis, we repeated the analysis with non-imputed data.

Next, we performed elastic net regression for each outcome including all 40 cleaning products and potential confounders.[11] When assessing multiple correlated exposures simultaneously (see correlation matrix, Figure S3), penalized regression techniques, such as elastic net, have been shown—in simulation studies—to outperform conventional logistic regression approaches in recovering the underlying causal model.[12,13] By penalizing the magnitude of the coefficients, "unimportant" variables shrink toward zero, thus allowing selection of the most important variables.[12] An advantage of elastic net regression analysis is that the results are relatively straightforward to interpret and, therefore, actionable—unlike some other machine learning techniques.[12] The regression coefficients should, however, be interpreted with caution, because they are not corrected for the (intentional) bias towards zero introduced by the shrinkage. To find the optimal balance between ridge and lasso regression (alpha), we used repeated 5-fold cross-validation. Model selection was done using elastic net on the different imputed datasets with 5-fold cross-validation over different lambdas. ORs and bootstrap-based 95%CIs were calculated. In addition, variable importance measures (i.e. posterior effect probabilities) based on model averaging weights were calculated averaged over the imputed datasets (R package *MAMI*).[14]

All analyses were performed in R 3.6.0.[15] The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) recommendations were followed for reporting.[16]

3. Results

In total, 1,586 cleaners (99% women) responded to the questionnaire (Table 1). The median age was 38 years (interquartile range [IQR] 31–48). The median number of years working as a cleaner was 9 (IQR 5–15). A median working week consisted of 28 hours (IQR 22–32). The prevalence of work-related respiratory outcomes ranged from 8% for work-related sore throat to 28% for rhinitis. According to our operational definition, 31% of the participants had chronic bronchitis (Table 2).

The median number of liquid cleaning products with a low-volatility potential used was 13 per week (IQR 6.0–20.0), with the most frequently used in this group being floor cleaner (median 3/week, [IQR 2.0–4.5]), toilet cleaner (3/week, [IQR 1.5–4.5]) and all-purpose cleaner (2.5/week, [IQR 1.5–4.0]) (Figure 1). Liquid cleaning products containing bleach and/or disinfectants (median 0.5/week, [IQR 0.0–2.0]) or ammonia (only used by 3% of the participants at least once a week) were used less frequently. The median number of sprays used was 12 per week, these being most frequently bathroom spray (2.5/week, [IQR 1.0–4.0]), all-purpose spray (2.5/week, [IQR 1.5–4.0]), and limescale removal spray (1.5/week, [IQR 1.0–4.0]). Correlations between the use of the various products are shown in Figure S1.

Table 1. Demographic characteristics of the study population (n = 1,586)

	n (%) or median (IQR)* (total n = 1,586)
Demographic data	
Gender	
Woman	1,559 (99%)
Man	19 (1%)
Other	3 (0.2%)
Age (years)	38 (31–48)
Country of origin	
Belgium	1,203 (78%)
Poland	172 (11%)
Romania	43 (3%)
France	31 (2%)
The Netherlands	14 (1%)
Portugal	14 (1%)
Other	74 (5%)
Education (highest achieved diploma)	
None	10 (1%)
Primary education	177 (11%)
Secondary education	1,149 (74%)
Higher education	214 (14%)
Work experience	
Total n° of years working as a cleaner	9 (5–15)
Working hours per week	28 (22–32)
Currently on sick leave	227 (14%)
Total number of clients	8 (6–10)
Smoking	
Never smoker	450 (40%)
Former smoker	308 (28%)
Current smoker	356 (32%)
Number of cigarettes / day (in current smokers)	10 (8–15)
Packyears (in current/former smokers)	8 (4–15)

* *IQR = interquartile range*

Table 2. Exposure and respiratory outcomes of the study population (n = 1,586)

	n (%) or median (IQR)* (total n = 1,586)
Product use	
Product categories	
Liquid cleaning products with a low-volatility potential	
Times used per week	13.0 (6.0–20.0)
Participants using ≥ 1x/week	1,169 (92%)
Liquid cleaning products containing bleach and/or disinfectants	
Times used per week	0.5 (0.0–2.0)
Participants using ≥ 1x/week	509 (40%)
Liquid cleaning products containing ammonia	
Times used per week	0.0 (0.0–0.0)
Participants using ≥ 1x/week	43 (3%)
Cleaning products in spray form	
Times used per week	12.0 (5.0–21.0)
Participants using ≥ 1x/week	1,152 (91%)
Mixing products	
Often	28 (2%)
Sometimes	214 (18%)
Rarely or never	965 (80%)
Being able to choose the products used in ≥50% of the clients	741 (63%)
Exposure to mouldy smell or visible moulds in the room at work at least 1 day per week	306 (28%)
Respiratory outcomes	
Work-related eye symptoms	281 (21%)
Work-related rhinitis symptoms	387 (28%)
Work-related sore throat	104 (8%)
Work-related inducible laryngeal obstruction symptoms	206 (16%)
Work-related asthma symptoms	184 (13%)
Work-related cough	341 (24%)
Chronic bronchitis	423 (31%)

** IQR = interquartile range*

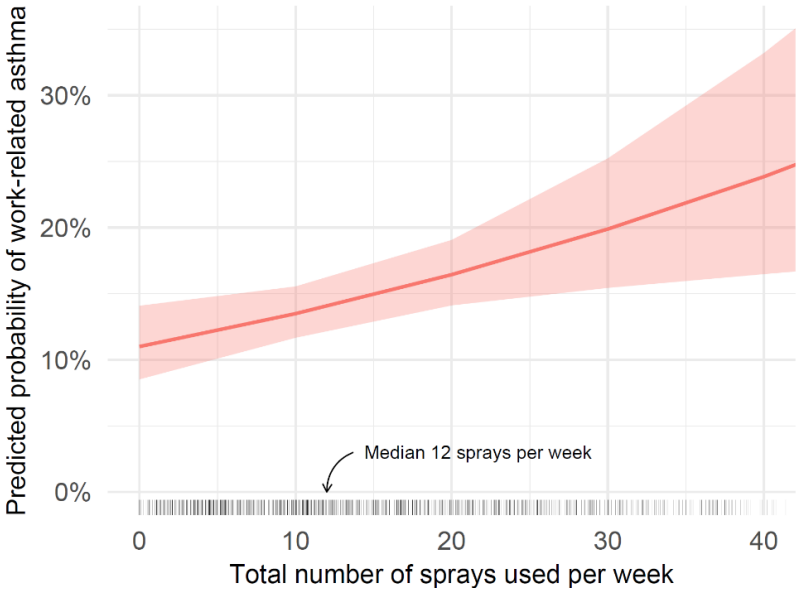
Figure 1. Frequency of reported use of 40 types of cleaning products (number of times per week)

*Histograms showing the number of times per week participants report using a type of cleaning product. For each type, white bars indicate the percentage of participants using zero products per week. Bar plots show the median number of times participants use this product (lower and upper hinges correspond to the first and third quartile; whiskers extend from the hinge to the largest value no further than 1.5 * interquartile range from the hinge).*

3.1. Associations between product use and respiratory outcomes—multivariable logistic regressions

The crude associations are shown in the supplemental material (Table S3). The adjusted associations (Table 3) showed that the number of cleaning sprays used weekly was significantly positively associated with all studied outcomes, with ORs ranging from 1.016 to 1.038 per spray used per week. For example, the odds of having work-related asthma were increased by 3.8% for each additional spray used per week. Figure 2 visualizes the estimated predicted probability of work-related asthma in relation to the number of sprays per week.[17]

Figure 2. Marginal effects plot showing the probability of work-related asthma in relation to the number of sprays used per week as predicted by the multivariable logistic regression model



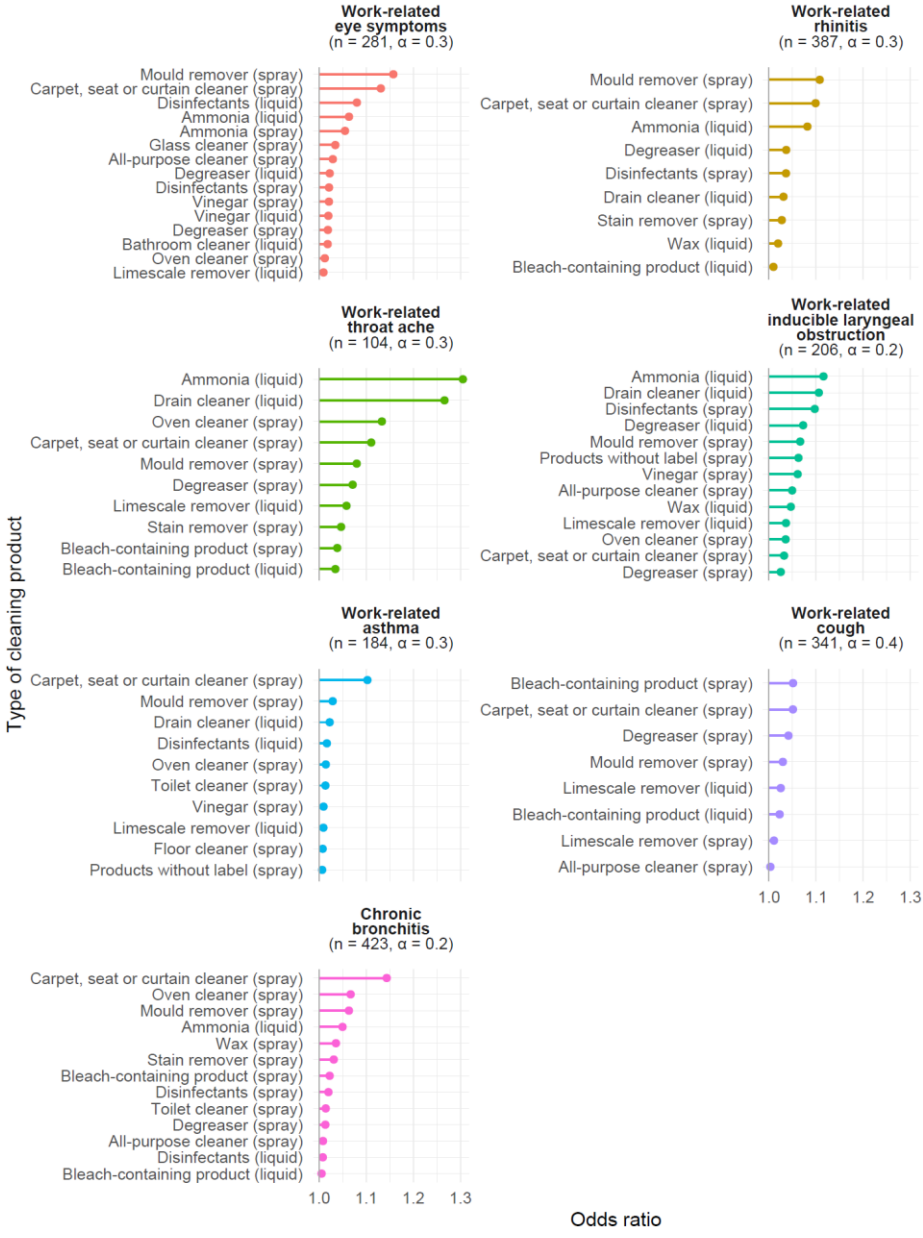
Probability of work-related asthma (with 95% confidence interval) in relation to the number of sprays used per week predicted by the multivariable logistic regression model, while holding covariates constant. Rug plot showing the number of sprays used by the individual participants.

Table 3. Associations between the use of cleaning products and respiratory symptoms: adjusted odds ratios (aOR) and 95% confidence intervals (95%CI) from the multivariable logistic regression models for each outcome (n = 1,586)

	Work-related eye symptoms (n = 281)	**Work-related rhinitis** (n = 387)	**Work-related sore throat** (n = 104)	**Work-related inducible laryngeal obstruction** (n = 206)	**Work-related asthma** (n = 184)	**Work-related cough** (n = 341)	**Chronic bronchitis** (n = 423)
General liquid products (per product/week)	0.979 (0.961–0.998)*	0.983 (0.966–1.000)§	0.962 (0.934–0.991)*	0.955 (0.933–0.977)*	0.967 (0.945–0.989)*	0.984 (0.966–1.002)§	0.976 (0.958–0.994)*
Bleach/disinfectant-containing liquids (per product/week)	1.100 (1.017–1.190)*	1.064 (0.990–1.144)§	1.092 (0.981–1.217)	1.040 (0.952–1.137)	1.104 (1.008–1.208)*	1.043 (0.968–1.124)	1.074 (0.992–1.163)§
Ammonia-containing liquids (per product/week)	1.159 (0.869–1.545)	1.174 (0.891–1.548)	1.381 (0.988–1.929)§	1.218 (0.914–1.624)	1.165 (0.854–1.589)	0.881 (0.671–1.157)	1.463 (1.053–2.035)*

	Work-related eye symptoms (n = 281)	**Work-related rhinitis** (n = 387)	**Work-related sore throat** (n = 104)	**Work-related inducible laryngeal obstruction** (n = 206)	**Work-related asthma** (n = 184)	**Work-related cough** (n = 341)	**Chronic bronchitis** (n = 423)
Sprays (per spray/week)	1.020 (1.005–1.036)*	1.016 (1.002–1.030)*	1.036 (1.014–1.059)*	1.038 (1.019–1.056)*	1.024 (1.006–1.041)*	1.023 (1.008–1.037)*	1.022 (1.007–1.037)*
Mixing products (ever vs never)	0.995 (0.704–1.406)	1.243 (0.904–1.709)	1.399 (0.887–2.205)	1.210 (0.836–1.752)	0.886 (0.578–1.359)	1.001 (0.724–1.386)	1.121 (0.809–1.553)
Being able to choose products (≥ 50% vs <50% of the clients)	0.758 (0.576–0.996)*	0.746 (0.578–0.963)*	0.964 (0.619–1.502)	1.003 (0.734–1.370)	0.933 (0.680–1.280)	0.697 (0.539–0.901)*	0.983 (0.762–1.269)

*Column headers show the number of participants with the outcome, i.e. prevalent cases (n). Crude odds ratios are shown in the supplemental material (Table S3). Data shown here as aOR (95%CI) with adjustments for all other cleaning product categories, self-reported mixing of products, being able to choose their own products, and potential confounders (education, mould at the workplace, smoking [number of years and number of cigarettes daily], number of years working as a cleaner, and number of hours working per week). Results are pooled across 30 imputed datasets. * indicates p-value <0.05, § p-value <0.1*


Work-related eye symptoms (n = 281, α = 0.3)
Mould remover (spray)
Carpet, seat or curtain cleaner (spray)
Disinfectants (liquid)
Ammonia (liquid)
Ammonia (spray)
Glass cleaner (spray)
All-purpose cleaner (spray)
Degreaser (liquid)
Disinfectants (spray)
Vinegar (spray)
Vinegar (liquid)
Degreaser (spray)
Bathroom cleaner (liquid)
Oven cleaner (spray)
Limescale remover (liquid)
Work-related rhinitis (n = 387, α = 0.3)
Mould remover (spray)
Carpet, seat or curtain cleaner (spray)
Ammonia (liquid)
Degreaser (liquid)
Disinfectants (spray)
Drain cleaner (liquid)
Stain remover (spray)
Wax (liquid)
Bleach-containing product (liquid)
Work-related throat ache (n = 104, α = 0.3)
Ammonia (liquid)
Drain cleaner (liquid)
Oven cleaner (spray)
Carpet, seat or curtain cleaner (spray)
Mould remover (spray)
Degreaser (spray)
Limescale remover (liquid)
Stain remover (spray)
Bleach-containing product (spray)
Bleach-containing product (liquid)
Work-related inducible laryngeal obstruction (n = 206, α = 0.2)
Ammonia (liquid)
Drain cleaner (liquid)
Disinfectants (spray)
Degreaser (liquid)
Mould remover (spray)
Products without label (spray)
Vinegar (spray)
All-purpose cleaner (spray)
Wax (liquid)
Limescale remover (liquid)
Oven cleaner (spray)
Carpet, seat or curtain cleaner (spray)
Degreaser (spray)
Work-related asthma (n = 184, α = 0.3)
Carpet, seat or curtain cleaner (spray)
Mould remover (spray)
Drain cleaner (liquid)
Disinfectants (liquid)
Oven cleaner (spray)
Toilet cleaner (spray)
Vinegar (spray)
Limescale remover (liquid)
Floor cleaner (spray)
Products without label (spray)
Work-related cough (n = 341, α = 0.4)
Bleach-containing product (spray)
Carpet, seat or curtain cleaner (spray)
Degreaser (spray)
Mould remover (spray)
Limescale remover (liquid)
Bleach-containing product (liquid)
Limescale remover (spray)
All-purpose cleaner (spray)
Chronic bronchitis (n = 423, α = 0.2)
Carpet, seat or curtain cleaner (spray)
Oven cleaner (spray)
Mould remover (spray)
Ammonia (liquid)
Wax (spray)
Stain remover (spray)
Bleach-containing product (spray)
Disinfectants (spray)
Toilet cleaner (spray)
Degreaser (spray)
All-purpose cleaner (spray)
Disinfectants (liquid)
Bleach-containing product (liquid)
1.0
1.1
1.2
1.3
Type of cleaning product
Odds ratio

← **Figure 3.** Results from the model selection using elastic net regression showing cleaning products most strongly associated with the different respiratory health effects.

Odds ratios for the cleaning products selected by the elastic net regression procedure and positively associated with the respiratory health outcomes. All 40 types of cleaning products and potential confounders (smoking [number of years, cigarettes/day], years working as a cleaner, education, presence of mouldy odour and/or visible mould in the workplace, number of clients and number of hours working per week) were included. As results are pooled across 30 imputed datasets, a variable is selected when it is selected in at least one imputed dataset—but its overall impact depends on how often it is selected. Variables with posterior effect probability (variable importance) > 0.60 are shown. For each outcome, the optimal alpha is shown in the header. Full models are shown in Table S6.

After adjustment, the use of bleach/disinfectant-containing liquid products was significantly positively associated with work-related eye symptoms (OR 1.100 per product used in 1 week; 95%CI 1.017–1.190) and asthma (OR 1.104; 95%CI 1.008–1.208). The use of ammonia-containing liquid products was associated with chronic bronchitis (OR 1.463; 95%CI 1.053–2.035). The use of general liquid cleaning products with a low-volatility potential was *negatively* associated with work-related eye symptoms (OR 0.979 per product used in 1 week; 95%CI 0.961–0.998), sore throat (OR 0.962; 95%CI 0.934–0.991), inducible laryngeal obstruction (OR 0.955 95%CI 0.933–0.977), asthma (OR 0.967; 95%CI 0.945–0.989), and chronic bronchitis (OR 0.976; 95%CI 0.958–0.994). Mixing of products was not associated with any outcome. Also, no statistically significant interaction terms were found between the use of ammonia, bleach/disinfectants and product mixing.

Cleaners having the ability to choose their cleaning products were less likely to report work-related eye symptoms (OR 0.758; 95%CI 0.576–0.996), rhinitis (OR 0.746; 95%CI 0.578–0.963) or cough (OR 0.697; 95%CI 0.539–0.901) in the multivariable analyses.

Repeating the multivariable logistic regression models in a sensitivity analysis excluding cleaners who were currently on sick leave yielded comparable results (data not shown). Also, excluding respondents employed for 2 years or less, nor restricting the analysis to non-imputed data did not substantially change the regression coefficients (Table S4 and S5).

3.2. Associations between product use and respiratory outcomes—elastic net regressions

Results from the model selection using elastic net regression are shown in Figure 3. For each outcome, ORs for the cleaning products most strongly associated with the respiratory health effects are shown (ORs, bootstrap-based 95%CIs and variable importance measures for the full models are shown in Table S6).

Carpet, seat or curtain sprays were identified as being associated to all respiratory outcomes: for work-related rhinitis OR was 1.099 per spray used

per week (95%CI 1.001–1.304), for work-related asthma, OR was 1.103 (95%CI1.017–1.322), and for chronic bronchitis, OR was 1.143 (95%CI 0.998–1.336). Also, mould removal spray was associated with all respiratory outcomes (rhinitis, OR 1.108 [95%CI 1.006–1.248]; asthma, OR 1.029 [95%CI 0.995–1.199]; chronic bronchitis, OR 1.063 [95%CI 0.954–1.221]). Ammonia (liquid) was associated with work-related eye symptoms (OR 1.063; 95%CI 1.039–1.263), rhinitis (OR 1.081; 95%CI 1.002–1.372), inducible laryngeal obstruction (OR 1.116; 95%CI 1.017–1.702), sore throat (OR 1.305; 95%CI 1.107–1.978) and chronic bronchitis (OR 1.050; 95%CI 1.014–1.400).

Also, drain cleaners (liquid), disinfectant sprays, degreasing sprays, oven sprays, limescale remover (liquid), bleach (liquid), and all-purpose cleaner (spray) were associated with at least four outcomes (Figure 3).

4. Discussion

In our survey of a large sample of domestic cleaners, we show that the number of cleaning sprays used per week was significantly associated with all studied work-related respiratory outcomes and with chronic bronchitis. Bleach/disinfectant-containing liquid products were associated with work-related eye symptoms and asthma; liquid ammonia with chronic bronchitis. Moreover, cleaners able to choose their own products reported fewer work-related eye symptoms, rhinitis or cough. Using elastic net regression analysis, we assessed in detail which cleaning products—of the 40 questioned—were most strongly related to work-related respiratory symptoms.

A recent systematic review and meta-analysis estimated a 50% increased risk of asthma and 43% of COPD among occupational cleaners.[1] Working as a cleaner has also been associated with eye,[18] nose,[18–20], and throat symptoms.[18] In our study, we assessed respiratory symptoms that have a *short-term time relationship* with work.[21] We defined "work-related" respiratory symptoms as symptoms that disappear or improve on days off-work—which has been shown to be a typical clinical feature of work-related asthma and rhinitis (defined as asthma/rhinitis *caused* or *exacerbated* by

work).[22] Our study design did not allow us to differentiate sensitizer-induced, irritant-induced and work-exacerbated symptoms.

As our questionnaire was distributed in the weeks before the first Belgian lockdown due to the COVID-19 pandemic, i.e., when no recommendations were yet in place to increase disinfectant use, the frequencies of use in our study represent product use "pre-COVID-19".

4.1. Liquid cleaning products

Our results show that the more general liquid products (non-spray and with a low-volatility potential) cleaners use, the less likely they are to report work-related respiratory symptoms (OR<1 for all outcomes). Previously, in a nested case-control study in Spanish domestic cleaners, liquid multi-use cleaning products were also less used by cases with asthma than by controls.[23] Cleaners using more general liquid cleaning products are probably less likely to use other—potentially more hazardous—"competing" products, which might explain these findings.[23] In a small Spanish panel study in cleaners, multi-use products were not associated with lower respiratory tract symptoms (OR 1.0, 95%CI 0.6–1.8), nor with short-term changes in FEV_1.[24] Also, in the ECRHS general population cohort using ≥ 1x/week liquid multi-use products was not associated with new-onset asthma.[25]

In our study, the use of bleach/disinfectant-containing liquid products was significantly associated with work-related eye symptoms and asthma. Also, the use of these products increased the odds of work-related rhinitis and chronic bronchitis, although the associations were not statistically significant. This is in line with previous studies showing associations between the use of hypochlorite (household bleach) and upper and lower respiratory tract symptoms,[21,24,26] including short-term decline in FEV_1 in subjects with and without bronchial hyperreactivity.[27]

In addition, the use of liquid ammonia in our study was associated with work-related sore throat and chronic bronchitis. However, in the elastic net regression (see below), ammonia was also associated with other upper

respiratory tract symptoms. Ammonia was used by a minority of the participants—only 3.4% of the cleaners reported using ammonia-containing products at least once a week. The use of ammonia has been previously related to upper [24] and lower respiratory tract symptoms.[21,23]. Due to its water-solubility, acute irritant effects of ammonia are generally limited to the upper respiratory tract.[28]

4.2. Cleaning sprays

Our results indicate that applying sprays was common among the participants (median 12 sprays per week). Multivariable regression analysis showed that the total number of cleaning sprays used per week was significantly associated with all studied respiratory outcomes. Recently, Clausen et al. reviewed the literature on the respiratory health effects of spray use—including epidemiological, clinical and toxicological studies—showing overwhelming evidence that the use of cleaning sprays is associated with a range of adverse respiratory outcomes.[3] Also, associations with *short-term* respiratory symptoms in individuals with asthma or chronic bronchitis have been reported.[21,24] Although several ingredients have been linked to respiratory disorders—such as bleach and quaternary ammonium compounds (QACs)—there is uncertainty about *which* sprays are most hazardous.

4.3. Products most strongly associated with respiratory outcomes

We used elastic net regression to identify which of 40 types of products had the strongest associations with the outcomes. The results show that carpet, seat or curtain sprays and mould removal sprays (generally bleach-based products) were relevant for all outcomes (Figure 3). The use of carpet, seat or curtain sprays —used at least once per week by 9.3% of the participants—was most strongly associated with work-related asthma (OR 1.103 per spray per week [95%CI 1.017–1.322]). An Australian study in professional cleaners previously reported an OR of 3.25 [95%CI 1.16–9.10] for asthma (users vs non-users).[29] In the ECRHS cohort, however, no

increased incidence of new-onset asthma was found for the use of these sprays (used ≥1/week by 1.3% of the participants).[25]

We also found that disinfectant sprays—and to a lesser extent liquid disinfectant—were associated with a wide range of symptoms (Figure 3). Previous studies in healthcare workers have shown associations between exposure to disinfectants and work-related nasal symptoms,[30] asthma,[30,31] and COPD.[32] Vandenplas et al. found that QACs were the most common agent resulting in positive specific inhalation challenge (SIC) tests when assessing occupational asthma in cleaners (10 out of 44 cleaners who underwent SIC).[33]

Oven cleaning sprays were associated with work-related eye and throat symptoms, inducible laryngeal obstruction, asthma and chronic bronchitis. However, several previous studies did not find associations between lower respiratory tract symptoms/asthma and oven sprays [25,29]. With degreasing sprays similar associations were shown, although not with work-related asthma. Previous studies have linked degreasing sprays to short-term lower respiratory tract symptoms (OR 6.9 [95%CI 2.9–16]),[21,24] and asthma (OR 3.3 [95%CI 1.3–8.2]).[34]

In summary, our study—and the existing literature—show a complex picture of the associations between specific types of sprays and respiratory outcomes, which can be at least partly attributed to the fact that using sprays belonging to the same category can lead to very different actual exposures, because of different (concentrations of) ingredients and size distributions of the generated aerosol (which largely depend on the spray nozzle and dispersion mechanism).[35]

4.4. Mixing

Mixing of products was not significantly associated with any outcome in the multivariable regression analyses. In a free text field in which participants could describe the products they mixed, only 22 cleaners (2%) mentioned (currently) mixing bleach with ammonia or acid-containing products—which could potentially generate hazardous volatile reaction products. Cleaners are

generally warned during their training against the hazards of mixing incompatible products.

4.5. Being able to choose

Of note, cleaners that indicated that they were able to choose themselves the products they work with, were less likely to report work-related eye symptoms, rhinitis or cough in the multivariable analysis. As these associations were adjusted for product use, this indicates that, on average, among cleaners using the same number of products of each category, those who can choose their products themselves, reported fewer symptoms than those who do not have a choice. These findings suggest that cleaners experiencing work-related symptoms might adjust their product use and switch to other, less aggressive, products—potentially within the same product category.

However, the association between being able to choose themselves the products they work with, and work-related respiratory symptoms can be potentially confounded by other factors, such as psychological well-being or sense of job control in general, for which we were unable to adjust. This unmeasured potential confounding limits a straightforward interpretation of the association. Nevertheless, our findings suggest that it might be useful to include factors related to having a sense of control over product use, in studies on the health effects of cleaning products.

This novel observation demonstrates the importance of understanding the relation between cleaners and their clients when aiming for better prevention. Although the official employer of the cleaners is the “service voucher company”, it is the client, who provides them with the cleaning products. Therefore, cleaners are not always able to avoid products that they may estimate or experience to be harmful. In addition to training cleaners about the hazards of certain products, empowering them to negotiate which products to use might be beneficial for prevention. Service voucher companies might inform their clients about certain products’ hazards—for the cleaners as well as for the residents of the homes (particularly children

and elderly).[36–38] Moreover, providing a (binding) list of products that the cleaners may or may not use in the client's homes, and checking compliance with such a list (for example by home visits) should be considered.

4.6. Strengths and limitations

Our study was one of the largest workforce-based studies in domestic cleaners to date. The sample was demographically comparable to the total population working in the sector. When compared to data from the Belgian National Social Security Office, our study population was similar to the entire population working in the service voucher sector, albeit slightly younger (Table S2).[6]

The available studies of domestic cleaners have generally involved far fewer participants [19,21,23,39] because in most countries domestic cleaning is part of the informal sector, thus complicating the recruitment of high numbers of participants in this sector. The existence of the service voucher system in Belgium and a close collaboration with stakeholders, including employers and unions, has allowed us to "recruit" more than 1000 participants in a few weeks. In fact, we were surprised that so many women (many of whom of foreign origin and with rather low educational level) were prepared to participate (voluntarily and without any incentive) in an internet survey. Because we were unable to ascertain how many workers actually received and/or read our invitation, we do not know the precise participation rate, although we estimate it to be between 1% and 10%. Nevertheless, the high number of respondents gives us confidence about the external validity of our findings, even if it is conceivable that mainly the most health-conscious fraction of the workforce participated in the survey. The high number of participants is also a testament of the concern existing about health issues among cleaners.

The use of elastic net regression analysis is another strength of our study. Studies using simulated data with multiple correlated exposures have shown that elastic net regression outperforms conventional logistic regression approaches in recovering the underlying causal model. Nevertheless, few

studies have hitherto used this technique.[12,13] In our study, elastic net regression identified several known associations between products and respiratory symptoms—such as the specific irritant effects of ammonia on the eyes and upper airways—which strengthened our confidence in the technique. Moreover, the results provide various clues for further research, for example, on the respiratory effects of using carpet/seat/curtain or mould removal sprays.

However, our study has some limitations. As our study population was a non-probability sample, the descriptive statistics—especially the prevalence of work-related symptoms—cannot be claimed representative for the overall population of cleaners. Nevertheless, we believe that after controlling for key covariates, the identified associations are reasonable reflections of a general trend. We also think that the influence of self-selection on these associations was limited since some products were significantly associated with reported symptoms and conditions, while others were not.

As we wanted to study the association of *current* product use with *current* work-related respiratory symptoms—i.e., symptoms improving when off-work— a cross-sectional design was appropriate. However, our study design does not allow us to making inferences on which products might have caused the *onset* of these respiratory health effects. Experiencing respiratory symptoms could induce changes in product use—if the worker can convince the client of providing other products. Although this might bias associations between product use and *incidence* of respiratory symptoms (healthy worker effect),[40] this bias is expected to influence the associations between product use and short-term work-related symptoms to a lesser extent.

Serious respiratory symptoms may result in leaving the job permanently or temporarily. Our sample included 227 (14%) cleaners who were currently on sick leave. Although we are unaware of the reasons for sick leave (e.g., musculoskeletal, mental health, skin or other problems), a sensitivity analysis excluding these workers did not substantially change the effect estimates.

Although we did not have objective tests for the respiratory outcomes — such as spirometry—we used validated questionnaire-based definitions for rhinitis, inducible laryngeal obstruction, asthma and chronic bronchitis that have been shown to be specific.[7–9] For example, the ECRHS asthma definition has been shown to be 95% specific for the presence of bronchial hyperresponsiveness.[9]

Another limitation is the exposure assessment. Exposure estimates were based on self-reported frequency of use of 40 types of products, without information on important determinants such as the specific ingredients, exact duration of use, room size and ventilation. Improving exposure assessment in studies among domestic cleaners is crucial.[2] While workplace measurements are challenging, Quinot et al have developed a promising approach using a smartphone app with which users can scan product barcodes, linked to an ingredient database, enabling modelling of exposures.[41]

5. Conclusions

Based on our findings, which are generally consistent with the literature, we recommend a reduction of the use of sprays by professional domestic cleaners.[42] Our findings also lead us to conclude that allowing domestic cleaners to choose their cleaning products may represent a way to reduce the use of harmful cleaning products. Such empowerment should be backed by information given by the employers to the workers and the clients and by regulatory measures ensuring effective implementation of the preventive measures in the workplace.

Contributors

KDT: writing-original draft**,** methodology**,** data acquisition, statistical analysis; **JDM:** writing-review & editing, methodology, statistical analysis**; EV:** writing-review & editing, data acquisition; **JAV**: writing-review & editing; **PHMH**: writing-review & editing; **BN:** writing-review & editing, conceptualization**; CV:** writing-review & editing, conceptualization**; LC:** writing-review & editing, conceptualization, methodology, supervision; **SR:** writing-review & editing, methodology, conceptualization, data acquisition, statistical analysis, project administration.

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Role of the funding source

The funding source had no involvement in study design, in the collection, analysis and interpretation of data, in the writing of the report, or in the decision to submit the article for publication.

Competing interests

The authors declare they have no actual or potential competing financial interests.

Ethics approval

The study was approved by the Ethics Committee Research UZ/KU Leuven (S62943).

Data availability statement

Data are available upon reasonable request (steven.ronsmans@kuleuven.be)

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Supplementary material

Table S1 Classification of the cleaning products based on their potential to be inhaled

Product category	Type of product
(a) General liquid cleaning products with a low-volatility potential	All-purpose cleaner (liquid)
	Floor cleaner (liquid)
	Glass cleaner (liquid)
	Degreaser (liquid)
	Oven cleaner (liquid)
	Drain cleaner (liquid)
	Limescale remover (liquid)
	Vinegar (liquid)
	Wax or polish (liquid)
	Cleaner for carpets, seats, curtains (liquid)
	Stain remover (liquid)
	Cleaning product for bathroom (liquid)
	Cleaner for kitchen work surface and tiles (liquid)
	Toilet cleaner (liquid)
(b) Liquid cleaning products containing ingredients with high volatility—bleach and/or disinfectants	Disinfectants (liquid)
	Products containing bleach (liquid)
	Mould remover (liquid)
(c) Liquid cleaning products containing ingredients with high volatility—ammonia	Ammonia (liquid)
(d) Cleaning products in spray form	All sprays

Table S2 Comparison of age, sex and working hours per week between our study population and the population working in the service voucher sector according to the National Social Security Office (Belgium) in the first trimester of 2020

	Study population (n=1,586)	National Social Security Office (n=150,498)
	N (%)	N (%)
Age		
<25y	75 (4.7%)	5,386 (3.6%)
25-39	761 (47.9%)	51,782 (34.4%)
40-49	407 (25.7%)	43,366 (28.8%)
50-64	311 (21.5%)	48,509 (32.2%)
≥65	32 (0.2%)	1,455 (1.0%)
Sex		
Men	19 (1.2%)	4,158 (2.8%)
Women	1,559 (98.8%)	146,340 (97.2%)
Working hours per week		
<17h/week	110 (7.0%)	23,688 (15.7%)
17 - 25h/week	466 (29.7%)	48,369 (32.1%)
25.5 - 36h/week	827 (52.7%)	62,436 (41.5%)
36.5-37.5h/week	25 (1.6%)	4,321 (2.9%)
38h/week or more	142 (9.0%)	11,684 (7.8%)

Figure S1: Correlation matrix showing correlations between frequency of use of the different types of cleaning products

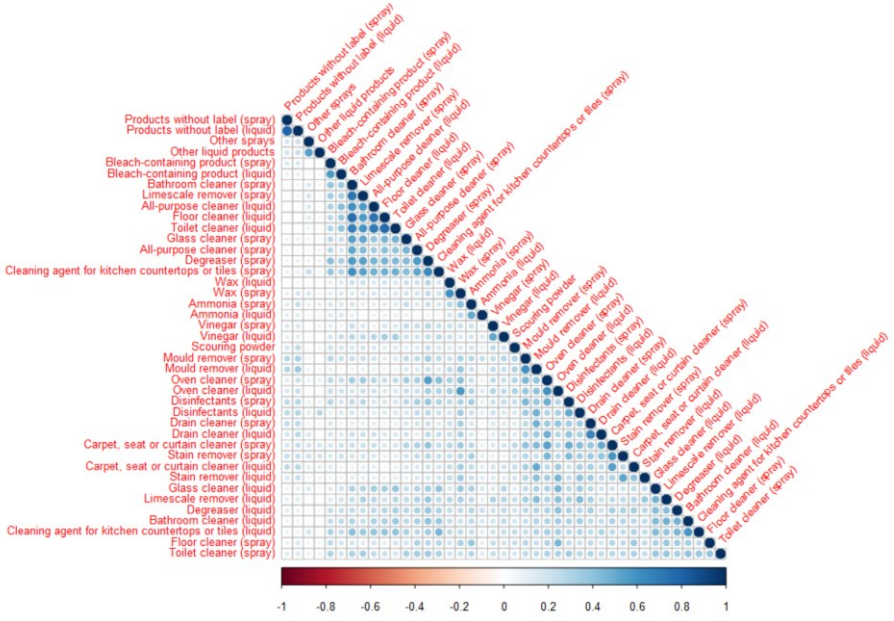

Table S3: Associations between the use of cleaning products and respiratory symptoms: unadjusted (OR) and adjusted odds ratios (aOR) and 95% confidence intervals (95%CI) from the univariable and multivariable logistic regression models for each outcome

	Work-related eye symptoms (n = 281)		**Work-related rhinitis** (n = 387)		**Work-related sore throat** (n = 104)	
	OR (95%CI)	aOR (95%CI)	OR (95%CI)	aOR (95%CI)	OR (95%CI)	aOR (95%CI)
General liquid products (per product/week)	1.017 (1.007–1.027)*	0.979 (0.961–0.998)*	1.012 (1.003–1.021)*	0.983 (0.966–1.000)§	1.022 (1.008–1.036)*	0.962 (0.934–0.991)*
Bleach/disinfectant-containing liquids (per product/week)	1.140 (1.082–1.202)*	1.100 (1.017–1.190)*	1.103 (1.049–1.160)*	1.064 (0.990–1.144)§	1.174 (1.099–1.254)*	1.092 (0.981–1.217)
Ammonia-containing liquids (per product/week)	1.385 (1.085–1.769)*	1.159 (0.869–1.545)	1.356 (1.062–1.732)*	1.174 (0.891–1.548)	1.662 (1.281–2.158)*	1.381 (0.988–1.929)§
Sprays (per spray/week)	1.020 (1.012–1.028)*	1.020 (1.005–1.036)*	1.016 (1.009–1.023)*	1.016 (1.002–1.030)*	1.027 (1.017–1.038)*	1.036 (1.014–1.059)*
Mixing products (ever vs never)	1.078 (0.779–1.492)	0.995 (0.704–1.406)	1.331 (0.980–1.809)§	1.243 (0.904–1.709)	1.611 (1.050–2.471)*	1.399 (0.887–2.205)
Being able to choose products (≥ 50% vs <50% of the clients)	0.711 (0.544–0.929)*	0.758 (0.576–0.996)*	0.724 (0.564–0.929)*	0.746 (0.578–0.963)*	0.868 (0.569–1.324)	0.964 (0.619–1.502)

*In the multivariable regression, odds ratios are adjusted for all other cleaning product categories, self-reported mixing of products, being able to choose their own products, and potential confounders (education, mould at the workplace, smoking [number of years and number of cigarettes daily], number of years working as a cleaner, and number of hours working per week). Results are pooled across 30 imputed datasets. * indicates p-value <0.05, § p-value <0.1*

Table S3 (continuation)

Work-related inducible laryngeal obstruction (n = 206)		**Work-related asthma** (n = 184)		**Work-related cough** (n = 341)		**Chronic bronchitis** (n = 423)	
OR (95%CI)	aOR (95%CI)	OR (95%CI)	aOR (95%CI)	OR (95%CI)	aOR (95%CI)	OR (95%CI)	aOR (95%CI)
1.006 (0.994–1.017)	0.955 (0.933–0.977)*	1.008 (0.997–1.020)	0.967 (0.945–0.989)*	1.013 (1.003–1.022)*	0.984 (0.966–1.002)§	1.008 (0.999–1.017)§	0.976 (0.958–0.994)*
1.083 (1.020–1.149)*	1.040 (0.952–1.137)	1.114 (1.052–1.180)*	1.104 (1.008–1.208)*	1.095 (1.040–1.152)*	1.043 (0.968–1.124)	1.106 (1.049–1.165)*	1.074 (0.992–1.163)§
1.347 (1.061–1.709)*	1.218 (0.914–1.624)	1.349 (1.052–1.729)*	1.165 (0.854–1.589)	1.096 (0.868–1.382)	0.881 (0.671–1.157)	1.710 (1.255–2.330)*	1.463 (1.053–2.035)*
1.017 (1.008–1.026)*	1.038 (1.019–1.056)*	1.015 (1.006–1.024)*	1.024 (1.006–1.041)*	1.017 (1.009–1.025)*	1.023 (1.008–1.037)*	1.014 (1.007–1.022)*	1.022 (1.007–1.037)*
1.415 (0.992–2.018)§	1.210 (0.836–1.752)	1.007 (0.673–1.508)	0.886 (0.578–1.359)	1.056 (0.773–1.444)	1.001 (0.724–1.386)	1.248 (0.918–1.697)	1.121 (0.809–1.553)
0.933 (0.689–1.263)	1.003 (0.734–1.370)	0.869 (0.640–1.178)	0.933 (0.68–1.280)	0.668 (0.520–0.858)*	0.697 (0.539–0.901)*	0.986 (0.776–1.254)	0.983 (0.762–1.269)

Table S4. Sensitivity analysis excluding cleaners that have been working 2 years or less (n = 1,356). Associations between the use of cleaning products and respiratory symptoms: adjusted odds ratios (aOR) and 95% confidence intervals (95%CI) from the multivariable logistic regression models for each outcome

	Work-related eye symptoms (n = 252)	**Work-related rhinitis** (n = 339)	**Work-related sore throat** (n = 84)	**Work-related inducible laryngeal obstruction** (n = 178)	**Work-related asthma** (n = 162)	**Work-related cough** (n = 297)	**Chronic bronchitis** (n = 363)
General liquid products (per product/week)	0.975 (0.955–0.995)*	0.980 (0.962–0.998)*	0.959 (0.928–0.990)*	0.953 (0.929–0.977)*	0.965 (0.943–0.989)*	0.981 (0.962–1.000)§	0.974 (0.955–0.993)*
Bleach/disinfectant-containing liquids (per product/week)	1.115 (1.026–1.211)*	1.078 (0.998–1.164)§	1.092 (0.973–1.227)	1.037 (0.943–1.140)	1.115 (1.014–1.226)*	1.037 (0.957–1.123)	1.081 (0.993–1.178)§
Ammonia-containing liquids (per product/week)	1.127 (0.824–1.542)	1.134 (0.840–1.531)	1.185 (0.810–1.732)	1.149 (0.838–1.574)	1.237 (0.879–1.739)	0.818 (0.606–1.104)	1.540 (1.028–2.306)*
Sprays (per spray/week)	1.022 (1.006–1.038)*	1.017 (1.002–1.032)*	1.039 (1.015–1.064)*	1.040 (1.020–1.061)*	1.024 (1.006–1.042)*	1.026 (1.010–1.042)*	1.024 (1.009–1.040)*
Mixing products (ever vs never)	1.030 (0.711–1.491)	1.279 (0.907–1.802)	1.382 (0.834–2.292)	1.175 (0.778–1.773)	0.852 (0.542–1.338)	0.934 (0.660–1.322)	1.208 (0.849–1.719)
Being able to choose products (≥ 50% vs <50% of the clients)	0.741 (0.553–0.992)*	0.765 (0.583–1.004)§	0.939 (0.592–1.487)	0.968 (0.696–1.347)	0.941 (0.672–1.319)	0.738 (0.560–0.973)*	0.958 (0.730–1.259)

*Data shown as aOR (95%CI) with odds ratios adjusted for all other cleaning product categories, self-reported mixing of products, being able to choose their own products, and potential confounders (education, mould at the workplace, smoking [number of years and number of cigarettes daily], number of years working as a cleaner, and number of hours working per week). Results are pooled across 30 imputed datasets. * indicates p-value <0.05, § p-value <0.1*

Table S5. Sensitivity analysis using non-imputed data. Associations between the use of cleaning products and respiratory symptoms: adjusted odds ratios (aOR) and 95% confidence intervals (95%CI) from the multivariable logistic regression models for each outcome

	Work-related eye symptoms (n = 281)	**Work-related rhinitis** (n = 387)	**Work-related sore throat** (n = 104)	**Work-related inducible laryngeal obstruction** (n = 206)	**Work-related asthma** (n = 184)	**Work-related cough** (n = 341)	**Chronic bronchitis** (n = 423)
General liquid products (per product/week)	0.982 (0.959–1.003)	0.988 (0.968–1.008)	0.970 (0.936–1.003)§	0.959 (0.933–0.985)*	0.978 (0.951–1.004)	0.988 (0.967–1.008)	0.975 (0.953–0.997)*
Bleach/disinfectant-containing liquids (per product/week)	1.087 (0.991–1.193)§	1.057 (0.971–1.15)	1.050 (0.920–1.195)	0.953 (0.856–1.059)	1.108 (0.994–1.235)§	1.043 (0.957–1.137)	1.106 (1.006–1.218)*
Ammonia-containing liquids (per product/week)	1.098 (0.791–1.528)	1.155 (0.849–1.598)	1.068 (0.712–1.574)	1.211 (0.870–1.688)	1.178 (0.796–1.695)	0.843 (0.609–1.138)	2.066 (1.250–4.128)*
Sprays (per spray/week)	1.019 (1.002–1.037)*	1.012 (0.997–1.028)	1.04 (1.013–1.068)*	1.045 (1.024–1.068)*	1.031 (1.011–1.052)*	1.021 (1.005–1.038)*	1.021 (1.004–1.039)*
Mixing products (ever vs never)	0.870 (0.570–1.303)	1.155 (0.803–1.648)	1.366 (0.754–2.387)	1.023 (0.649–1.578)	0.675 (0.391–1.116)	0.974 (0.665–1.41)	1.015 (0.677–1.514)
Being able to choose products (≥ 50% vs <50% of the clients)	0.738 (0.535–1.020)§	0.676 (0.505–0.904)*	0.844 (0.511–1.411)	0.983 (0.680–1.431)	0.872 (0.590–1.298)	0.682 (0.506–0.922)*	1.095 (0.791–1.519)

*Data shown as aOR (95%CI) with odds ratios adjusted for all other cleaning product categories, self-reported mixing of products, being able to choose their own products, and potential confounders (education, mould at the workplace, smoking [number of years and number of cigarettes daily], number of years working as a cleaner, and number of hours working per week). * indicates p-value <0.05, § p-value <0.1*

Table S6 Full models of the elastic net regression analyses showing the associations between each outcome and all types of cleaning products

Work-related eye symptoms (n = 281)	OR	95%CI	VI
Mould remover (spray)	1.158	(1.075–1.439)	0.96
Carpet, seat or curtain cleaner (spray)	1.131	(1.008–1.293)	0.93
Disinfectants (liquid)	1.080	(1.013–1.227)	0.86
Ammonia (liquid)	1.063	(1.039–1.263)	0.63
Ammonia (spray)	1.055	(0.988–1.494)	0.68
Glass cleaner (spray)	1.034	(1.004–1.133)	0.80
All-purpose cleaner (spray)	1.029	(0.996–1.094)	0.76
Degreaser (liquid)	1.023	(1.002–1.136)	0.71
Disinfectants (spray)	1.021	(0.996–1.042)	0.73
Vinegar (spray)	1.021	(0.982–1.034)	0.74
Vinegar (liquid)	1.020	(1.002–1.117)	0.69
Degreaser (spray)	1.019	(1.001–1.127)	0.69
Bathroom cleaner (liquid)	1.018	(0.998–1.075)	0.66
Bleach-containing product (spray)	1.016	(0.970–1.092)	0.60
Drain cleaner (liquid)	1.012	(0.965–1.225)	0.46
Bleach-containing product (liquid)	1.012	(0.990–1.068)	0.55
Oven cleaner (spray)	1.012	(0.931–1.103)	0.62
Limescale remover (liquid)	1.009	(0.946–1.034)	0.62
Products without label (spray)	1.005	(0.983–1.106)	0.51
Wax (liquid)	1.001	(0.951–1.099)	0.47
Stain remover (spray)	1.001	(0.971–1.125)	0.46
Carpet, seat or curtain cleaner (liquid)	1.000	(0.834–1.067)	0.49
Bathroom cleaner (spray)	0.999	(0.961–1.018)	0.46
Cleaning agent for kitchen countertops or tiles (liquid)	0.999	(0.963–1.007)	0.46
Floor cleaner (liquid)	0.996	(0.985–1.033)	0.49
Toilet cleaner (spray)	0.996	(0.946–1.006)	0.53
Stain remover (liquid)	0.996	(0.835–1.164)	0.48
Products without label (liquid)	0.992	(0.875–1.084)	0.47
Cleaning agent for kitchen countertops or tiles (spray)	0.991	(0.902–0.995)	0.59
Limescale remover (spray)	0.989	(0.942–1.001)	0.59
Oven cleaner (liquid)	0.989	(0.890–1.104)	0.54
Toilet cleaner (liquid)	0.987	(0.936–0.998)	0.57
Wax (spray)	0.981	(0.645–1.076)	0.56
Floor cleaner (spray)	0.957	(0.879–1.004)	0.70
Mould remover (liquid)	0.956	(0.885–1.158)	0.64
Other liquid products	0.955	(0.822–1.094)	0.63
All-purpose cleaner (liquid)	0.949	(0.892–0.993)	0.77
Glass cleaner (liquid)	0.944	(0.847–1.006)	0.76
Other sprays	0.815	(0.691–0.971)	0.79

Odds ratios (OR) and bootstrap-based 95% confidence intervals (95%CI) for the cleaning products from the elastic net regression models. All 40 cleaning products and potential confounders (smoking [number of years, cigarettes/day], years working as a cleaner, education, presence of mouldy odour and/or visible mould in the workplace, number of clients and number of hours working per week) were included. As results are pooled across 30 imputed datasets, a variable is selected when it is selected in at least one imputed dataset—but its overall impact depends on how often it is selected. The variable importance (VI) sums up the weights of those candidate models that contain the relevant variable and lies between 0 (unimportant) and 1 (very important). It is similar to the Bayesian posterior effect probability [Schomaker & Heumann, Comput Stat Data Anal 2014;71:758–70.]

Work-related rhinitis (n = 387)	OR	95%CI	VI
Mould remover (spray)	1.108	(1.006–1.248)	0.94
Carpet, seat or curtain cleaner (spray)	1.099	(1.001–1.304)	0.93
Ammonia (liquid)	1.081	(1.002–1.372)	0.74
Degreaser (liquid)	1.037	(0.999–1.085)	0.78
Disinfectants (spray)	1.036	(0.999–1.104)	0.85
Drain cleaner (liquid)	1.031	(0.986–1.136)	0.66
Stain remover (spray)	1.027	(0.990–1.152)	0.67
Wax (liquid)	1.019	(0.995–1.136)	0.73
Carpet, seat or curtain cleaner (liquid)	1.014	(0.940–1.143)	0.50
Degreaser (spray)	1.010	(0.987–1.050)	0.59
Bleach-containing product (liquid)	1.009	(1.000–1.072)	0.62
Bleach-containing product (spray)	1.008	(0.967–1.058)	0.54
Disinfectants (liquid)	1.007	(0.990–1.088)	0.57
Vinegar (liquid)	1.007	(0.981–1.070)	0.58
Glass cleaner (spray)	1.006	(0.994–1.057)	0.55
All-purpose cleaner (spray)	1.005	(0.996–1.046)	0.54
Oven cleaner (spray)	1.005	(0.981–1.068)	0.51
Products without label (liquid)	1.004	(0.964–1.368)	0.48
Products without label (spray)	1.003	(0.994–1.326)	0.39
Bathroom cleaner (spray)	1.001	(0.990–1.016)	0.45
Cleaning agent for kitchen countertops or tiles (liquid)	1.001	(0.988–1.078)	0.58
Vinegar (spray)	1.001	(0.945–1.021)	0.45
Wax (spray)	1.001	(0.773–1.022)	0.48
Stain remover (liquid)	1.001	(0.780–1.002)	0.47
Floor cleaner (liquid)	1.000	(0.983–1.027)	0.40
Limescale remover (spray)	1.000	(0.954–1.001)	0.44
Mould remover (liquid)	1.000	(0.806–1.022)	0.46
Cleaning agent for kitchen countertops or tiles (spray)	0.999	(0.970–1.012)	0.44
Bathroom cleaner (liquid)	0.998	(0.975–1.024)	0.53
Toilet cleaner (liquid)	0.998	(0.959–1.005)	0.47
Limescale remover (liquid)	0.993	(0.924–1.004)	0.56
Ammonia (spray)	0.993	(0.871–1.137)	0.51
Toilet cleaner (spray)	0.990	(0.950–1.005)	0.61
All-purpose cleaner (liquid)	0.981	(0.947–1.002)	0.70
Glass cleaner (liquid)	0.979	(0.916–1.004)	0.71
Floor cleaner (spray)	0.976	(0.926–1.016)	0.69
Other liquid products	0.950	(0.829–1.003)	0.67
Other sprays	0.914	(0.828–1.000)	0.75
Oven cleaner (liquid)	0.864	(0.716–0.985)	0.77

Work-related sore throat (n = 104)	OR	95%CI	VI
Ammonia (liquid)	1.305	(1.107–1.978)	0.82
Drain cleaner (liquid)	1.266	(1.020–1.316)	0.98
Oven cleaner (spray)	1.133	(1.009–1.338)	0.93
Carpet, seat or curtain cleaner (spray)	1.111	(0.995–1.383)	0.91
Mould remover (spray)	1.080	(1.006–1.351)	0.81
Degreaser (spray)	1.071	(1.000–1.159)	0.83
Limescale remover (liquid)	1.058	(0.985–1.158)	0.68
Stain remover (spray)	1.047	(0.991–1.362)	0.74
Products without label (spray)	1.040	(0.889–1.150)	0.56
Bleach-containing product (spray)	1.039	(0.994–1.142)	0.73
Bleach-containing product (liquid)	1.035	(0.996–1.144)	0.66
Vinegar (spray)	1.020	(1.000–1.151)	0.59
All-purpose cleaner (spray)	1.014	(0.988–1.082)	0.57
Cleaning agent for kitchen countertops or tiles (spray)	1.009	(0.988–1.061)	0.46
Toilet cleaner (spray)	1.005	(0.976–1.072)	0.39
Glass cleaner (spray)	1.003	(0.979–1.070)	0.47
Degreaser (liquid)	1.001	(0.969–1.151)	0.43
All-purpose cleaner (liquid)	1.000	(0.984–1.009)	0.44
Glass cleaner (liquid)	0.999	(0.897–1.048)	0.36
Products without label (liquid)	0.999	(0.625–1.701)	0.39
Disinfectants (liquid)	0.998	(0.889–1.056)	0.40
Bathroom cleaner (liquid)	0.996	(0.956–1.038)	0.44
Bathroom cleaner (spray)	0.993	(0.942–1.007)	0.49
Disinfectants (spray)	0.992	(0.933–1.034)	0.47
Ammonia (spray)	0.989	(0.938–1.322)	0.41
Floor cleaner (liquid)	0.988	(0.964–1.007)	0.49
Wax (liquid)	0.985	(0.876–1.137)	0.50
Limescale remover (spray)	0.978	(0.853–1.014)	0.58
Floor cleaner (spray)	0.977	(0.741–1.016)	0.57
Carpet, seat or curtain cleaner (liquid)	0.975	(0.941–1.160)	0.45
Stain remover (liquid)	0.975	(0.617–1.032)	0.51
Mould remover (liquid)	0.972	(0.813–1.133)	0.51
Vinegar (liquid)	0.969	(0.863–1.001)	0.64
Cleaning agent for kitchen countertops or tiles (liquid)	0.968	(0.931–1.016)	0.64
Wax (spray)	0.964	(0.702–1.023)	0.55
Toilet cleaner (liquid)	0.950	(0.883–0.997)	0.71
Other liquid products	0.905	(0.810–1.006)	0.62
Oven cleaner (liquid)	0.881	(0.765–1.004)	0.69
Other sprays	0.810	(0.622–1.005)	0.75

Work-related inducible laryngeal obstruction (n = 206)	OR	95%CI	VI
Ammonia (liquid)	1.116	(1.017–1.702)	0.68
Drain cleaner (liquid)	1.106	(0.947–1.162)	0.91
Disinfectants (spray)	1.097	(1.016–1.236)	0.97
Degreaser (liquid)	1.072	(1.008–1.176)	0.79
Mould remover (spray)	1.066	(0.969–1.179)	0.78
Products without label (spray)	1.063	(0.981–1.582)	0.69
Vinegar (spray)	1.061	(1.003–1.139)	0.84
All-purpose cleaner (spray)	1.049	(1.000–1.132)	0.81
Products without label (liquid)	1.047	(0.973–1.508)	0.59
Wax (liquid)	1.046	(1.016–1.277)	0.72
Limescale remover (liquid)	1.036	(0.972–1.085)	0.69
Oven cleaner (spray)	1.035	(1.008–1.228)	0.69
Carpet, seat or curtain cleaner (spray)	1.032	(0.974–1.232)	0.71
Degreaser (spray)	1.025	(0.966–1.143)	0.67
Carpet, seat or curtain cleaner (liquid)	1.018	(0.948–1.106)	0.57
Limescale remover (spray)	1.014	(1.001–1.082)	0.59
Glass cleaner (spray)	1.011	(1.005–1.078)	0.55
Cleaning agent for kitchen countertops or tiles (spray)	1.007	(0.933–1.017)	0.47
Bleach-containing product (spray)	1.006	(0.980–1.067)	0.52
Bleach-containing product (liquid)	1.006	(0.982–1.039)	0.50
Stain remover (spray)	1.005	(0.970–1.123)	0.46
Disinfectants (liquid)	0.999	(0.952–1.052)	0.47
Bathroom cleaner (liquid)	0.993	(0.921–1.007)	0.53
Toilet cleaner (spray)	0.993	(0.959–1.027)	0.54
Bathroom cleaner (spray)	0.988	(0.888–1.010)	0.54
Oven cleaner (liquid)	0.987	(0.727–1.070)	0.52
Mould remover (liquid)	0.986	(0.810–1.097)	0.52
Floor cleaner (liquid)	0.981	(0.967–1.037)	0.60
Cleaning agent for kitchen countertops or tiles (liquid)	0.978	(0.909–1.008)	0.63
Vinegar (liquid)	0.963	(0.900–1.007)	0.68
Wax (spray)	0.960	(0.723–1.043)	0.56
Ammonia (spray)	0.955	(0.710–1.161)	0.51
Floor cleaner (spray)	0.947	(0.854–1.024)	0.70
Toilet cleaner (liquid)	0.937	(0.885–0.995)	0.86
Glass cleaner (liquid)	0.937	(0.838–0.985)	0.77
Other liquid products	0.924	(0.734–1.095)	0.70
All-purpose cleaner (liquid)	0.919	(0.808–0.961)	0.86
Other sprays	0.908	(0.515–1.027)	0.64
Stain remover (liquid)	0.824	(0.510–0.887)	0.74

Work-related asthma (n = 184)	OR	95%CI	VI
Carpet, seat or curtain cleaner (spray)	1.103	(1.017–1.322)	0.99
Mould remover (spray)	1.029	(0.995–1.199)	0.83
Drain cleaner (liquid)	1.023	(0.979–1.302)	0.75
Disinfectants (liquid)	1.017	(0.999–1.225)	0.84
Oven cleaner (spray)	1.014	(1.001–1.214)	0.73
Toilet cleaner (spray)	1.013	(0.986–1.074)	0.71
Limescale remover (liquid)	1.009	(1.001–1.121)	0.68
Vinegar (spray)	1.009	(1.002–1.189)	0.74
Floor cleaner (spray)	1.008	(0.984–1.060)	0.65
Products without label (spray)	1.007	(0.966–1.091)	0.62
Bleach-containing product (spray)	1.005	(0.992–1.048)	0.56
Ammonia (liquid)	1.003	(0.854–1.117)	0.54
Disinfectants (spray)	1.002	(0.960–1.024)	0.56
Degreaser (liquid)	1.001	(0.982–1.057)	0.53
Limescale remover (spray)	1.001	(1.000–1.087)	0.67
Vinegar (liquid)	1.001	(0.959–1.094)	0.58
Wax (spray)	1.001	(0.948–1.546)	0.60
Mould remover (liquid)	1.001	(0.918–1.084)	0.50
Products without label (liquid)	1.001	(0.995–1.365)	0.51
All-purpose cleaner (spray)	1.000	(0.997–1.063)	0.48
All-purpose cleaner (liquid)	1.000	(0.951–1.013)	0.43
Degreaser (spray)	1.000	(0.953–1.029)	0.39
Bathroom cleaner (spray)	1.000	(1.000–1.082)	0.46
Bathroom cleaner (liquid)	1.000	(0.946–1.001)	0.57
Cleaning agent for kitchen countertops or tiles (spray)	1.000	(0.954–1.017)	0.46
Cleaning agent for kitchen countertops or tiles (liquid)	1.000	(0.913–1.006)	0.61
Carpet, seat or curtain cleaner (liquid)	1.000	(0.977–1.317)	0.45
Glass cleaner (spray)	1.000	(0.967–1.039)	0.40
Glass cleaner (liquid)	1.000	(0.958–1.070)	0.47
Bleach-containing product (liquid)	1.000	(0.957–1.012)	0.62
Oven cleaner (liquid)	1.000	(0.880–1.010)	0.60
Wax (liquid)	1.000	(0.910–1.034)	0.56
Stain remover (spray)	1.000	(0.898–1.009)	0.50
Ammonia (spray)	1.000	(0.816–1.232)	0.51
Floor cleaner (liquid)	0.999	(0.945–1.011)	0.55
Other sprays	0.999	(0.801–1.001)	0.59
Other liquid products	0.998	(0.855–1.005)	0.68
Toilet cleaner (liquid)	0.995	(0.912–1.001)	0.76
Stain remover (liquid)	0.995	(0.632–0.993)	0.69

Work-related cough (n = 341)	OR	95%CI	VI
Carpet, seat or curtain cleaner (spray)	1.051	(1.001–1.120)	0.85
Bleach-containing product (spray)	1.051	(1.005–1.137)	0.95
Degreaser (spray)	1.041	(0.995–1.077)	0.94
Mould remover (spray)	1.029	(1.002–1.251)	0.79
Limescale remover (liquid)	1.025	(0.998–1.099)	0.83
Bleach-containing product (liquid)	1.023	(0.997–1.127)	0.75
Limescale remover (spray)	1.011	(0.992–1.047)	0.79
Carpet, seat or curtain cleaner (liquid)	1.007	(0.992–1.090)	0.58
Disinfectants (spray)	1.007	(0.989–1.056)	0.55
Oven cleaner (spray)	1.005	(0.993–1.154)	0.42
Products without label (spray)	1.005	(1.001–1.349)	0.49
Degreaser (liquid)	1.004	(0.990–1.053)	0.58
All-purpose cleaner (spray)	1.003	(0.992–1.047)	0.62
Drain cleaner (liquid)	1.003	(0.962–1.118)	0.56
Products without label (liquid)	1.003	(0.945–1.010)	0.54
Disinfectants (liquid)	1.002	(0.991–1.129)	0.59
Ammonia (liquid)	1.002	(0.981–1.178)	0.53
Bathroom cleaner (liquid)	1.001	(0.997–1.036)	0.51
Toilet cleaner (spray)	1.001	(0.996–1.032)	0.48
Glass cleaner (liquid)	1.001	(0.992–1.040)	0.47
All-purpose cleaner (liquid)	1.000	(0.996–1.013)	0.41
Floor cleaner (spray)	1.000	(0.968–1.080)	0.37
Bathroom cleaner (spray)	1.000	(0.963–1.000)	0.49
Cleaning agent for kitchen countertops or tiles (spray)	1.000	(0.957–1.029)	0.45
Glass cleaner (spray)	1.000	(0.995–1.064)	0.48
Vinegar (spray)	1.000	(0.979–1.046)	0.55
Vinegar (liquid)	1.000	(0.988–1.045)	0.45
Wax (liquid)	1.000	(0.987–1.069)	0.39
Stain remover (spray)	1.000	(0.973–1.069)	0.47
Floor cleaner (liquid)	0.999	(0.949–1.009)	0.54
Toilet cleaner (liquid)	0.999	(0.965–1.011)	0.51
Wax (spray)	0.998	(0.811–1.035)	0.59
Ammonia (spray)	0.997	(0.807–1.007)	0.49
Cleaning agent for kitchen countertops or tiles (liquid)	0.996	(0.949–1.006)	0.69
Mould remover (liquid)	0.993	(0.735–0.996)	0.66
Other sprays	0.989	(0.813–0.999)	0.60
Stain remover (liquid)	0.986	(0.749–0.998)	0.69
Oven cleaner (liquid)	0.968	(0.735–0.997)	0.71
Other liquid products	0.954	(0.800–1.004)	0.78

Chronic bronchitis (n = 423)	OR	95%CI	VI
Carpet, seat or curtain cleaner (spray)	1.143	(0.998–1.336)	0.99
Oven cleaner (spray)	1.067	(1.044–1.233)	0.94
Mould remover (spray)	1.063	(0.954–1.221)	0.91
Ammonia (liquid)	1.050	(1.014–1.400)	0.80
Wax (spray)	1.036	(0.972–1.225)	0.77
Stain remover (spray)	1.031	(0.998–1.243)	0.79
Bleach-containing product (spray)	1.022	(0.994–1.141)	0.71
Disinfectants (spray)	1.020	(0.958–1.071)	0.73
Toilet cleaner (spray)	1.014	(0.995–1.093)	0.72
Degreaser (spray)	1.013	(0.961–1.052)	0.61
Drain cleaner (liquid)	1.013	(0.963–1.160)	0.56
All-purpose cleaner (spray)	1.008	(0.997–1.034)	0.64
Carpet, seat or curtain cleaner (liquid)	1.008	(0.930–1.113)	0.51
Disinfectants (liquid)	1.008	(0.966–1.059)	0.61
Stain remover (liquid)	1.006	(0.991–1.203)	0.45
Floor cleaner (spray)	1.005	(0.931–1.085)	0.53
Bleach-containing product (liquid)	1.005	(0.990–1.065)	0.65
Degreaser (liquid)	1.004	(0.986–1.072)	0.42
Cleaning agent for kitchen countertops or tiles (spray)	1.004	(0.982–1.068)	0.59
Products without label (spray)	1.004	(0.920–1.231)	0.52
Mould remover (liquid)	1.003	(0.969–1.150)	0.43
Vinegar (spray)	1.002	(0.944–1.018)	0.54
Oven cleaner (liquid)	1.002	(0.884–1.086)	0.43
Glass cleaner (liquid)	1.001	(0.970–1.028)	0.50
All-purpose cleaner (liquid)	1.000	(0.977–1.026)	0.47
Bathroom cleaner (liquid)	1.000	(0.926–1.005)	0.57
Cleaning agent for kitchen countertops or tiles (liquid)	1.000	(0.994–1.101)	0.53
Glass cleaner (spray)	1.000	(0.949–1.013)	0.47
Products without label (liquid)	1.000	(0.879–1.076)	0.54
Limescale remover (liquid)	0.999	(0.959–1.038)	0.52
Other sprays	0.999	(0.852–1.048)	0.47
Bathroom cleaner (spray)	0.998	(0.953–1.004)	0.55
Limescale remover (spray)	0.998	(0.918–0.991)	0.62
Wax (liquid)	0.998	(0.906–1.062)	0.59
Ammonia (spray)	0.996	(0.780–1.023)	0.61
Vinegar (liquid)	0.993	(0.928–1.035)	0.61
Other liquid products	0.992	(0.834–1.052)	0.58
Floor cleaner (liquid)	0.988	(0.951–1.009)	0.65
Toilet cleaner (liquid)	0.964	(0.903–0.972)	0.81

3.4. Discussion

3.4.1. Summary of the main findings

Since 2004, in Belgium, domestic cleaning and other paid domestic tasks have been organized in a so-called service voucher system intended to offer a regulated work environment.[1] Currently, around 150,000 workers are employed by approximately 1,800 “service voucher companies” that employ workers to provide domestic services to private clients. The domestic cleaners work for one up to ten fixed clients each week. Salaries (currently 9 € per hour) and other administrative aspects are legally and contractually defined, but the working conditions—including psychosocial and physical demands—are essentially determined by the clients, who provide the cleaners with the cleaning products. In this unique context, we have set up a project with the long-term aim of improving respiratory health through preventive actions.

In our survey of a large sample of domestic cleaners, we show that the number of cleaning sprays used per week was significantly associated with all studied short-term work-related ocular and respiratory outcomes, and with chronic bronchitis. Bleach/disinfectant-containing liquid products were associated with work-related eye symptoms and asthma; liquid ammonia with chronic bronchitis. Using elastic net regression analysis, we assessed in detail which of 40 types of cleaning products were most strongly related to work-related respiratory symptoms. We found that work-related rhinitis was most strongly associated with mould removal spray, carpet/seat/curtain spray and ammonia; work-related asthma with carpet/seat/curtain spray, mould removal spray and drain cleaner.

Moreover, cleaners able to choose their own products reported fewer work-related eye symptoms, rhinitis or cough. This novel observation demonstrates the importance of understanding the relation between cleaners and their clients when aiming for better prevention. Although the official employer of the cleaners is the “service vouchers company”, it is the client, who provides them with the cleaning products. Therefore, cleaners

are not always in a position to avoid products that they estimate or experience to be harmful. In addition to training cleaners about the hazards of certain products, empowering them to negotiate which products they use might be beneficial for prevention. Service voucher companies might inform their clients about the hazards of certain products—which can affect the health of the cleaners as well as of the residents of the homes (particularly children and elderly).[2–4] Moreover, providing a (binding) list of products that the cleaners may or may not use in the client's homes, and checking compliance with such a list (for example by home visits) should be considered.

3.4.2. Preventing respiratory symptoms in domestic cleaners

In general, an effective primary preventive approach would aim to reduce hazardous ingredients in cleaning products. Identifying cleaning agents potentially capable of damaging the respiratory system—and their interactions—is difficult, primarily because manufacturers are protected by industrial trade secrets (i.e. not all ingredients must be disclosed in products labels), and also not all the agents reported in the cleaning products have been tested for potential respiratory health effects. Nevertheless, manufacturers of cleaning products should avoid known hazardous ingredients (e.g. bleach, ammonia, quaternary ammonium compounds), or at least use less harmful formulations (e.g. less volatile ortho-phthalaldehyde instead of glutaraldehyde), and eliminate—as much as possible—cleaning products in spray formulations.

Currently, a growing number of so-called 'green' cleaning products are available on the market. A recent cross-sectional study performed in 329 custodians found a higher prevalence of upper and lower respiratory symptoms associated with high exposure to traditional cleaning products compared with high exposure to environmentally preferable cleaning products. Nevertheless, it was observed that these 'green' products are not totally safe if inhaled.[5]

Another important primary preventive intervention should be to inform cleaners (and employers/clients) about the potential risks of cleaning job tasks, and to train them to safely use cleaning products. Inhalation accidents in cleaners, such as mixing bleach and ammonia in a small, poorly ventilated area, have been associated with asthma symptoms, reactive airway dysfunction syndrome, irritant-induced occupational asthma and work-exacerbated asthma.[6] The findings from our study suggest that mixing incompatible products is now infrequent in Belgian domestic cleaners (possibly thanks to training).

In many countries, domestic cleaners are mostly employed in the informal sector and/or in conditions characterized by a precarious status, low wages, limited workers' organization and few legal protections. The workforce mostly consists of women, with a high percentage of immigrant workers. Many cleaners have limited impact on the products they have to use. Therefore, preventive approaches based on participation and empowerment of workers could be helpful to induce sustainable changes in product use.[7]

Personal respiratory protective equipment should be always considered the last resort, and there is no evidence or agreement on a specific respirator type capable of protecting against all cleaning-related respiratory health effects.

As secondary prevention, occupational respiratory health surveillance programs should be implemented among cleaners. For example, periodical questionnaires could be administered to cleaners as a screening tool for the early detection of work-related respiratory symptoms. Also, periodic spirometries could detect cleaners with excessive declines of the lung function. However, occupational respiratory health surveillance programs can only be effective if there is clear guidance for occupational health services, general practitioners and respiratory physicians on when to refer and how to handle cases of suspected work-related respiratory disease.

Unfortunately, the high turnover and job instability of this type of workforce make the implementation of occupational respiratory health surveillance

challenging. When there is no adequate “safety net”, workers will be reluctant to report any symptoms for fear of losing their job.

Finally, as tertiary prevention, any respiratory health condition suspected to be work-related among cleaners should be diagnosed as soon as possible to avoid further exposure to the potential causal agent at work and so, hopefully, slow down disease progression. In addition, the diagnosis should be reported to national compensation authorities. For now, in Belgium, only cases of sensitizer-induced occupational asthma are eligible for compensation. Efforts should be made to adapt this far too restrictive approach which excludes the majority of work-related respiratory problems in professional cleaners.

Also, for preventive and epidemiological purposes, reporting cases to a national (voluntary) surveillance scheme (in analogy to the notification of acute intoxications to the Belgian Poison Centre) could help to estimate the public health burden and incidence trends, identify potential new causal agents, and characterize associated respiratory phenotypes.

3.4.3. Perspectives

The aim of our project was to establish a collaboration with the service voucher sector to study the respiratory health effects of cleaning products and, improve— in the long term—the prevention of respiratory problems. After setting up a steering committee at the level of the sector, we have aimed for active participation of the domestic cleaners themselves (within the possibilities given the COVID-19 pandemic): in the first phase, by trying to reach as many cleaners as possible with an online questionnaire; in a second phase, by developing a smartphone app which cleaner could use at the workplace. We believe that we have created the basis for a long-term collaboration to facilitate the continuation of our project and the dissemination of the results and preventive measures.

Initially we had assumed that respiratory problems caused by cleaning products would not be a priority for this target group, but this assumption

turned out to be wrong. We were surprised that we recruited over 1,500 workers to participate in an internet survey, and over 500 to install a smartphone app to scan product barcodes (scanning in total around 16,700 barcodes). Also, in the free text fields of our online survey participants often emphasised the need for more guidance on which products are safe to use.

In the long term, we hope to arrive at a 'list' of products which are safer to use. By compiling this list within the framework of this project (and with the support of the partners in the sector), we hope to 1) give the workers a tool to propose alternative products to their clients, 2) give the service voucher companies a tool to communicate with their clients about cleaning products. In addition, we also want to investigate in the future how we could adapt the smartphone app, for example, so that domestic cleaners could use it to obtain more information about the safety of a product by scanning its barcode.

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Epilogue —
Where silica and cleaning products meet

The reader might (rightly) wonder what the topics that have been discussed in this doctoral thesis have in common. Sarcoidosis (Chapter 1), silicosis (Chapter 2), and respiratory health effects of cleaning products (Chapter 3) are seemingly disparate issues, except for being related to the general subject of "occupational exposure and respiratory diseases". In the epilogue of this thesis, I have made an (admittedly far-fetched) attempt to unite these subjects. Nevertheless, if the reader estimates this attempt to be unsuccessful, I hope it can still be of interest.

In this epilogue, I explore an episode in history where silica and cleaning products have met and have affected workers' health. I describe the largely undocumented history of workers developing autoimmune diseases after exposure to high airborne concentrations of finely milled crystalline silica in the scouring powder industry.

Why would history matter in occupational medicine? Workers' health is not a purely medical issue. Historical, socio-economic and technological factors often determine the *occurrence* of occupational diseases, as well as the *response* to this occurrence. Therefore, studying the history of occupational medicine is not merely interesting "in itself", but can be a tool to protect the health of today's workers.[1]

Technologic changes continually introduce new occupational hazards, leading to entirely novel conditions as well as to evolving patterns of established diseases. Well-known occupational diseases, thought to have disappeared, can re-emerge. Outbreaks of silicosis have frequently occurred throughout the past century, often in new production processes or industries, because the collective memory of the disease repeatedly appears to have fallen below a critical point of awareness.[2,3] The outbreak among artificial stone workers is only the most recent example. This process of diseases getting "forgotten" and then "re-discovered" decades later could be avoided by valuing the history of the field.[4]

Knowing the history of how societies and industries have been responding to the discovery of diseases caused by occupational exposures is crucial to understand the (often) long latency periods between the identification of a hazardous exposure and its control. The communication strategies used by industries producing hazardous products have been well documented for the cigarette and asbestos industry but have been repeated numerous times (creating and exaggerating doubt in popular media and scientific journals, intimidating scientists, lobbying with policy makers to delay regulation, etc.)[5–8]

Additionally, also disease *definitions* can be the result of historical "negotiations", which might surprise clinicians not familiar with the field of occupational medicine. Because questions of liability and compensation have always been part of occupational medicine (Who to blame? Who will pay?), struggles over causes and definitions of occupational diseases have often occurred. The definition of silicosis is probably one of the best examples demonstrating how the history of the recognition of a disease informs current medical issues. As has been described by Rosental and colleagues,[3,9] the definition of silicosis, as we know it today, is largely the result of a (political) negotiation that has occurred in 1930 at the International Labor Office (ILO) Conference on silicosis in Johannesburg, South Africa. Convened by the International Labor Office and by the employers' organization, the Transvaal Chamber of Mines, this conference paved the way to the adoption of the 1934 ILO convention which finally recognized silicosis as an occupational disease. However, to reach a compromise, the hazards of silica were reduced to "established" silicosis, while excluding from the definition the earlier stages of silicosis (which were well known at the time) or other health effects of silica exposure. Although the Johannesburg definition of silicosis is questioned nowadays, it is still the basis for most textbook descriptions of silicosis and for the criteria employed to be eligible for compensation by the Belgian Federal Agency for Occupational Risks (FEDRIS). Therefore, the negotiations that have occurred

at the 1930 Johannesburg conference have had a decisive influence on the ideas of clinicians about silicosis throughout the past century.

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The history of the Colinet-Caplan syndrome and the outbreak of autoimmune disease in scouring powder workers

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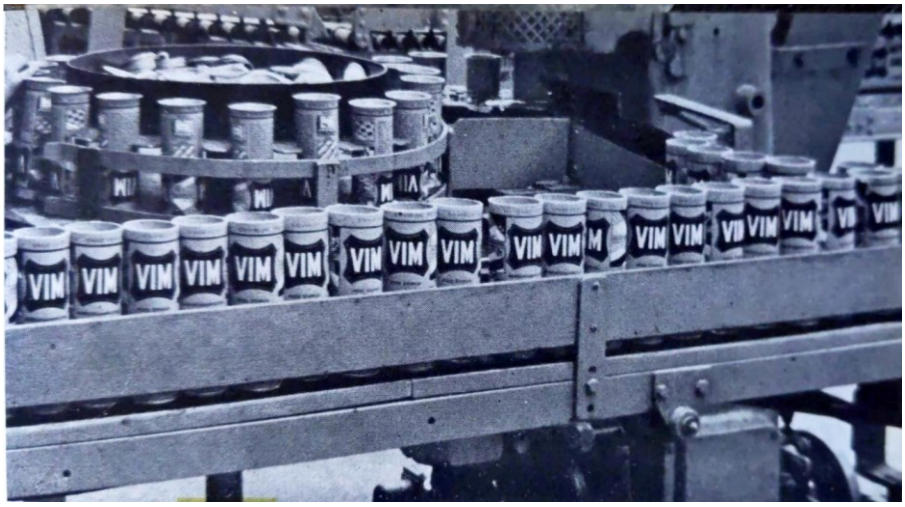

Figure—Vim scouring powder production line. Source: booklet « Savonneries Lever frères à Forest-Bruxelles » (1955)

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Abstract

The first modern description of an association between rheumatoid arthritis (RA) and pneumoconiosis is generally attributed to British physician, Anthony Caplan, who reported in 1953 on a "peculiar" radiographic pattern in Welsh coal miners with RA. However, as early as in 1950 Émile Colinet, a Belgian rheumatologist, had described a case in a 30-year-old woman, soon followed by a second case. Although initially called Colinet-Caplan syndrome in the French language literature, Colinet's name was later dropped from the eponym. Because Colinet had never clearly described the occupational category of his cases, "Caplan syndrome" has been considered as uniquely a coal miner's disease.

We reconstruct the working conditions of Colinet's cases, finding that they were packing *Vim,* a silica-based scouring powder, at the *Savonneries Lever Frères* factory in Brussels, Belgium. Colinet's cases emerged as only the first two in a series of reports on RA and other autoimmune diseases in silica-based scouring powder workers across Europe, mainly young women. A review of the literature shows that except from one study showing 32 cases of autoimmune disease among 50 workers from a Spanish scouring powder manufacturing facility, no systematic efforts have been undertaken to map autoimmune diseases in scouring powder workers.

Due to the substitution of silica in scouring powders by less hazardous materials no further cases have been reported with exposures after 1989. Nevertheless, the Colinet-Caplan syndrome and other autoimmune disorders due to silica have not disappeared and are currently re-emerging in artificial silica-based stone workers.

Introduction

Exposure to respirable crystalline silica has been linked to a spectrum of autoimmune disorders. Currently, the strongest evidence exists for the association of silica with systemic sclerosis (SSc)[1], rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and ANCA-positive vasculitis.[2,3] The epidemiology on these associations is quite convincing: not only do most studies point in the same direction, they do so regardless of study design, study population or method of exposure assessment. Moreover, an exposure-response gradient has been shown.[2]

The recognition that occupational exposure might be related to autoimmune disorders is not new. In his 1775 textbook *Précis d'opérations de chirurgie* [Essentials of surgical procedures],[4] the French surgeon Louis Le Blanc wrote *"… that the sandstone dust penetrates… the body of the workers who work daily in these workshops filled with dust. They are struck by a cruel disease called 'sandstone disease' [maladie du grès] or 'Saint Roch's disease' [maladie de Saint-Roch] which appears to be caused by the presence of the sandstone particles. They are most often affected by fatigue and spontaneous or rheumatic pains in all their limbs, and particularly in their joints*." (p. 585; original text in French, translated by the authors)[4] Although Le Blanc seems to describe an inflammatory polyarthritis, other 18th century authors have been using the term 'maladie de Saint-Roch' rather as a synonym for *lung disease* in stonemasons (Saint Roch being the patron saint of stone quarries).[5,6]

In 1914, Byrom Bramwell, a Scottish physician, was the first to notice that 5 out of his 9 patients with systemic sclerosis (which he called "diffuse sclerodermia") were stonemasons, although he did not suspect silica dust to have caused the disease but attributed it to "holding cold chisels."[7] In 1933, Collis and Yule, who were pioneers in the epidemiological research on dust-related diseases, observed a fourfold increase in the mortality rate of 'chronic rheumatic diseases' among silica-exposed workers.[8,9]

The first modern description of an association between rheumatoid arthritis (RA) and pneumoconiosis is generally attributed to British physician, Anthony Caplan, in 1953 in South Wales coal miners. Of note, however, as early as in 1950 Émile Colinet, a Belgian rheumatologist at the Saint-Pierre Hospital in Brussels (Belgium), already had described a case of concomitant rheumatoid arthritis and pneumoconiosis in a 30-year-old woman working "in a factory where large quantities of silica flour were handled."[10] The term "silica flour" refers to finely ground crystalline silica that includes particles in respirable size range.[11]

Although this syndrome initially had been called Colinet-Caplan syndrome in the French language literature, Colinet's name was later dropped from the eponym. Also, because of the relatively limited description of the working conditions Colinet had provided, it had never been clear what occupational category of workers he was referring to. Therefore, "Caplan syndrome" has generally been considered as uniquely a coalminer's disease without consideration of silica exposures independent of coal.

It was only later that Colinet's initial case emerged as only the first in a series of reports on autoimmune diseases in silica-based scouring powder workers. In this paper we aim to explore and reconstruct this hitherto unpublished history of workers, mainly young women, developing autoimmune diseases after relatively short periods of heavy exposure to high airborne concentrations of finely milled crystalline silica in the scouring powder industry.

Methods

We performed a standard medical literature search using PubMed, including articles in English, French, German, Italian, Spanish and Dutch. Further, the reference citations of pertinent publications were also reviewed. Additionally, the Royal Library of Belgium (Brussels), the archives of the KU Leuven University Library, and the archives of the Belgian labour inspection (Federal Public Service Employment, Labour and Social Dialogue, Brussels) were consulted. Sources included the 1930 International Labour Organisation

Conference proceedings, Belgian government publications such as Arbeidsblad/Revue du Travail, newspapers, and publicly available jurisdiction from court cases. Unilever's archives stated that they did not to hold past medical records of workers.

Results and Discussion

Caplan and the peculiar chest X-rays of South Wales coal miners

As noted previously, the first modern description of an association between rheumatoid arthritis and dust exposure is generally attributed to Anthony Caplan, a medical officer and member of the UK governmental Cardiff Pneumoconiosis Medical Panel. This association was initially acknowledged briefly in a 1952 report of a meeting of the Heberden Society but only fully reported in a 1953 Thorax publication.[12,13] In that single-authored paper, Caplan reported 51 cases with concomitant rheumatoid arthritis and pneumoconiosis among 14,000 South Wales coal miners who had applied for pneumoconiosis disability benefits.[13] In 13 out of these 51 cases, he identified a "peculiar" pattern on chest X-rays, i.e. multiple, well-defined, round opacities, 0.5 to 5 cm in diameter, distributed throughout both lung fields but particularly at the periphery, a pattern which he called "rheumatoid opacities" and which did not resemble the typical coal-workers pneumoconiosis (Figure 1A, 1B).[13]

In a subsequent study, Caplan's colleagues, led by Jethro Gough (who had pioneered the Gough-Wentworth large lung section technique) provided detailed pathological descriptions of these opacities.[14] Figure 1C shows the histology of a typical rheumatoid pneumoconiotic nodule with lines of stranded dust. The work by Caplan inarguably was pivotal in drawing attention to the relationship between rheumatoid arthritis and pneumoconiosis. Although initially the term "Caplan syndrome" referred to the co-occurrence of the typical large opacities on chest X-ray and rheumatoid arthritis in coal miners, Caplan later reported a case in a silica-exposed sandblaster,[15] but subsequently reversed himself on the syndrome occurring outside of coal mining, stating, "We have been unable to find any

… or evidence that the prevalence of rheumatoid arthritis is increased in this disease [silicosis]."[16]

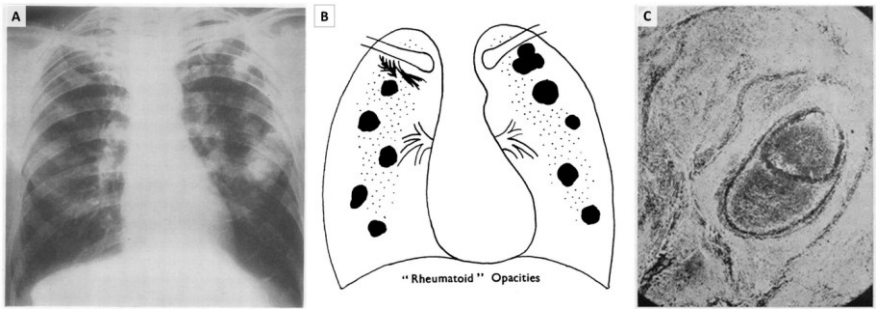

Figure 1—(A) Chest radiograph from Caplan's 1953 article showing the characteristic "rheumatoid" opacities. The shape, peripheral distribution, and multiplicity of the opacities, combined with the slight degree of simple pneumoconiosis, distinguish this type of lesions from the ordinary progressive massive fibrosis.[13] (B) Illustration of the "rheumatoid" opacities (from the same article).[13] (C) "Rheumatoid" pneumoconiotic nodule with lines of stranded dust from autopsy lung tissue from a coal miner with rheumatoid arthritis (from Gough, 1955).[14]

Colinet-Caplan syndrome

Caplan, however, was not the first modern clinician to describe this association between coal or silica and rheumatoid arthritis. As early as 1950, Émile Colinet, a Belgian rheumatologist at the Saint-Pierre Hospital in Brussels, had published a case report describing a 30-year-old woman with a 10-year history of diffuse rheumatic arthritis whose symptoms had started two years after beginning to work "in a factory where large quantities of silica flour were handled."[10] Her chest X-ray, an image of which Colinet did not include in this initial report, was described as showing "silico-tuberculosis." He noted that several of the female co-workers of his patient had previously died from "silico-tuberculosis." In this report, Colinet hypothesized that there could be an association between silico-tuberculosis and rheumatoid arthritis.

In March 1953, Colinet published a second case: a 34-year-old woman with clinical manifestations of both rheumatoid arthritis and systemic sclerosis,

who had begun working at age 15 in the same factory as the first case. Of note, in this second report, Colinet mentioned that he had learned about the (still unpublished) findings of Caplan. Because nor Caplan, nor himself had actually been able to detect mycobacteria in the sputum of their patients, Colinet slightly adjusted his initial hypothesis and concluded that silicosis, "even without progressing towards a [silico-]tuberculosis", could be held responsible for inducing the rheumatoid arthritis.

Reconstructing the working conditions of Colinet's cases

Colinet did never specify what was produced at the factory where his reported cases were working.[17] Consequently, although publications on "Caplan syndrome" often cite the initial reports of Colinet, the precise nature of the employment of his cases, not surprisingly, are never described. Nonetheless, there is one important but rarely cited exception: in December 1953, Dr Joseph Clerens, a colleague of Colinet who had been trained in pulmonology, recapitulated Colinet's two case histories, of what he referred to as "Colinet-Caplan syndrome," in a French language publication in the Belgian journal *"Archives Belges de Médecine Sociale, Hygiène, Médecine du Travail et Médecine Légale/Belgisch Archief van Sociale Geneeskunde, Hygiëne, Arbeidsgeneeskunde en Gerechtelijke Geneeskunde"*.[18]

Clerens provided key information on the patients' jobs and described their workplace. He reported that they had worked at 'a factory producing cleaning and laundry products that included not only soap, but also finely milled silica' (Figure 2). The first patient started working in the factory at the age of 18 and developed the first symptoms 2 years later. She worked at the end of the packing line and had to retrieve boxes with powder that had broken apart. Subsequently, she had to pour the salvaged powder into a large container. The second worker had worked at the factory for 11 years. Her first symptoms appeared 4 years after quitting this job (15 years after initial exposure). She worked at the same production line as the first case, but was 'less exposed' according to Clerens, without specifying her precise tasks.

Figure 2—Lever Brothers, Port Sunlight Works (near Liverpool, UK), Vim packing department—probably at the end of the 1930s. The silica flour is mixed with powdered soda ash, soap, and sometimes other substances, either with a shovel, or in a mixing machine. Filling the cartons may also be done by hand, or by mechanical fillers; the lids are then placed and fixed by a machine."[19,20]

Moreover, Clerens published the radiographic image of Colinet's first patient which seems to demonstrate a typical "Caplan" pattern, i.e., multiple, well-defined, round opacities, particularly at the periphery (see Figure 3).

It is of further interest that Clerens initially thought that the association between the patients' jobs and their clinical syndrome was merely coincidence and he decided not to claim compensation for the patients at the *Fonds de Prévoyance* (the precursor of the later Belgian Fund for Occupational Diseases). He stated that his view later changed, however, because he learned of the work of Caplan which had been presented at the Heberden Society in London in October 1952.[12]

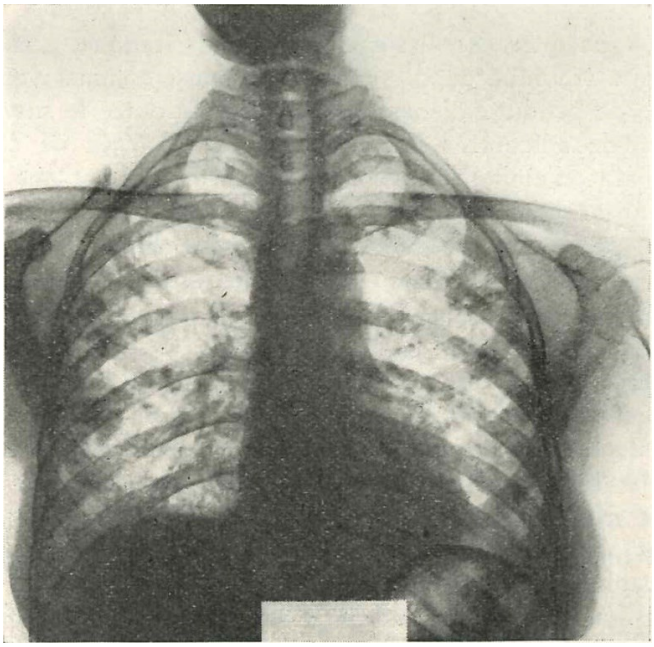

Figure 3—Chest radiography (positive image) of the first case described by Colinet with a typical "Caplan" pattern, i.e., multiple, well-defined, round opacities, particularly at the periphery (as published by his colleague Clerens in 1953).[18]

Production of Vim at the Savonneries Lever Frères in Forest-Brussels

Although neither Colinet nor Clerens ever identified by name the cleaning product manufacturer in question, the overwhelming likelihood is that this was the "Vim" scouring powder factory *Savonneries Lever Frères* in Forest-Brussels, less than 5 km from the Saint-Pierre Hospital, where these clinicians were active (Figure 4). This identification is further supported by a report from the internal medicine department of the same hospital from January 1953 of a 41-year-old woman, explicitly described as a Vim scouring powder worker, with fatal "acute" silicosis.[21] The authors found that the Vim powder looked "the same" under polarized light as the crystals present in the alveoli in their patient's biopsy. Moreover, the Belgian labour inspection had reported in 1935 already the case of a 28-year old worker with silicosis who had been manipulating (unloading, mixing, cutting) for 5 years the raw materials to make Vim powder.[22]

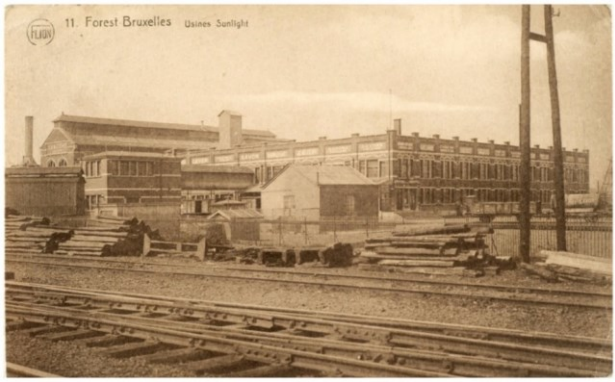

Figure 4— "Forest-Bruxelles: Usines Sunlight" (date unknown), from the Collection Belfius Banque – Académie Royale de Belgique

In 1888, the Lever brothers had started producing soap in a large factory in "Port Sunlight" near Liverpool, UK. They were dominating the English market with their Sunlight soap by the beginning of the 20th century. By 1904, they had also started producing Vim scouring powder at their UK factory. Vim consisted of soap, soda and finely milled silica (coming from quarries in North Wales) and was marketed as "the housewife's handy helper" for cleaning and polishing: quick, efficient and without leaving scratches on glass, metals or ceramics (Figure 5).

Figure 5—Advertisement published in the newspaper "De Volksstem" [The People's Voice], 10 October 1935

In 1905, the Lever brothers opened the factory *Savonneries Lever Frères* in Forest-Brussels (later becoming Unilever) where initially Sunlight soap was produced, from palm oil from the Belgian Congo. Gradually, more types of household cleaning and laundry products were introduced. The production of Vim scouring powder in Brussels had started in 1929 (only six years before the first report of silicosis noted above).[22]

Scouring powder and acute silicosis

By the time Colinet published his cases, work-related disease had been recognized among scouring powder workers for at least two decades. Indeed, the production of silica-based scouring powder was one of the first industries that has been struck by cases of "acute" silicosis. In contrast to the classic (chronic) silicosis, acute silicosis occurred in workers after relatively brief exposures to very high levels of silica resulting in rapidly progressive disease, which most often was fatal. The history of acute silicosis in scouring powder workers, arguably pathologically the same as alveolar proteinosis, has been described previously in detail by Blanc.[23] First reports on outbreaks of acute silicosis in the scouring powder industry started to appear in the period 1928-1930, initially in the UK,[24–26] then in Germany[27] and the United States.[20,28] In the proceedings of the 1930 Johannesburg Conference on Silicosis, the British Medical Inspector of Factories, Dr Middleton, described a factory of this then relatively new industry. It had 22 employees of which 4 workers (three women) between 17 and 23 years old had died of silicosis after only a few years of exposure.[20,23]

This first UK outbreak had occurred in a Battersea, London factory manufacturing a silica-based scouring powder branded as "scourine." Run by Poli-Varn Limited, the manufacturer appears to be unrelated, corporately, to the Lever Brothers. In June 1932, Horatio Ballantyne, the technical managing director of Lever Brothers—seemingly alarmed by the proceedings of the 1930 ILO conference—published an article in the Journal of State Medicine, stating that "No case of silicosis has yet occurred in any of the company's factories."[29] In contradistinction to this claim, in an article

published a few months earlier (December 1931) Gerlach and Gander from the University of Basel, Switzerland had described two 20-year-old women with acute silicosis who had been packing Vim in a scouring powder factory ["made out of pure English quartz sand"].[30] Subsequently, reports started to appear that described cases of acute silicosis in scouring powder factories across Europe, many after working for merely 2-5 years in the factory.[30–34]

Many authors speculated on the reasons why these exposures could induce such rapidly evolving disease.[31] As the scouring powders consisted of ground crystalline silica mixed with soap and washing soda, some had hypothesized that these additives could render the silica more dangerous. Arguing against this, similar disease has been described in other workers exposed to very high silica concentrations, such as sandblasters and tunnel workers.[35] Therefore, a modern understanding of the rapidity of the disease onset in these cases would attribute it to the intensity of the exposure to the finely ground crystalline silica.[36]

Silicosis in scouring powder workers recognized as an occupational disease in Belgium

Since 1937, Belgian workers with silicosis have been eligible for compensation for occupational disease, but only once their industrial sector was officially considered at risk (which initially included only ceramic tile factories, glazing and porcelain factories, and factories of refractory products).[37] This list was extended only gradually. In 1941, during the occupation by Nazi Germany, the Belgian labour inspection reported severe "silico-tuberculosis" in 3 scouring powder workers barely 20 years old.[38] This report led to the inclusion of scouring powder factories in the list of sectors "at risk" for silicosis in 1944. (Notably, pneumoconiosis in coal miners, also known as "anthracosilicosis," was only officially recognized in 1964 due to continuous pressure from the Belgian coal mining industry to delay its recognition).[39,40]

In his 1950 article, Colinet already had noted that several of the (female) co-workers of his first case had died from "silico-tuberculosis."[10] Between 1945

and 1963, 38 scouring powder workers were officially recognized with silicosis as occupational disease by the national compensation fund (*Fonds de Prévoyance*) with a peak around 1955.[41] By 1960, almost no more cases were reported. Reviewing these Belgian statistics, none clearly differentiate acute silicosis from chronic silicosis or silico-tuberculosis.

Scouring powder and autoimmune diseases

In the years following the cases described by Colinet, publications appeared on a range of autoimmune diseases in workers producing silica-containing scouring powder as well as in household consumers of such products. For example, in 1968, Titscher (Vienna, Austria) described a 63-year-old woman with Caplan syndrome who had worked as a packer of "Silax" scouring powder between 1941 and 1961.[42] Kroeger and colleagues (Paris, France) described two cases of silica-associated autoimmune disease who had been exposed to Ajax scouring powder (Colgate-Palmolive company, France): one was a 43-year-old man with systemic lupus erythematosus who had worked between 1970 and 1989 in an Ajax manufacturing plant, the other a 37-year-old women with Sjögren syndrome, Raynaud phenomenon and inflammatory polyarthritis who had used Ajax powder 6 hours per day for 12 years (1968-1980) for the scouring of sanitary-ware.[43] Of note, the exposure of the latter case was only revealed when the discovery of "Caplan" nodules (containing silica-laden macrophages) on a lung biopsy had led the clinicians to perform a thorough occupational history.[43]

The largest reported outbreak of autoimmune disease occurred in a Spanish scouring powder manufacturing facility.[44] When clinicians at the University Hospital of Sevilla realized in the early 1990s that 4 of their patients with prominent autoimmune disease-related symptoms had worked at the same factory, they encouraged the patients to contact their ex-colleagues. By then, the production of the scouring powder had already ceased ten years earlier. Among 50 former workers (44 women and 6 men) that were recruited (out of a workforce of about 300), 32 had a definite autoimmune disorder: 5 had systemic sclerosis, 3 had systemic lupus erythematosus, 5 had systemic

sclerosis and lupus, 6 had Sjögren syndrome, and 19 had undifferentiated systemic disease. They had worked at the factory on average 6.1 years. Out of the 50 workers, 18 had silicosis (of which 14 had an autoimmune disorder). Through numerous court cases, we know that these workers were employed at the "Persan" factory in the outskirts of Sevilla, producing "San" scouring powder in very dusty working conditions ("I left working with my clothes and body 'literally' white").[45]

Additionally, case reports have appeared from domestic "users" of silica-based scouring powder.[46,47] Dumontet and colleagues described a patient that had developed acute silicosis after intentionally inhaling Ajax scouring powder over a 6-month period three times a day, because it "had a nice smell."[48] Five years later, she had developed an autoimmune mixed-connective tissue disease (Sharp's syndrome).[46] Mehlhorn (in Germany) described a professional cleaner with systemic sclerosis who had been using 1-2 packages (250-500 g) of ATA scouring powder each day for 14 years.[49]

Conclusion

Throughout the 20th century, a largely invisible outbreak of acute silicosis and autoimmune diseases has struck scouring powder workers, especially young women packing the powder.

In the beginning of the 1950s, Colinet and his colleague Clerens were the first to describe the combination of rheumatoid arthritis and pneumoconiosis in two young women packing silica-based scouring powder, working at the *Savonneries Lever Frères* factory in Brussels, Belgium. Although this syndrome had initially been called Colinet-Caplan syndrome in the French language literature, Colinet's name later was dropped from the eponym. Because of the relatively limited description of the working conditions Colinet himself had provided, it had never been clear in the medical literature that he had been referring to scouring powder workers. In addition, Caplan self-promoted his construct of the syndrome as being specific to coal miner's and dismissed a role for silica in other settings. Thus, "Caplan syndrome" has generally been considered solely as a coal miner's disease.

In the decades after Colinet's initial reports, further cases of fatal acute silicosis, most likely alveolar proteinosis, and various autoimmune diseases have been described in scouring powder workers across Europe. It is also noteworthy that although exposure to respirable crystalline silica has been considered a hazard related to jobs mainly done by men, such as coal miners and sandblasters,[35] the scouring powder workers struck by acute silicosis/autoimmune diseases were mainly young women.

It was not until the 1980s that scouring powder producers stopped using silica and replaced it with less hazardous materials such as calcium carbonate. Nonetheless, it is unclear why this protective substitution finally occurred. There seems to be no published communication of the scouring powder industry to inform consumers about the hazards of silica-based powders. Analogous histories of hazardous compounds in consumer products, such as vinyl chloride in hairsprays, have shown that industries might prefer a "silent" substitution to avoid consumer lawsuits.[50] No further cases of autoimmune disorders related to exposure to scouring powder after 1989 have been reported.[43,48]

Unfortunately, this does not mean that autoimmune disorders due to silica have disappeared. In occupational medicine, old hazards often re-emerge in new applications or new industries.[51] Recently, a global outbreak of (rapidly progressing) silicosis has emerged amongst silica-based artificial stone workers. In addition to silicosis, these workers also manifest high rates of a range of autoimmune disorders. Shtraichman *et al* found autoimmune disorders in 9 of 40 artificial stone workers who were on the list of a transplantation centre because of silicosis (three systemic sclerosis; two rheumatoid arthritis; two mixed connective tissue disease; and one each with Sjögren's syndrome and polymyositis).[52] Rose *et al* found four workers with rheumatoid arthritis and one with systemic sclerosis among 18 cases of silicosis in US artificial stone workers.[53] Among Australian artificial stone workers, such cases of autoimmune disease also have been found.[54]

As the association between silica and autoimmune conditions has only gradually become known over the course of the second half of the 20th century, and given the high rates of autoimmune disease we are witnessing today in artificial stone workers, the cases among scouring powder workers that have been published are probably just the tip of an iceberg.

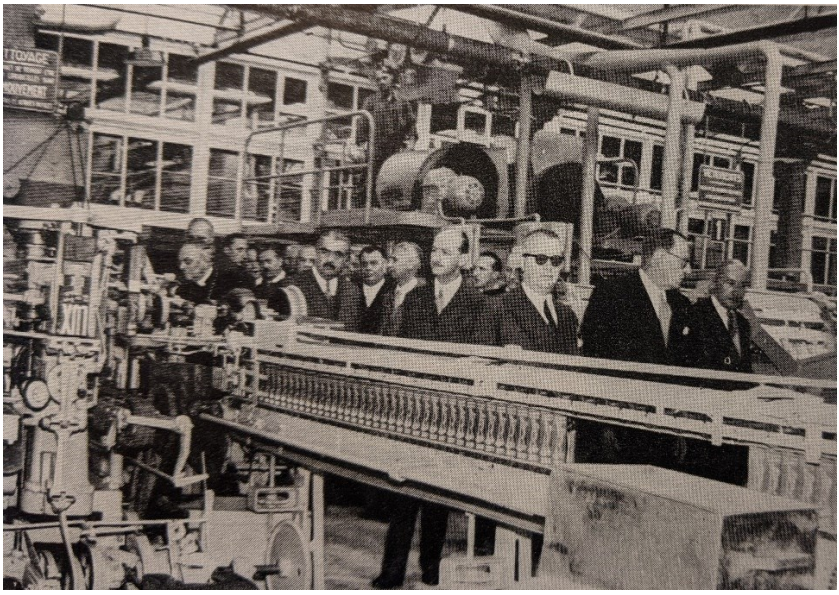

Figure 6—In 1955, for the 50th anniversary of the Vim factory in Brussels, the factory management organised a guided tour of the workplace for various important public persons such as the Minister of Labor, the Chief of Staff of the Ministry of Economic Affairs, and representatives of all major Belgian universities, including Monseigneur Van Waeyenbergh, rector of the Catholic University of Leuven. In this photo (at the far left among the visitors) , he seems to be meticulously inspecting the production line. This picture was published in the booklet "50me anniversaire des Savonneries Lever Frères à Forest— 1905-1955" published by the company.[55] Notably the writer of the booklet states: "*That a soap company is so clean, could seem obvious to a layman. However, that the handling of these oils, fats and powders does not leave a mark on the floor and on the machines, this is what confused all visitors*." (p 29; translation by the authors, originally written in French).[55]

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Appendices

Summary

PhD Thesis—OCCUPATIONAL EXPOSURE AND RESPIRATORY DISEASES—
Steven Ronsmans

During the 20th century coal workers' pneumoconiosis—or *anthraco-silicosis*—and asbestos-related diseases were the major occupational respiratory diseases among Belgian workers, both in terms of public health impact as well as public visibility. Except for asbestos-induced mesothelioma, the occurrence of these occupational diseases has been declining in recent decades, due to improved prevention but to a large extent also because many hazardous industries, such as coal mining, were closed or have moved to the global south. In Europe, this has led many to think that occupational respiratory diseases can be considered diseases 'of the past'.

However, workplace exposures do still contribute substantially to respiratory diseases. By bridging the gaps between the clinic, the university and the workplace, we can increase our understanding and improve the prevention of adverse health effects of occupational exposure to hazardous agents. This PhD project focuses on three topics, all requiring a different research approach: (1) the search for a cause of an enigmatic disease—sarcoidosis, (2) the re-emergence of an "old" disease in a new industry—silicosis in artificial stone workers, and (3) respiratory health effects of cleaning products in domestic cleaners.

(1) Sarcoidosis is a systemic disease characterized by the formation of immune granulomas in various organs. The lungs and intrathoracic lymph nodes are the most commonly affected organs, but also the eyes, skin, liver, spleen, heart, and other organs can be involved. It is unclear what causes sarcoidosis. Several lines of evidence indicate that the disease results from an immune reaction in genetically susceptible persons upon exposure to one or several antigens. Many occupational and environmental exposures have been associated to sarcoidosis: inhaled organic dust, inorganic dust—including metals and minerals—and infectious agents—such as mycobacteria and *Cutibacterium acnes.* The diverse clinical manifestations and the wide range of associated exposures fuel the hypothesis that sarcoidosis has more than one cause, each of which may promote a different disease phenotype. However, the relationship between exposure and disease phenotype has barely been studied.

In a retrospective study of 238 sarcoidosis patients, we showed that different occupational and environmental exposures are associated with different organ involvements. Sarcoidosis limited to pulmonary involvement was associated with

exposure to inorganic dust prior to diagnosis (odds ratio [OR] 2.11; 95% confidence interval [CI] 1.11–4.17). Patients with liver involvement had higher odds of contact with livestock (OR 3.68; 95%CI 0.91–12.7) or having jobs with close human contact (OR 4.33; 95%CI 1.57–11.3) than patients without liver involvement. Similar associations were found for splenic involvement (livestock: OR 4.94, 95%CI 1.46–16.1; close human contact: OR 3.78; 95%CI 1.47–9.46). Cardiac sarcoidosis was associated with exposure to reactive chemicals (OR 5.08; 95%CI 1.28–19.2) or livestock (OR 9.86; 95%CI 1.95–49.0). Active smokers had more ocular sarcoidosis (OR 3.26; 95%CI 1.33–7.79).

(2) In recent years, outbreaks of silicosis in artificial stone workers have been reported around the globe. Artificial stones consist of a very high percentage of crystalline silica (70-95% quartz or cristobalite) bound together with synthetic resins. They are increasingly used to make kitchen or bathroom countertops. For the workers who process the stones, the risk of silicosis is particularly high because the grinding and cutting of these stones generates high concentrations of respirable particles of crystalline silica. In Belgian artificial stone workers, silicosis has been probably underdetected. Via the clinic for occupational and environmental medicine in the University Hospitals Leuven, we initially confirmed silicosis in two referred workers from a 2-man company in the province of Antwerp, Belgium, which were the first cases reported in Belgium.

We also describe an outbreak at a company producing silica-based artificial kerbstones—that were made for hygienic wall protection in the food industry—suggesting that silica-based artificial stones might have more applications than we had previously assumed. We report on 5 workers—of whom 4 had developed definite silicosis. Annual spirometries—but no chest X-rays—had been performed since 8 to 10 years prior to diagnosis. The four men with silicosis proved to have undergone an excessively rapid FEV_1 decline [between 98 (95%CI 79–116) and 221 mL/year (95%CI 214–228)], many years before their first symptoms appeared. High respirable quartz concentrations (>0.1 mg/m³) were measured during various operations, especially during dry finishing of the cured kerbstones (1.080 mg/m³).

The discovery of rapidly progressive serious lung disease in workers producing silica-based artificial kerbstones shows that the hazards of artificial stone production/processing reach beyond the kitchen/bathroom countertop industry. Increasing awareness, improving prevention and establishing workers' health surveillance programmes—or improving the quality of existing programmes—are crucial.

(3) Professional domestic cleaners have an increased risk of asthma-like and other respiratory symptoms and conditions—which has been associated with the use of bleach, ammonia, disinfectants, and sprays. There is, however, uncertainty about which products are most hazardous. We did a questionnaire-based cross-sectional study in the Belgian service voucher sector to investigate, among professional domestic cleaners, the associations of the use of 40 types of cleaning products at work (liquids and sprays) with the occurrence of work-related eye and respiratory outcomes (eye symptoms, rhinitis, sore throat, inducible laryngeal obstruction, asthma and cough) and with chronic bronchitis. We defined "work-relatedness" as symptoms that disappear or improve on days off-work—which has been shown to be a typical clinical feature of work-related asthma and rhinitis.

Among 1,586 domestic cleaners, the total number of cleaning sprays used per week (median 12/week) was significantly associated with all studied respiratory outcomes, with odds ratios ranging from 1.016 to 1.038 per spray per week. Bleach/disinfectant-containing liquid products were associated with work-related eye symptoms (OR 1.100 per product per week; 95%CI 1.017–1.190) and asthma (OR 1.104; 95%CI 1.008–1.208); liquid ammonia with chronic bronchitis (OR 1.463; 95%CI 1.053–2.035). Using elastic net regression, we identified several specific types of products that were strongly related to respiratory outcomes, such as mould removal sprays and carpet/seat/curtain sprays. Notably, cleaners capable of choosing their own products had fewer work-related eye symptoms (OR 0.758; 95%CI 0.576–0.996), rhinitis (OR 0.746; 95%CI 0.578–0.963) or cough (OR 0.697; 95%CI 0.539–0.901), suggesting that empowering domestic cleaners to choose their products may reduce the burden of symptoms.

Samenvatting

Doctoraatsthesis—Beroepsmatige blootstelling en respiratoire aandoeningen—Steven Ronsmans

Gedurende de 20ste eeuw waren de mijnwerkerspneumoconiose—of *stoflong*—en asbestgerelateerde ziekten de belangrijkste respiratoire beroepsziekten onder Belgische arbeiders, zowel wat betreft de gevolgen voor de volksgezondheid als de publieke zichtbaarheid. Behalve voor asbestgeïnduceerd mesothelioom, is het vóórkomen van deze beroepsziekten de afgelopen decennia afgenomen, dankzij verbeterde preventie, maar in grote mate ook omdat veel gevaarlijke industrieën, zoals steenkoolwinning, werden gesloten of gedelokaliseerd. In Europa heeft dit ertoe geleid dat velen respiratoire beroepsziekten zijn gaan beschouwen als ziekten 'van het verleden'.

Blootstelling op de werkplek kan echter nog steeds aanzienlijk bijdragen aan respiratoire aandoeningen. Door de kloof tussen de kliniek, de universiteit en de werkplek te overbruggen, kunnen we ons begrip vergroten en de preventie van nadelige gezondheidseffecten van beroepsmatige blootstelling aan gevaarlijke stoffen verbeteren. Dit doctoraatsproject richt zich op 3 onderwerpen die allemaal een andere onderzoeksbenadering vereisen: (1) de zoektocht naar een oorzaak van een raadselachtige ziekte—sarcoïdose, (2) de "come-back" van een 'oude' ziekte in een nieuwe industrie—silicose bij composietsteenbewerkers, en (3) respiratoire gezondheidseffecten van schoonmaakproducten bij huishoudelijke schoonmakers.

(1) Sarcoïdose is een systemische ziekte die wordt gekenmerkt door de vorming van immuungranulomen in verschillende organen. De longen en intrathoracale lymfeklieren zijn de meest frequent aangetaste organen, maar ook de ogen, huid, lever, milt, hart en andere organen kunnen betrokken zijn. Het is onduidelijk wat sarcoïdose veroorzaakt. Verschillende types evidentie wijzen erop dat de ziekte het gevolg is van een immuunreactie bij genetisch gevoelige personen na blootstelling aan een of meer antigenen. Veel beroepsmatige en milieublootstellingen zijn reeds in verband gebracht met sarcoïdose: ingeademd organisch stof, anorganisch stof—inclusief metalen en mineralen—en infectieuze agentia—zoals mycobacteriën en *Cutibacterium acnes*. De diverse klinische manifestaties en het brede scala aan geassocieerde blootstellingen voeden de hypothese dat sarcoïdose meer dan één oorzaak heeft, die elk een ander fenotype kunnen uitlokken. De relatie tussen blootstelling en fenotype is echter nauwelijks onderzocht.

In een retrospectieve studie bij 238 sarcoïdosepatiënten tonen we aan dat verschillende beroepsmatige en milieublootstellingen geassocieerd zijn met verschillende orgaanbetrokkenheid. Sarcoïdose beperkt tot pulmonale betrokkenheid was geassocieerd met blootstelling aan anorganisch stof (odds ratio [OR] 2,11; 95% betrouwbaarheidsinterval [BI] 1,11–4,17). Patiënten met leverbetrokkenheid hadden een grotere kans contact te hebben met vee (OR 3,68; 95% BI 0,91–12,7) of een job met nauw menselijk contact (OR 4,33; 95% BI 1,57–11,3) dan patiënten zonder leverbetrokkenheid. Vergelijkbare associaties werden gevonden voor miltbetrokkenheid (vee: OR 4.94, 95%CI 1.46–16.1; nauw menselijk contact: OR 3.78; 95%CI 1.47–9.46). Cardiale sarcoïdose was geassocieerd met blootstelling aan reactieve chemicaliën (OR 5.08; 95%CI 1.28–19.2) of vee (OR 9.86; 95%CI 1.95–49.0). Actieve rokers hadden meer oculaire sarcoïdose (OR 3.26; 95%CI 1.33–7.79).

(2) In de afgelopen jaren zijn wereldwijd verschillende uitbraken van silicose bij composietsteenbewerkers gemeld. In vergelijking met de meeste natuurstenen bestaan composietstenen uit een zeer hoog percentage kristallijn silica (70-95% kwarts of cristobaliet) samengebonden met kunstharsen. Ze worden steeds vaker gebruikt om werkbladen voor keukens of badkamers te maken. Voor de werknemers die de stenen verwerken, is het risico op silicose bijzonder hoog, aangezien het slijpen van deze stenen hoge concentraties van inadembare deeltjes kristallijn silica genereert. Bij Belgische composietsteenbewerkers is silicose waarschijnlijk ondergedetecteerd. Via de raadpleging voor beroeps- en omgevingsgebonden aandoeningen in het UZ Leuven vonden we aanvankelijk 2 arbeiders met silicose in een 2-mansbedrijf, de eerste gevallen die in België werden gerapporteerd.

We beschrijven ook een uitbraak bij een bedrijf dat composietstootranden produceert op basis van silica—bedoeld voor hygiënische muurbescherming in de voedingsindustrie—hetgeen suggereert dat silica-gebaseerde composietmaterialen mogelijk meer toepassingen hebben dan we tot nu toe hadden aangenomen. We rapporteren over 5 werknemers, van wie er 4 duidelijke silicose hadden ontwikkeld. Jaarlijkse spirometrie—maar geen thoraxfoto's—waren uitgevoerd sinds 8 tot 10 jaar voorafgaand aan de diagnose. De vier mannen met silicose bleken een te snelle daling van FEV_1 te hebben ondergaan [tussen 98 (95%BI 79–116) en 221 ml/jaar (95%BI 214–228)], vele jaren voordat hun eerste symptomen verschenen. Hoge inadembare kwartsconcentraties (>0,1 mg/m³) werden gemeten op verschillende werkposten, vooral tijdens het droog afwerken van de uitgeharde stootranden (1.080 mg/m³).

Deze uitbraak toont aan dat de gevaren van de productie/verwerking van composietmaterialen verder reiken dan de productie van keuken- en badkamerbladen. Het verhogen van het bewustzijn, het verbeteren van preventie en het opzetten van programma's voor gezondheidstoezicht voor werknemers, of het verbeteren van de kwaliteit van bestaande programma's, is cruciaal.

(3) Professionele huishoudelijke schoonmakers hebben een verhoogd risico op astma-achtige en andere ademhalingssymptomen en aandoeningen, die reeds herhaaldelijk werden geassocieerd met het gebruik van bleekmiddel, ammoniak, ontsmettingsmiddelen en sprays. Er is echter onzekerheid over welke producten het gevaarlijkst zijn. We hebben een cross-sectionele vragenlijststudie gedaan in de Belgische dienstenchequesector om, bij professionele huishoudelijke schoonmakers, de associaties te onderzoeken van het gebruik van 40 types schoonmaakproducten op het werk (vloeistoffen en sprays) en het optreden van werkgerelateerde oog/ademhalingsproblemen (oogsymptomen, rhinitis, keelpijn, larynxobstructie, astma en hoesten) en met chronische bronchitis. We definieerden 'werkgerelateerdheid' als symptomen die verdwijnen of verbeteren op vrije dagen, wat een typisch klinisch kenmerk is van werkgerelateerd astma en rhinitis.

In ons onderzoek bij 1586 huishoudelijke schoonmakers was het totaal aantal gebruikte sprays per week (mediaan 12/week) significant geassocieerd met alle bestudeerde respiratoire uitkomsten, met odds ratio's variërend van 1.016 tot 1.038 per spray per week. Vloeibare producten die bleekmiddel/desinfectiemiddel bevatten waren geassocieerd met werkgerelateerde oogsymptomen (OR 1.100 per product per week; 95%BI 1.017–1.190) en astma (OR 1.104; 95%BI 1.008–1.208); vloeibaar ammoniak met chronische bronchitis (OR 1.463; 95%BI 1.053–2.035). Met behulp van *elastic net* regressie analyse konden we verschillende specifieke soorten producten identificeren die sterk gerelateerd waren met respiratoire uitkomsten, zoals schimmelverwijderende sprays en mat/stoel/gordijnsprays. Schoonmakers die hun eigen producten konden kiezen, hadden minder werkgerelateerde oogsymptomen (OR 0,758; 95%BI 0,576–0,996), rhinitis (OR 0,746; 95%BI 0,578–0,963) of hoest (OR 0,697; 95%BI 0,539–0,901), hetgeen suggereert dat het belangrijk is om huishoudelijke schoonmakers te *empoweren* om hen in staat te stellen veranderingen in productgebruik te kunnen verwezenlijken.

List of publications

Occupational and environmental exposures and sarcoidosis

1. Ronsmans S, Verbeken EK, Adams E, Keirsbilck S, Yserbyt J, Wuyts WA, et al. *Granulomatous lung disease in two workers making light bulbs*. **Am J Ind Med**. 2019;62(10):908–13 (Case report)
2. De Ridder J, Ronsmans S, Vanderschueren S, et al*. Clinical characteristics of sarcoidosis patients in Belgium.* **Acta Clin Belg** *2020;0:1–8. doi:10.1080/17843286.2020.1821493* (Research paper)
3. Ronsmans S, De Ridder J, Vandebroek E, *et al. Associations between occupational and environmental exposures and organ involvement in sarcoidosis: a retrospective case-case analysis*. ***Respir Res*** 2021;**22**:224. doi:10.1186/s12931-021-01818-5 (Research paper)

Silicosis in artificial stone workers

1. Ronsmans S, Nemery B. *Sand particles—an overlooked occupational hazard*. **Nature**. 2019 Aug 13;572:312–312 (Correspondence)
2. Ronsmans S, Decoster L, Keirsbilck S, Verbeken EK, Nemery B. *Artificial stone-associated silicosis in Belgium*. **Occup Environ Med** 2019;76:133–4. doi:10.1136/oemed-2018-105436 (Case report)
3. [submitted] Ronsmans S, Goeminne P, Jerjir N, *et al*. *Outbreak of silicosis in workers producing silica-based artificial kerbstones. (Research paper)*

Respiratory health effects of cleaning products in domestic cleaners

1. De Matteis S, Ronsmans S, Nemery B. *Respiratory Health Effects of Exposure to Cleaning Products*. **Clin Chest Med** 2020;**41**:641–50. doi:10.1016/j.ccm.2020.08.010 (Review)
2. [under review] De Troeyer K, De Man J, Vandebroek E, Nemery B, Vanroelen C, Casas L*, Ronsmans S* (*shared last author). *Identifying cleaning products associated with short-term work-related respiratory symptoms: a workforce-based study in domestic cleaners (Research paper)*

Occupational asthma, rhinitis, rhinosinusitis

1. Ronsmans S, Steelant B, Backaert W, Nemery B, Van Gerven L. *Diagnostic approach to occupational rhinitis: the role of nasal provocation tests*. **Curr Opin Allergy Clin Immunol**. 2020;20:122–30. doi:10.1097/ACI.0000000000000608 (Review)
2. Tsui HC, Ronsmans S, De Sadeleer LJ, et al. *Skin Exposure Contributes to Chemical-Induced Asthma: What is the Evidence? A Systematic Review of Animal Models.* **Allergy Asthma Immunol Res** *2020;12:579–98. doi:10.4168/aair.2020.12.4.579* (Review)
3. Dietz de Loos DAE, Ronsmans S, Cornet ME, Hellings PW, Hox V, Fokkens WJ, Reitsma S. *Occupational exposure influences control of disease in patients with chronic rhinosinusitis*. **Rhinology** 2021;**59**:380–6. doi:10.4193/Rhin21.091

Occupational exposure and autoimmune diseases

1. Ronsmans S, Nemery B. *The presence of autoimmune antibodies in pulmonary alveolar proteinosis does not necessarily imply idiopathic disease*. **Lancet Respir Med** 2018;6:e48. doi:10.1016/S2213-2600(18)30299-6 (Correspondence)
2. Celen H, Dens A-C, Ronsmans S, Michiels S, De Langhe E. *Airborne pollutants as potential triggers of systemic autoimmune rheumatic diseases: a narrative review*. **Acta Clin Belg**. 2021;0(0):1-9. doi:10.1080/17843286.2021.1992582 (Review)
3. [accepted for publication] Ronsmans S, Hougaard KS, Nawrot TS, et al. *The EXIMIOUS project—Mapping exposure-induced immune effects: connecting the exposome and the immunome.* **Environmental Epidemiology**
4. [in preparation] Ronsmans S, Blanc PD. *The history of the Colinet-Caplan syndrome and the outbreak of autoimmune disease in scouring powder workers*

Other publications

1. Pauwels S, Swinnen C, Temmerman A-M, Ronsmans S, et al. *PROBE Study: A Sentinel Surveillance System to Monitor Exposure*

of Belgian Employees to Hazardous Chemicals: A Feasibility Study. **J Occup Environ Med** 2020;62:e748. (Research paper)

PRESENTATIONS

International meetings and conferences

- Case presentation: Ronsmans S, Adams E, Yserbyt J, Wuyts WA, Verbeken E, Swennen R, Nemery B. *An interstitial lung disease case in the workplace.* GORDS (Group of Occupational Respiratory Disease Specialists) @ Soho House, Birmingham, UK (06-02-2018)
- Poster: Ronsmans S, Verbeken E, Keirsbilck S*,* Adams E, Swennen R, Nemery B. 786 *Sarcoidosis in two workers making light bulbs*. Occup Environ Med 2018;75**:**A449. ICOH (International Congress on Occupational Health) @ Dublin, Ireland (30-04-2018 - 03-05-2018)
- Poster: Ronsmans S, Pauwels S, Temmerman A, De Schryver A, Rusu D, Braeckman L, Godderis L. 742 *Prioritisation exercise for the PROBE project (hazardous chemical products register for occupational use in Belgium)*. Occup Environ Med 2018;75**:**A385. ICOH (International Congress on Occupational Health) @ Dublin, Ireland (30-04-2018 - 03-05-2018)
- Presentation: Ronsmans S, Vandebroek E, Keirsbilck S, Adams E, Verbeken E, Decoster L, Nemery B. *Occupational lung diseases in the (artificial) Stone Age.* GORDS (Group of Occupational Respiratory Disease Specialists) @ Royal Brompton Hospital, London, UK (05-02-2019)
- Presentation*:* Ronsmans S. *Old hazards in new places—The silica case; as* trainer at the DIMOPEX Training School (COST Action) @ University of Tallinn, Estonia (26-03-2019)
- Presentation: Ronsmans S, Vandebroek E, Keirsbilck S, De Langhe E, Nemery B. *Non-silicotic silica flour workers.* GORDS (Group of Occupational Respiratory Disease Specialists) @ KU Leuven (14-02-2020)

- Invited lecture: Ronsmans S. *Old hazards in new places. Silicosis in artificial stone workers.* Contactgroep Gezondheid en Chemie & Nederlandse Vereniging voor Arbeids- en Bedrijfsgeneeskunde (CGC/NVAB), The Netherlands (18-06-2020)
- Presentation: Ronsmans S, Vandebroek E, Keirsbilck S, et al*. Associations between occupational and environmental exposures and organ involvement in sarcoidosis. European Respiratory Society (ERS)* International Congress 2021 Virtual (07-09-2021)

National meetings and lectures

General Practitioners

- *'*Work *and health',* General Practitioners in training, Antwerp, Belgium, 23-01-2018; LOK, WGC De Botermarkt, Ghent, 11-09-2018; LOK, WGC De Kaai, Ghent, 16-05-2019

Occupational health physicians

- Case presentations at the course 'Problem Oriented Case Discussions' for master students in Occupational Medicine at KU Leuven, 19-03-2018 and 16-12-2019
- Presentation: *'Respiratory health effects of exposure to mineral dust: new developments'*, Seminar 'Deeltjes en Vezels en ander stof tot nadenken' - Vlaamse Wetenschappelijke Vereniging voor Arbeidsgezondheidskunde (VWVA), 10-10-2019
- Presentation: '*Silicosis in artificial stone workers'* @ Co-Prev board of medical directors of external health and safety services, Brussels, 15-10-2019
- Ad hoc classes for master students in occupational medicine: Occupational asthma (3h, 18-12-2019), Occupational cancer (3h, 14-10-2020)
- Presentation: *'Early detection of occupational diseases'*, Seminar organised by FEDRIS and Vlaamse Wetenschappelijke Vereniging voor Arbeidsgezondheidskunde (VWVA), 09-02-2021

Pneumologists - allergologists

- *Presentation* '*Role of occupational exposure in the pathogenesis of (non-infectious) granulomatous diseases'*, LOK Pneumology Leuven, University Hospital Leuven, 13-12-2018
- *Presentation* '*Occupational rhinitis and asthma'*, LOK Allergy Leuven, KU Leuven, 19-12-2019
- *Presentation* '*Occupational allergy*, LOK Allergy Leuven, KU Leuven, 17-12-2020
- *Presentation*: *Associations between occupational and environmental exposures and organ involvement in sarcoidosis.* BeRS-GSK Clinical Science Awards 2021 @ Cercle du Lac, Louvain-la-Neuve (26-05-2021)
- *Presentation* '*Occupational diseases'*, Postgraduate course for pulmonologists-in-training, University Hospital Leuven, 30-06-2021
- *Presentation* '*Occupational diseases'*, LOK Pneumology, University Hospital Antwerp (UZA), 29-09-2021

Occupational hygienists

- *Presentation* '*Health effects of exposure to mineral dust: new developments*', Workshop BSOH (Belgian Society of Occupational Hygiene), "Work related diseases: presentation, prevention, exposure", Brussels, 02-10-2019
- *Lectures 'Human Toxicology' (3h), 'Health effects of particle exposure' (3h)*, '*Health effects of fibres' (3h)*. Aanvullende vorming voor preventieadviseurs – specialisatie arbeidshygiëne, KU Leuven 16-01-2020, 11-06-2020, 29-10-2020.

Nurses

- *Presentation* '*Occupational Diseases'*, Permanente vorming pneumologie voor verpleegkundigen, KU Leuven, 06-01-2020

Employee and employer representatives

- *Presentation* '*Silica*', Workshop Algemene Centrale, Brussels, 23-04-2019
- *Presentation* '*Artificial stone silicosis'*, Technical Steering Group Constructiv, Brussels, 15-01-2019

Global health

- *Invited* lecture '*Effect of environmental pollution on health in LMICs'* and debate at the Institute for Tropical Medicine, Antwerp, 08-05-2018
- *Lecture* 'Occupational cancer' for Master in Global Health, KU Leuven, 12-11-2020 and 21-10-2021

Others

- *Introduction* to Health & Safety for new PhD students @ KU Leuven (video; 15 min), 2020
- *Departmental* Research Seminar "Occupational exposure and respiratory diseases — From the clinic to the workplace, and back", Department of Public Health and Primary Care, KU Leuven, 26-11-2020

NON-ACADEMIC publications

Interview (by Marc De Wilde). "*Bewerken van composietsteen houdt ernstig risico in op silicose*". Bouwbedrijf, May 2019 (magazine of the building sector organization *Confederatie Bouw*)

Interview (by Nils De Neubourg). "*Stoflong terug van nooit weggeweest?"* Visie 2020 - nr. 1 (magazine for members of CM [Christian Mutuality] and ACV/CSC [Confederation of Christian Trade Unions])

Ronsmans S. *A global outbreak of silicosis in an unexpected industry* / 1. HesaMag, 2020, n°21 - 51-55 (magazine of the European Trade Union Institute)

Ronsmans S. *De zoektocht naar mogelijke oorzaken van sarcoïdose in werk- of thuisomgeving*. Sarcoidosis patient magazine (spring 2021).

Ronsmans S. *Silicose bij bewerkers van composietsteen.* Veiligheidsnieuws 211 (magazine for health and safety professionals). June 2021

Short curriculum vitae

Steven Ronsmans has been trained as a Candidate Civil Engineering (KU Leuven, 2003), Bachelor of Medicine (2006), Master of Medicine (2010), Master of Family Medicine (2012), and Master of Occupational Medicine (2017). As a medicine student, he became interested in health inequities and social determinants of health and disease (Master thesis, 2010), and while working as a general practitioner, he saw that work was one of the key determinants of health in patients' lives (Master thesis, 2012), which led him to study occupational medicine. In his work as an occupational physician, he mainly focused on the prevention of work-related musculoskeletal disorders and psychosocial risks (Master thesis, 2017). It was only after joining the team of Professor Benoit Nemery at the Clinic for Occupational and Environmental Medicine at the Department of Respiratory Diseases at the University Hospitals Leuven, that he realized the importance of occupational diseases due to chemical exposures at work—but also that expertise in this domain was very scarce. In 2017, he started a PhD at the Centre for Environment and Health at the KU Leuven under the supervision of professors Jonas Yserbyt, Peter Hoet, Kristiaan Nackaerts, and Benoit Nemery. His PhD focused on clinical-epidemiological research on occupational respiratory diseases—occupational and environmental causes of sarcoidosis, artificial stone-related silicosis, and respiratory health effects of cleaning products in domestic cleaners. He is currently involved as a task leader in the Horizon 2020 EXIMIOUS project (Mapping Exposure-Induced Immune Effects: Connecting the Exposome and the Immunome) (2020-2024). In the past few years, he has taken every opportunity to give talks on current topics in occupational medicine to general practitioners, occupational physicians, pulmonologists, occupational hygienists, employers, trade unions, and others. Since September 2021, he has been teaching in the courses of *Occupational Toxicology* and *Health Effects of Exposure to Chemical Agents* in the Master of Occupational Medicine, and in the course *Medical Implications of Safety* in the Master of Safety Engineering (KU Leuven).

Scientific acknowledgements

Chapter 1 — Occupational and environmental exposure and sarcoidosis

Ronsmans S, Verbeken EK, Adams E, Keirsbilck S, Yserbyt J, Wuyts WA, Swennen R, Hoet PH, Nemery B. *Granulomatous lung disease in two workers making light bulbs*. **Am J Ind Med**. 2019;62(10):908–13

Personal contribution: clinical management of the patients and drafting the manuscript

Scientific acknowledgements: BN had the idea for the case report and co-drafted the manuscript. EKV, EA, SK, JY, WAW, RS, PHMH revised the manuscript. EKV, EA, SK, JY, WAW, BN took part in the clinical management of the patient. PHMH collaborated in the lymphocyte proliferation testing. RS did the identification and elemental analysis of the dust samples.

Ronsmans S, De Ridder J, Vandebroek E, Keirsbilck S, Nemery B, Hoet PHM, Vanderschueren S, Wuyts WA, Yserbyt J. *Associations between occupational and environmental exposures and organ involvement in sarcoidosis: a retrospective case-case analysis*. ***Respir Res*** 2021;**22**:224. doi:10.1186/s12931-021-01818-5

Personal contribution: drafting the grant proposal (KU Leuven C2), study design, (part of) data extraction, statistical analysis, drafting the manuscript.

Scientific acknowledgements: JY and JDR extracted part of the clinical data from the medical records. SV, WAW and JY took part in the clinical management of the patients. EV and SK did the blinded exposure assessment. JDR, EV, SK, BN, PHMH, SV, WAW and JY contributed to the interpretation of the data and revised the manuscript.

Chapter 2 — Old hazards in new places: Silicosis in artificial stone workers

Ronsmans S, Decoster L, Keirsbilck S, Verbeken EK, Nemery B. *Artificial stone-associated silicosis in Belgium*. **Occup Environ Med** 2019;76:133–4. doi:10.1136/oemed-2018-105436

> **Personal contribution**: drafting the manuscript
>
> **Scientific acknowledgements:** BN had the idea for this letter. LD, SK, EKV, BN revised the manuscript. LD, SK, BN took part in the clinical management of the patient. EKV did the histopathological assessment.

Ronsmans S, Goeminne P, Jerjir N, Nowé V, Vandebroek E, Keirsbilck S, Weynand B, Hoet PHM, Vanoirbeek JAJ, Wuyts WA, Yserbyt J, Nemery B. *Outbreak of silicosis in workers producing silica-based artificial kerbstones*

> **Personal contribution**: clinical management of the patients, statistical analysis and drafting the manuscript
>
> **Scientific acknowledgements:** PG, NJ, VN, EV, SK, BW, PHMH, JAJV, WAW, JY, BN reviewed and edited the manuscript. PG, NJ, VN, EV, SK, WAW, JY and BN took part in the clinical management of the patient. BW performed the histological evaluation.

Chapter 3 — Respiratory health effects of cleaning products in domestic cleaners

De Matteis S, Ronsmans S, Nemery B. *Respiratory Health Effects of Exposure to Cleaning Products*. **Clin Chest Med** 2020;**41**:641–50. doi:10.1016/j.ccm.2020.08.010 (Review)

> **Personal contribution:** drafting the part of the manuscript on exposure science, mechanisms, and toxicology of cleaning products
>
> **Scientific acknowledgements**: SDM drafted the part of review on the epidemiological studies, BN reviewed and edited the manuscript.

De Troeyer K, De Man J, Vandebroek E, Nemery B, Vanroelen C, Casas L*, Ronsmans S* (*shared last author). *Identifying cleaning products associated*

with short-term work-related respiratory symptoms: a workforce-based study in domestic cleaners (Research paper)

Personal contribution: writing the grant proposal, project administration and supervision, study design, data acquisition, (part of) statistical analysis, partly drafting, partly reviewing & editing of the manuscript.

Scientific acknowledgements: KDT: writing-original draft, methodology, data acquisition, statistical analysis; JDM: writing-review & editing, methodology, statistical analysis; EV: writing-review & editing, data acquisition; JAV: writing-review & editing; PHMH: writing-review & editing; BN: writing-review & editing, conceptualization; CV: writing-review & editing, conceptualization; LC: writing-review & editing, conceptualization, methodology, supervision.

Epilogue

Ronsmans S, Blanc PD. *The history of the Colinet-Caplan syndrome and the outbreak of autoimmune disease in scouring powder workers*

Personal contribution: literature/archives search, drafting the manuscript

Scientific acknowledgements: PDB reviewed and edited the manuscript.

Conflict of interest statement

This work was supported KU Leuven C2 project funding (C24/18/085), the Fund Van Mulders-Moonens managed by the King Baudouin Foundation (2018-J3812960-209723) and the Machiel van der Woude Stipendium.

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I have provided expert witness testimony at the request and on behalf of patients with occupational diseases and their families, for which I have not received any personal financial compensation.

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