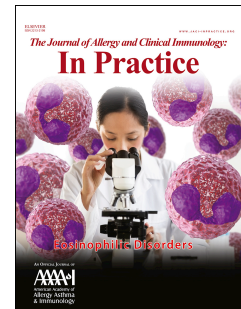


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Occupational asthma caused by quaternary ammonium compounds: A multicenter cohort study

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Occupational asthma caused by quaternary ammonium compounds:

A multicenter cohort study

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Running head: Occupational eosinophilic bronchitis

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Keywords: Asthma; Biocides; Cleaning agents; Occupational disease; Quaternary ammonium compounds.

Abstract

Background: Quaternary ammonium compounds (QACs) are used extensively for cleaning and disinfection and have been documented in scattered reports as a cause of occupational asthma (OA) through bronchoprovocation tests (BPT).

Objective: To examine the clinical, functional, and inflammatory profile of QAC-induced OA compared to OA caused by other low-molecular-weight (LMW) agents.

Methods: The study was conducted in a retrospective multicenter cohort of 871 subjects with OA ascertained by a positive BPT. Subjects with QAC-induced OA (n=22) were identified based on a positive BPT to QACs, after exclusion of those challenged with cleaning products or disinfectants that contained other potential respiratory sensitizers, and they were compared to 289 subjects with OA caused by other LMW agents.

Results: Most subjects with QAC-induced OA were working in the healthcare sector (n=14). A ≥ 2 -fold increase in the postchallenge level of nonspecific bronchial hyperresponsiveness was recorded in 8 of 11 (72.7%) subjects with QAC-induced OA, and in 49.7% of those with OA due to other LMW agents. Although sputum assessment was available in only 8 subjects with QAC-induced OA, they showed a significantly greater median (interquartile) increase in sputum eosinophils (18.1% [12.1 to 21.1]) compared to those with OA due to other LMW agents (2.0% [0 to 5.2], $P < 0.001$).

Conclusion: This study indicates that QAC-induced OA is associated with a highly eosinophilic pattern of airway response and provides further evidence supporting the sensitizing potential of QACs. The findings highlight the heterogeneous nature of the pathobiological pathways involved in OA caused by LMW agents.

Abstract word count: 248 words

1 **Highlights Box**

2 **What is already known about this topic?**

3 Occupational asthma caused by quaternary ammonium compounds (QACs) has been
4 documented in workers exposed to cleaning and disinfectant products, although the
5 underlying mechanisms remain largely unknown.

6 **What does this article add to our knowledge?**

7 This retrospective study demonstrates that asthmatic reactions induced by QACs are
8 associated with increases in nonspecific bronchial hyperresponsiveness and sputum
9 eosinophils that are consistent with a respiratory sensitizing mechanism.

10 **How does this study impact current management guidelines?**

11 This report further indicates that exposure to QACs should be considered as a potential
12 cause of sensitizer-induced occupational asthma among workers involved in cleaning and
13 disinfection tasks.

14

1 List of abbreviations

2	BPT:	Bronchial provocation test
3	CAS:	Chemical Abstracts Service
4	CI:	Confidence interval
5	FeNO:	Fractional exhaled nitric oxide
6	FEV ₁ :	Forced expiratory volume in one second
7	FVC:	Forced vital capacity
8	IQR:	Interquartile range
9	LMW:	Low-molecular-weight agents
10	NSBH:	Nonspecific bronchial hyperresponsiveness
11	QAC:	Quaternary ammonium compound
12	OA:	Occupational asthma
13	QSAR:	Quantitative structure activity relationship

14

1 INTRODUCTION

2 Quaternary ammonium compounds (QACs) have the generic chemical structure
3 $N(R_1R_2R_3R_4)^+ Cl^-$, where R_{1-4} are alkyl or aryl groups with varying carbon chain length.
4 These compounds are used extensively for the cleaning and disinfection of surfaces,
5 instruments, and equipment, especially in healthcare and food processing facilities, because
6 of their broad-spectrum antimicrobial activity [1, 2]. Asthmatic reactions induced by the most
7 widely used QACs, benzalkonium chloride (Chemical Abstracts Service [CAS] #8001-54-5)
8 and didecyl dimethyl ammonium chloride (CAS #7173-51-5), have been documented through
9 bronchial provocation tests (BPT) in a few case reports [3-5] and limited case series [6, 7]. A
10 physician-based notification scheme of work-related asthma in France reported a significant
11 upward trend in incident cases attributed to QACs from 1.4% of reported cases in 2001 to
12 8.3% in 2009, mainly in the health and social sectors [8]. Nevertheless, epidemiological
13 surveys of cleaners either did not address specifically exposure to QACs [9-13] or failed to
14 document an association between asthma and exposure to QACs [14, 15], with the notable
15 exception of Gonzalez et al. [16] who found an association between exposure to QACs and
16 increased risk of asthma in a survey of healthcare workers. Overall, the role of QAC
17 exposure in the development of asthma remains largely unknown and controversial [17, 18].

18 This study aimed to characterize the clinical, functional, and inflammatory profiles of
19 occupational asthma (OA) caused by QAC ascertained by a positive BPT and to compare
20 these phenotypic patterns with those of OA due to other low-molecular-weight (LMW) agents.

METHODS

Study design and population

This retrospective, observational study was conducted in a cohort of 871 subjects who showed a positive BPT with various occupational agents between January 2006 and December 2018 in six centers participating in the European network for the PHenotyping of Occupational Asthma (E-PHOCAS) [19-22]. This analysis was restricted to six E-PHOCAS centers which were selected based on the performance of induced sputum analysis before and after BPT, although this technique was not available throughout the whole 2006-2018 study period in each center. The recruitment of the population included in this analysis on cleaners' OA is described in Figure 1 and Table E1 of this article's Online Repository.

The data collection process used by the E-PHOCAS cohort has previously been described [19-22]. Briefly, detailed anonymized information on demographic, clinical, occupational, and physiological characteristics of the subjects at the time of the diagnostic evaluation was entered in a standardized Excel spreadsheet in each participating center. The requested data were retrieved from medical charts in 2 centers while in the other centers, all or most of the data had been prospectively entered in existing local databases. At the time of data collection, the local investigators were not aware of the specific aims of the analyzes that would be conducted subsequently. Important outcomes, such as the results of BPTs, asthma severity, and level of nonspecific bronchial hyperresponsiveness (NSBH) were interpreted and recoded a posteriori using uniform and validated criteria. The local databases were checked for missing data and inconsistencies by 3 investigators (O.V., C.R., and J.D.), pooled together, and centralized at the Strasbourg University.

Ethics

Approval for this retrospective analysis of anonymized data was obtained from each local Institutional Review Board. The central database at the Strasbourg University was approved by the "*Comité Consultatif sur le Traitement de l'Information en Matière de Recherche dans*

1 *le Domaine de la Santé*” and the “*Commission Nationale de l’Informatique et des Libertés*”.

2 **Identification of asthma induced by QACs**

3 First, the subjects with occupational asthma (OA) caused by cleaning agents were retrieved
4 by screening the recorded occupation and causal agent fields of the E-PHOCAS database. A
5 cleaning agent was defined as any material used for cleaning or disinfecting houses,
6 buildings, healthcare equipment, or specialised service and industrial facilities, with the
7 exceptions of degreasing metal parts [23] and textile dry cleaning. In case of doubt, further
8 information on job tasks and products used at work were requested from the local
9 investigators. This resulted in the identification of 55 subjects with cleaners’s OA.

10 OA caused by QACs was defined by a positive BPT response induced by a QAC alone, that
11 is in the absence of any other potential respiratory sensitizer. In order to identify these
12 subjects with QAC-induced OA, the safety data sheets of the cleaning products that elicited
13 positive BPTs were reviewed. The respiratory sensitization potential of their ingredients was
14 assessed using a validated quantitative structure-activity relationship (QSAR) model [23, 24]
15 that generates quantitative estimates of the probability that LMW organic agents have
16 respiratory sensitization potential based on their chemical structure (i.e., the “asthma hazard
17 index”) (see Appendix E2 of this article’s Online Repository}. Based on this approach, the
18 subjects were assigned to one of three categories: 1) positive BPT induced by a single
19 respiratory sensitizing agent (n=30); 2) positive BPT elicited by challenge exposure to one or
20 more products containing multiple potential sensitiser (n=21); and 3) positive BPT without
21 identified sensitizer (n=4). The potential respiratory sensitizers involved in the 55 subjects
22 with cleaner’s asthma are detailed in Table I. The single-sensitizer positive BPTs were
23 induced by QACs in 22 subjects, including didecyldimethylammonium chloride (n=16) and
24 benzalkonium chloride (n=6). Of note, no respiratory sensitizer was identified in four subjects
25 with a positive BPT. The characteristics of these four subjects are summarized in Table E4 in

this article's Online Repository. The 22 subjects with QAC-induced OA were compared to 289 subjects with OA caused by various other LMW agents (Table II).

Demographic and clinical characteristics

The E-PHOCAS used a standardized spreadsheet to gather information on the following: 1) causal agents and job; 2) demographic and clinical characteristics; 3) timing of work-related respiratory symptoms in relation to exposure to the causal agent; 4) co-existing conditions (i.e. physician-based diagnosis of work-related rhinitis, contact urticaria and/or dermatitis, and sinusitis); and 5) materials and methods used for SIC performance.

Lung function assessments

The database collected the baseline forced vital capacity (FVC) and forced expiratory volume in 1 sec (FEV₁) values as well as the level of nonspecific bronchial hyperresponsiveness (NSBH) measured at baseline and 24 hours after challenge exposure. The level of NSBH was categorized as "absent", "mild", or "moderate/severe" according to the bronchoprovocation method used in each center [19, 20] (see Appendix E2 in this article's Online Repository). A significant increase in post-challenge NSBH was defined by a ≥ 2 -fold increase in the level of NSBH measured 24 hours after the challenge exposure as compared to the baseline value (i.e., a baseline/post-challenge ratio of NSBH indices ≥ 2) [25].

Bronchoprovocation tests with occupational agents

BPTs conformed with international recommendations in terms of safety precautions, "placebo" challenge, and duration of functional monitoring (see Appendix 2 in this article's Online Repository) [25]. A positive BPT result was defined by either a $\geq 15\%$ fall in FEV₁ at any time during the post-challenge monitoring period or a ≥ 2 -fold increase in the post-challenge level of NSBH as compared to baseline value [25].

The BPTs with QACs aimed to recreate as close as possible the conditions of exposure at the workplace by wiping/brushing (n=21) and/or spraying (n=14) the commercial product that

1 contained QAC as the single potential sensitizer (n=13) or a pure QAC solution (n=9). The
2 products were diluted in water as recommended by the manufacturer.

3 **Markers of airway inflammation**

4 Data pertaining to markers of airway inflammation included, whenever available: 1) baseline
5 blood eosinophils (assessed within one month of the SIC procedure); 2) sputum eosinophils
6 and neutrophils expressed as a percentage of total cell count at baseline and 24 hours post-
7 challenge; and 3) fractional exhaled nitric oxide concentration (FeNO) at baseline and 24
8 hours after the BPT. Detailed information on the methodology used for sputum induction and
9 processing in the participating centers is available in Appendix E2 of this article's Online
10 Repository. An "eosinophilic response" was defined as a postchallenge increase in sputum
11 eosinophil count $\geq 2\%$ (post-BPT minus baseline percentage value). The FeNO level was
12 measured in five of the six centers according to recommendations from both the European
13 Respiratory Society and the American Thoracic Society recommendations [26].

14 **Data analysis**

15 Quantitative data are presented as a median and interquartile range (IQR). Comparison
16 between groups of subjects was made using the Fisher's exact or chi-squared test for
17 categorical variables and non-parametric tests for numerical variables. A multivariable linear
18 regression analysis was conducted using a generalized linear model and a stepwise
19 procedure based on the Akaike information criterion to select the most parsimonious model
20 among subjects with available sputum assessment and a positive BPT to QACs or other
21 LMW agents (n=79) in order to explore the factors that determined the magnitude of the post-
22 BPT change in sputum eosinophils (i.e. the difference between post- and pre-BPT sputum
23 eosinophil count expressed in % of total nonsquamous cells). The potential confounding
24 factors (i.e. independent variables) incorporated into this regression included: a positive BPT
25 induced by QACs (yes/no); age; gender; smoking status (current and ex-smokers vs. never
26 smokers); treatment with inhaled corticosteroid at the time of the BPT (yes/no); baseline

1 sputum eosinophil count (% total nonsquamous cells); and the time elapsed since last work
2 exposure (≤ 1 mo vs. > 1 mo). Statistical analysis was performed using the R software
3 version 3.4.1 (<https://cran.r-project.org>). A P -value < 0.05 was considered significant.

4

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RESULTS

Clinical and occupational characteristics

Twenty-two subjects with a positive BPT to QACs as the single identified sensitizer, including benzalkonium chloride (n=6) and didecyl dimethyl ammonium chloride (n=16) were identified. These subjects were most commonly working in healthcare environments (n=14), including cleaners (n=6), nurses (n=5), one hospital technologist, one dental assistant and one administrative worker, or in food processing facilities (n=4). Another two subjects were domestic cleaners and two subjects were employed in educational services. Notably, two of these subjects were administrative employees with indirect exposure to cleaning products in a healthcare facility and a school.

The clinical and functional characteristics of the subjects with OA caused by QACs are summarized in Table III. In comparison with OA due to other LMW agents, QAC-induced OA was associated with a significantly higher proportion of women and never-smokers. Subjects with QAC-induced OA showed greater median FVC and FEV₁ values while the FEV₁/FVC ratio did not differ between the groups. There was no difference in the level of baseline NSBH or the pattern of asthmatic reactions during the BPT between subjects with OA due to QACs and those challenged with other LMW agents. Among subjects with QAC-induced OA, a ≥ 2 -fold increase in the post-challenge level of NSBH was recorded in eight of 11 (72.7%) subjects with an available post-challenge measurement of NSBH, a proportion that tended to be higher but not significantly from OA due to other LMW agents (88 of 177, 49.7%).

Markers of airway inflammation

Suitable pre- and post-challenge sputum samples were available in only 8 of 22 (36.4%) subjects with QAC-induced OA and in 71 of 289 (24.6%, $P=0.220$) subjects with a positive BPT to other LMW agents (see Table E3 in this article's Online Repository). The median (IQR) baseline sputum eosinophil count was slightly higher (6.0% [2.0-10.0]) in the 8 subjects

1 with QAC-induced OA than in those with OA due to other LMW agents (1.0% [0.6-5.0],
2 $P=0.052$) (Table IV). Positive BPTs with QACs were associated with a significantly greater
3 median (IQR) post-challenge increase in sputum eosinophils (18.1% [12.1 to 21.1])
4 compared to the other LMW agents (2.0% [0-5.2], $P<0.001$). An “eosinophilic response” (i.e.
5 $\geq 2\%$ postchallenge increase in sputum eosinophils) was significantly more frequent (8 of 8
6 subjects) in QAC-induced OA than in subjects with a positive BPT elicited by other LMW
7 agents (37 of 71, 52.1%, $P=0.009$). The multivariate regression analysis retained only a
8 positive BPT induced by QACs as a factor associated with a greater increase in post-SIC
9 sputum eosinophils (Table V). There were no differences between OA caused by QACs and
10 the other LMW agents with regard to baseline blood eosinophil counts as well as the
11 baseline and post-challenge FeNO values.

12

DISCUSSION

As far as we know, this study is the first attempt at characterizing the clinical, functional, and inflammatory pattern of QAC-induced OA. The findings indicated that challenge exposure to QAC is associated with an increase in NSBH and a highly eosinophilic airway response, features that are consistent with an immunologically-mediated sensitizing mechanism.

Although a number of reports have documented asthmatic reactions after challenge exposure to QACs [3-7], the inflammatory pattern induced by these chemicals has never been specifically investigated. Previous studies reported an increase in sputum eosinophils after challenge exposure to the causal agent in subjects with OA independently from the type of agents (i.e., LMW vs. high-molecular-weight agents) and the pattern of asthmatic reaction (i.e., late vs. early reactions) [19, 27]. Nevertheless, a previous analysis of the E-PHOCAS cohort demonstrated that BPTs with acrylate compounds were more frequently (88%) associated with a significant increase in sputum eosinophils compared to other LMW agents (48%) [21]. On the other hand, acrylate-induced OA was more frequently associated with work-related rhinitis and acrylate compounds elicited a significantly higher increase in post-challenge FeNO compared to other LMW agents, whereas QACs failed to induce such changes in FeNO. Taken together, these observations highlight the heterogeneous nature of OA caused by LMW agents and the need to further explore differences in underlying pathobiological pathways. Interestingly, it has been recently demonstrated in a murine model that dermal exposure to the QAC dodecyl dimethyl ammonium bromide can induce the activation of type 2 innate lymphoid cells (ILC2s) in the skin [28]. Murine models of allergic asthma have shown that ILC2s are a potent source of the T_H2 cytokines IL-5 and IL-13 and are able to induce eosinophil recruitment, mucus hypersecretion, and NSBH [29], although the role of ILC2s in the development of airway sensitization to LMW chemicals warrants further investigation. Alternative mechanisms including neurogenic inflammation and mast cells degranulation resulting from direct stimulation of chemoreceptors at nerve endings,

1 especially the transient receptor potential channels, remain purely speculative in the case of
2 QACs [30].

3 The immunological mechanisms involved in the inception of OA caused by QACs remain
4 largely unknown. There are several reports of urticaria caused by QACs that may support the
5 possibility of an immediate-type, IgE-mediated, allergic mechanism [31]. However, in
6 previous reports of subjects with QAC-induced OA, skin-prick tests with QACs elicited an
7 immediate skin response in only one subject with associated urticaria, while these tests were
8 not completed in other cases [3, 5, 7]. Specific IgE antibodies against “quaternary
9 ammonium” were either not detected [4, 5] or their presence did not correlate with asthma
10 symptoms [16]. Skin-prick tests or determination of specific IgE have not been attempted in
11 the subjects included in our cohort. It is currently acknowledged that LMW agents causing
12 asthma are incomplete antigens (i.e. haptens) that combine with amino acid residues on
13 airway proteins to become immunogenic [32, 33]. However, the potential diversity of
14 chemical interactions with airway proteins could explain heterogeneous pathobiological
15 responses and our inability to identify specific IgE in OA caused by most LMW agents.

16 Most subjects with QAC-induced OA (63.6%) in our series were exposed to QACs in
17 healthcare environments. Exposure to cleaning and disinfecting products in healthcare
18 settings has been associated with an increased risk of new-onset asthma in nurses and
19 related occupations [10, 11], with current asthma in hospital cleaners [12], and with work-
20 related asthma symptoms in healthcare professionals [13]. These studies revealed broad
21 categories of tasks or products associated with asthma, such as “general purpose cleaning”
22 and “instrument cleaning/sterilisation” [11, 13, 34], but they failed to identify specific agents
23 involved in asthma onset. Using a specific job-task-exposure matrix, the Nurses’ Health
24 Study II [15] found that poor asthma control was associated with exposure to aldehydes,
25 hypochlorite bleach, hydrogen peroxide, and enzymatic cleaners, but not with QACs. Our
26 data provide clinical evidence supporting the findings of Gonzalez et al. [16] who established

a significant relationship between exposure to QACs and an increased likelihood of physician-diagnosed asthma at work among hospital healthcare workers.

Strengths and limitations

The strength of this study was its multicenter design that allowed for gathering a large series of patients with QAC-induced OA confirmed by BPT after exclusion of subjects concomitantly challenged with other potential respiratory sensitizers contained in cleaning products. Nevertheless, several limitations deserve further careful consideration. The major limitation of this study results from the limited number of subjects with available sputum samples. Nevertheless, the multivariate regression analysis confirmed that challenge exposure to QACs was the most significant determinant of the magnitude of the eosinophilic response to BPT in this cohort of subjects with OA induced by LMW agents, independently from potential confounders. In addition, the comparison of subjects with and without sputum samples suggests that there was no bias towards the performance of induced sputum in subjects with a higher likelihood of eosinophil recruitment in the airways. Indeed, Prince et al. [27] found that a lower baseline sputum eosinophil count, non-smoking, and a shorter exposure to the causal occupational agent were the only independent predictors for a greater eosinophilic response after BPTs with occupational agents.

This study may also be criticized on the ground of its retrospective design and the use of different – though validated – methods for assessing NSBH and sputum cells. However, these between-center differences in procedures are unlikely to have affected the findings since the collection and interpretation of data were standardized for the whole cohort. Although BPT, the “reference” method for establishing a diagnosis of OA [35, 36], is not thoroughly standardized, the centers participating in this cohort conformed with the main methodological requirements for safety and reliability issued by the European Respiratory Society, and airway responses to challenges exposures were interpreted using uniform criteria [25].

Another limitation arises from the lack of quantitative assessment of exposure to QACs at the workplace and during BPTs. Dose-dependent bronchoconstriction induced by nebulized benzalkonium chloride (formerly used as a preservative in nebulizer solutions) has been described in asthmatics, although changes in NSBH and airway eosinophils have never been documented in such human inhalation studies with benzalkonium chloride [17, 18, 37]. On the other hand, there is currently little information about exposure-response relationships since QACs have a low vapor pressure, and accurate sampling and analytical methods have only recently been developed in order to detect very low levels of QACs in the air [38].

The potential role of irritants was not systematically investigated in this study because evidence-based and validated lists of substances that should be considered as respiratory irritants are currently lacking [39]. Epidemiological studies [9, 10, 12, 13], surveillance programs [23, 40], and case series [41] have most commonly related asthma in cleaners to respiratory irritants, such as bleach, ammonia; acids and oxidizers, although OA and work-exacerbated asthma could not be differentiated in these studies and the specific causal agents were not identified because BPT were generally not performed. The cleaning and/or disinfectant products that induced a positive BPT in the 22 subjects with QAC-induced OA in this cohort did not contain known respiratory irritants. However, four subjects in this cohort developed an asthmatic response during BPT with cleaning/disinfecting chemicals (i.e., peracetic acid in three subjects and sodium octyl sulfate in one subject) that failed to meet the structural requirements for being considered as respiratory sensitizers [23] (Table E4 in this article's Online Repository). These findings further support previous reports of asthmatic reactions induced by peracetic/acetic acid mixtures [42, 43] and the possible role of irritant ingredients in the development of cleaners' asthma. Interestingly, the positive BPT responses in our subjects were not associated with an increase in the level of NSBH or in sputum eosinophils, which is consistent with the findings of Sastre et al. [44] who performed inhalation challenges with bleach in 13 cleaners.

Conclusion

Despite its inherent limitations, this retrospective study provides further insight into the inflammatory mechanisms involved in the development of QAC-induced OA by demonstrating that the condition is associated with a highly eosinophilic airway response. The findings also highlight the respiratory sensitizing potential of these widely used biocide compounds. Awareness of this possibility may be relevant to the investigation of work-related asthma symptoms in workers involved in cleaning and disinfection tasks. Further prospective investigation of inflammatory markers and immunological mechanisms involved in QAC-induced OA is required to confirm and expand the findings of our retrospective study.

Acknowledgement

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Table I. Potential respiratory sensitizers involved in positive bronchoprovocation tests with cleaning and disinfecting products

Single sensitizer (n=30):	
Quaternary ammonium compounds	
Didecyl dimethyl ammonium chloride (CAS# 7173-51-5)	16
Benzalkonium chloride (CAS# 8001-54-5)	6
Amines	
Ethanolamine (CAS# 141-43-5)	2
Ethylenediamine (CAS# 107-15-3)	2
Glutaraldehyde (CAS# 111-30-8)	3
Chloramine T (CAS# 127-65-1)	1
Multiple potential sensitizers (n=21):	
Quaternary ammonium compounds*	
Didecyl dimethyl ammonium chloride (CAS# 7173-51-5)	12
Benzalkonium chloride (CAS# 8001-54-5)	10
Amines	
Ethylenediaminetetraacetic acid (CAS# 60-00-4)	4
Lauryldimethylamine oxide (CAS# 1643-20-5)	3
N-(3-aminopropyl)-N-dodécylpropane-1,3-diamine (CAS# 2372-82-9)	1
Tetraacetylenediamine (CAS# 10543-57-4)	1
C12-14-alkyltrimethylenediamine (CAS# 90640-43-0)	2
N,N-dimethyltetradecylamine N-oxide (CAS# 3332-27-2)	1
Glutaraldehyde (CAS# 111-30-8)	9
Chloramine T (CAS# 127-65-1)	7
Chlorhexidine (CAS# 55-56-1)	6
Polyhexanide (CAS# 28757-47-3)	5
Octenidine dihydrochloride (CAS# 70775-75-6)	2
1,2-Benzisothiazol-3(2H)-one (CAS# 2634-33-5)	2
Sodium dichloroisocyanurate dehydrate (CAS# 51580-86-0)	2
Sodium dodecylbenzene sulphonate (CAS# 25155-30-0)	3
Enzymes (not detailed)	3
No identified sensitizer (n=4)	

Legend: Potential sensitizers identified using a quantitative structure-activity relationship (QSAR) model [23]. CAS, Chemical Abstracts Service.

* Among 21 positive bronchoprovocation tests performed with multiple potential sensitizers, 20 were challenged with products containing quaternary ammonium compounds while one subject showed a positive reaction to a cleaning product containing chloramine T and N,N-dimethyltetradecylamine.

1 **Table II. Low-molecular-weight agents involved in occupational asthma in the study**
2 **cohort**

LMW agents	n
Isocyanates	97
Persulfate salts	53
Metals	26
Wood dusts	25
Welding	22
Metal working fluids	10
Amines	10
Acid anhydrides	9
Epoxy resins	7
Drugs	6
Resins/glues/paints (NOS)	5
Colophony	5
Reactive dyes	2
Styrene	1
Various LMW agents	11
<i>Total:</i>	289

3 Legend: LMW, low-molecular-weight; NOS, not otherwise specified.

4

Table III. Clinical and functional characteristics of subjects with occupational asthma caused by quaternary ammonium compounds compared to other low-molecular-weight agents

Characteristic	OA due to QACs (n=22)	OA due to other LMW agents (n=289)	P-value
Age (yr)*	45 (40-52)	44 (34-52)	0.295
Sex (female)	19 (86.4)	115 (39.8)	<0.001
Body mass index (kg/m ²)	28.6 (22.8-33.03)	26.7 (24-29.8)	0.536
Smoking habits:			0.016
Current/ex-smokers	6 (27.2)	157 (54.3)	
Never-smoker	16 (72.7)	132 (45.7)	
Atopy [†]	11 (50.0)	117 (42.1)	0.507
Asthma pre-existing to the causal exposure	3 (13.6)	28 (9.7)	0.470
Duration of exposure before asthma onset (mo)*	75 (12-150)	82 (30-193)	0.245
Duration of symptomatic exposure (mo)*	28 (8-54)	29 (12-38)	0.621
Interval since last work exposure (mo)*	0.6 (0.1-6)	1.7 (0.1-10.0)	0.775
Coexisting conditions:			
Work-related rhinitis	10 (45.5)	167 (58.0)	0.271
Chronic rhinosinusitis	4 (18.2)	37 (12.8)	0.510
Work-related urticaria	2 (9.1)	24 (8.4)	0.706
Work-related contact dermatitis	5 (22.7)	37 (12.9)	0.198
Asthma treatment/severity at work [‡]			
No treatment	3 (13.6)	48 (16.6)	0.283
Mild (GINA treatment step 1-2)	7 (31.8)	44 (15.2)	
Moderate (GINA treatment step 3)	6 (27.3)	87 (30.1)	
Severe (GINA treatment step 4-5)	6 (27.3)	110 (38.1)	
Inhaled short-acting β_2 -agonist ≥ 1 /day	6 (27.2)	97 (33.6)	0.643
≥ 1 severe asthma exacerbation (last 12 mo)	7 (31.8)	79 (27.3)	0.628
Baseline spirometry			
FVC, % pred*	108 (100-114)	96 (86-107)	0.002
FEV ₁ , % pred*	96 (89-110)	89 (80-98)	0.029
FEV ₁ <80%	4 (18.2)	72 (24.9)	0.611
FEV ₁ /FVC*	78 (73-82)	76 (70-81)	0.390
FEV ₁ /FVC <70%	4 (18.2)	70 (24.2)	0.614
Maximum fall in FEV ₁ (% from baseline value)	22 (18-27) [§]	23 (18-29) [§]	0.441
Baseline level of NSBH	(n=22)	(n=272)	0.916
Absent	5 (22.7)	76 (27.9)	
Mild	12 (54.5)	138 (50.7)	
Moderate-to-severe	5 (22.7)	58 (21.3)	
Post-challenge change in NSBH	(n=11)	(n=177)	
Pre/post-challenge NSBH ratio*	3.0 (1.5-4.1)	2.0 (1.0-4.0)	0.289
Pre/post-challenge NSBH ratio ≥ 2	8 (72.7)	88 (49.7)	0.214
Pattern of bronchial response to BPT	(n=20) [§]	(n=255) [§]	0.729
Isolated early reaction	7 (31.8)	61 (21.7)	
Isolated late reaction	7 (31.8)	99 (35.2)	
Dual reaction	6 (27.3)	95 (33.8)	

Legend: BPT, bronchoprovocation tests; FEV₁, forced expiratory volume in one-second; FVC, forced vital capacity; LMW, low molecular weight; NSBH, nonspecific bronchial hyperresponsiveness; OA, occupational asthma; QAC, quaternary ammonium compound. GINA, Global Initiative for Asthma. Data are presented as n (% of available data) unless otherwise specified. Values in boldface are statistically significant.

* Median value with interquartile range (IQR) within parentheses.

[†] Atopy defined by the presence of at least one positive skin prick test result to common allergens.

[‡] The severity of asthma was graded according to the treatment steps proposed by the Global Initiative for Asthma [45] as "untreated" (step 0); "mild" (step 1-2); "moderate" (step 3); and "severe" (step 4-5).

1 [§] The BPT was considered positive based on a significant increase in the post-challenge level of NSBH compared to
2 baseline value (i.e. pre/post-challenge NSBH ratio ≥ 2) in the absence of a $\geq 15\%$ fall in FEV₁ in 2 of the 22 subjects
3 challenged with QACs and in 34 of the 289 subjects challenged with other LMW agents.
4

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1 **Table IV. Airway inflammation markers in subjects with OA caused by quaternary**
 2 **ammonium compounds compared to other low-molecular-weight agents**

Characteristic	OA due to QACs (n=22)	OA due to other LMW agents (n=289)	P-value
Blood eosinophils Cells/ μ l*	(n=13) 244 (190 to 460)	(n=150) 229 (159 to 400)	0.451
>300/ μ l	6 (46.2)	56 (37.3)	0.561
Baseline FeNO ppb*	(n=15) 23 (13 to 38)	(n=98) 19 (10 to 31)	0.528
Postchallenge FeNO ppb*	25 (15 to 50)	26 (15 to 52)	0.912
Change (ppb)*	4 (-1 to 7)	6 (1 to 18)	0.324
Baseline sputum eosinophils %*	(n=8) 6.0 (2.0 to 10.0)	(n=71) 1.0 (0.6 to 5.0)	0.052
$\geq 3\%$	5 (62.5)	26 (36.6)	0.252
Postchallenge sputum eosinophils %*	24.2 (17.6 to 29.2)	4.0 (2.0 to 9.0)	<0.001
Change compared to baseline value (%)*	18.1 (12.1 to 21.1)	2.0 (0 to 5.2)	<0.001
Increase $\geq 2\%$	8 (100)	37 (52.9)	0.009
Baseline sputum neutrophils %*	(n=8) 46.5 (36.4 to 60.1)	(n=71) 55 (40 to 68)	0.597
Post-challenge sputum neutrophils %*	51.8 (46.7 to 60.8)	56 (35 to 68)	0.715
Change compared to baseline value (%)*	3.0 (-7.4 to 6.4)	1.0 (-12.1 to 14.4)	0.726

3 Legend: BPT, bronchoprovocation test; FeNO, fractional exhaled nitric oxide; LMW, low-molecular-weight; OA,
 4 occupational asthma; QAC, quaternary ammonium compound. Data are presented as n (% of available data) unless
 5 otherwise specified. Values in boldface are statistically significant ($P < 0.05$).

6 * Median value with interquartile range (IQR) within parentheses.
 7

1 **Table V. Multivariate regression analysis for the changes in post-challenge sputum**
 2 **eosinophil count**

Independent variables	Adjusted β coefficient (95% confidence interval)	P-value
Challenge with QAC as single-sensitizer (yes/no)	10.778 (3.625 to 17.932)	0.004
Age (yr)	0.069 (-0.114 to 0.252)	0.457
Gender (female)	2.663 (-2.015 to 7.340)	0.260
Current and ex-smokers vs. never smokers	-3.185 (-7.367 to 0.996)	0.133
Treatment with inhaled corticosteroid at the time of BPT (yes/no)	2.146 (-2.226 to 6.517)	0.331
Baseline sputum eosinophil count (%)	-0.054 (-0.379 to 0.271)	0.742
Time elapsed since last work exposure (≤ 1 mo vs. > 1 mo)	0.506 (-3.519 to 4.530)	0.803

3 Legend: BPT, bronchoprovocation test; QAC, quaternary ammonium compound
 4 This multivariate linear regression model incorporated 79 subjects with available sputum analysis and
 5 a positive BPT to QAC or other low-molecular-weight agents. Bold indicates statistical significance (P
 6 < 0.05).
 7

LEGEND TO FIGURES

Figure 1

Flowchart of the study. *BPT*, bronchoprovocation tests; *FEV₁*, forced expiratory volume in one-second; *LMW*, low molecular weight; *NSBH*, nonspecific bronchial hyperresponsiveness; *OA*, occupational asthma; *QAC*, quaternary ammonium compound; *QSAR*, quantitative structure-activity relationship

* Twenty-six subjects with acrylate-induced *OA* were excluded from the initial cohort since this subset has been recently documented as demonstrating a distinct phenotype compared to other *LMW* agents [21]. Nine subjects with *OA* due to aldehydes used for non-cleaning purposes were also excluded.

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3

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Initial cohort recruitment

OA ascertained by a positive BPT (January 2006-December 2018) in 6 tertiary centers
➔ **1,016 subjects**

Verification of criteria for a positive BPT

Fall in $FEV_1 \geq 15\%$ or >2 -fold increase in post-challenge NSBH without changes in FEV_1
➔ **Exclusion: 53 subjects**

Verification of key asthma outcomes

Missing data about asthma medications, severe exacerbations, or spirometry
➔ **Exclusion: 92 subjects**

Study cohort: 871 subjects

Workplace exposure to cleaning agents and/or disinfectants?

'Cleaners'
(n=55)

Identification of potential respiratory sensitizers through QSAR models

OA due to QAC as a single sensitizer
(n=22)

'Non-cleaners'
(n=816)

*

OA due to other LMW agents
(n=289)*