ASTHMA RELATED TO CLEANING AGENTS: A CLINICAL INSIGHT

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ASTHMA RELATED TO CLEANING AGENTS: A CLINICAL INSIGHT

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Running head: Cleaners' asthma

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List of abbreviations

AHR: Non-specific airway hyperresponsiveness

FEV_1: Forced expiratory volume in one second

OA: Occupational asthma

PC_{20}: Provocative concentration of histamine causing a 20% fall in FEV_1

PEF: Peak expiratory flow

QAC: Quaternary ammonium compound

SIC: Specific inhalation challenge

WCB: Workers' Compensation Board

ARTICLE SUMMARY

Article focus

- There is accumulating evidence of an increased risk of asthma among cleaning workers, although the agents and mechanisms involved in the development of cleaning-related asthma remain largely uncertain.
- We undertook a retrospective case series analysis of all subjects who completed a specific inhalation challenge with cleaning/disinfecting materials over the period 1992-2011 in order to assess the pattern of bronchial responses induced by these agents and to evaluate the mechanisms involved in cleaning-related asthma.

Key messages

- The asthmatic reactions induced by challenge exposures to cleaning agents were associated with a significant increase in post-challenge nonspecific airway hyperresponsiveness to histamine and/or an increase in sputum eosinophils
- This study based on specific inhalation challenges indicates that a substantial proportion of subjects who experience asthma symptoms related to cleaning materials may actually suffer from sensitizer-induced OA, predominantly caused by quaternary ammonium compounds.

Strengths and limitations

- This is the first report describing the pattern of functional and sputum cell changes induced by cleaning/disinfecting materials. The findings provide further insight into the mechanisms of cleaning-related asthma and may have practical implications for the diagnosis and management of this condition.
- The major limitations of this study result from the lack of quantitative exposure assessment during the challenge tests and the selection of the studied population. The subjects described in this report may not accurately represent the whole population of workers with asthma related to cleaning activities; they may represent only a subset of

cleaning workers whom symptoms are severe enough for seeking specialized medical advice and they did not include subjects with acute irritant-induced asthma.

ABSTRACT

Objective: To determine the agents causing asthmatic reactions during specific inhalation challenges (SICs) in workers with cleaning-related asthma symptoms and to assess the pattern of bronchial responses in order to identify the mechanisms involved in cleaning-related asthma.

Design: A retrospective case series analysis.

Setting: The study included all subjects who completed a SIC procedure with the cleaning/disinfecting products suspected of causing work-related asthma over the period 1992-2011 in a tertiary centre, which is the single specialized centre of the French-speaking part of Belgium where all subjects with work-related asthma are referred for SIC.

Results: The review identified 44 subjects who completed an SIC with cleaning/disinfecting agents. Challenge exposure to the suspected cleaning agents elicited a ≥20% fall in FEV_1 in 17 (39%) subjects. The cleaning products that induced a positive SIC contained quaternary ammonium compounds (n=10), glutaraldehyde (n=3), both of these agents (n=1), and ethanolamines (n=2). Positive SICs were associated with a significant decrease in the median (interquartile range) value of the provocative concentration of histamine causing a 20% fall in FEV_1 (PC_{20}) from 1.4 (0.2-4.2) mg/ml at baseline to 0.5 (0.4-3.0) mg/ml after the challenge and a significant increase in sputum eosinophils from 1.8 (0.8-7.2)% at baseline to 10.0 (4.1-15.9)% 7 hours after the challenge exposure while these parameters did not significantly change in subjects with a negative SIC. Overall, 11 of 17 subjects with positive SICs showed a >3-fold decrease in post-challenge histamine PC_{20} value, a >2% increase in sputum eosinophils, or both of these outcomes.

Conclusions: These data indicate that a substantial proportion of workers who experience asthma symptoms related to cleaning materials show a pattern of bronchial reaction consistent with sensitizer-induced occupational asthma. The results also suggest that quaternary ammonium compounds are the principal cause of sensitizer-induced OA among cleaners.

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INTRODUCTION

In recent years, there has been a growing concern about the potential role of exposure to cleaning products in the initiation and aggravation of asthma.[1, 2] Epidemiological surveys have consistently documented increased prevalence[3-5] and incidence[6-8] rates of asthma in workers exposed to cleaning materials and/or disinfectants, especially in domestic cleaners[3, 4] and healthcare workers[9-12]. In addition, some studies have reported an increased risk of work-related asthma symptoms in exposed workers.[5, 12, 13]

However, there is still limited knowledge on the specific exposures and pathophysiological mechanisms involved in cleaning-related asthma.[1, 2] Cleaning materials typically contain a wide variety of ingredients, some of which are respiratory irritants, such as chlorine-releasing agents and ammonia, while others are potential airway sensitizers.[14, 15] Asthma in cleaners has been mostly associated with the irritant effects of cleaning products, which may exacerbate asthma and, at high exposure levels, cause acute irritant-induced asthma (or "reactive airways dysfunction syndrome").[10, 16-19] Nevertheless, occasional case reports have described occupational asthma (OA) due to specific airway hypersensitivty to components of detergents or disinfectants,[2] Overall the determinants of cleaning-related-asthma symptoms remain largely uncertain since most available studies have relied on self-reported symptoms or physician-based diagnosis. Only two studies have investigated the effects of cleaning exposures on peak expiratory flow (PEF) variability with inconsistent results.[20, 21]

Therefore, the data of subjects who completed specific inhalation challenges (SICs) with the cleaning agents and/or disinfectants suspected of causing their work-related asthma symptoms were reviewed in order: 1) to determine the prevalence and causes of asthmatic reactions induced by these agents; and 2) to compare the clinical features as well as the changes in nonspecific airway hyperresponsiveness (AHR) and sputum cell counts in subjects with positive or negative responses to SIC.

METHODS

This study was a retrospective analysis of the charts of all subjects investigated through a SIC in our tertiary centre during the period of 1992-2011 for asthma symptoms related to cleaning products and/or disinfectants. The study was approved by the *Comité d'éthique médicale* of the *Centre Hopitalier Universitaire de Mont-Godinne*; approval number 84/2012.

Subjects

In our centre, SICs with the occupational agent(s) suspected of causing work-related symptoms are routinely performed to diagnose OA provided that the baseline FEV_1 is equal to or above 60% of the predicted value.[22] The subjects are referred either by their attending physicians or by the Belgian Workers' Compensation Board (WCB). All French-speaking workers submitting a claim for work-related asthma to the WCB are referred to our centre in order to perform a SIC procedure.

The subjects who completed a SIC procedure with cleaning agents and/or disinfectants were identified from a database of 713 subjects who underwent a SIC for possible work-related asthma from 1992 up to 2011. Professional cleaners who had been challenged with latex gloves (n=23) or non-cleaning chemicals present at the workplace (n=3) were excluded from this analysis.

Specific inhalation challenges

SICs were completed according to a standardized protocol, which remained unchanged throughout the studied period.[23]. On the first test day, a "control" challenge was performed by exposing the subjects to a paint diluent nebulised in a five-cubic-meter challenge room for 30 min in order to ensure that fluctuations in FEV_1 were ≤12%. On the following day(s), the subjects were challenged with the cleaning product(s) suspected of causing their asthma symptoms at work. Exposure to these products was generated through a "realistic" approach aimed at reproducing as close as possible the conditions of exposure at the workplace.[24]

The tested cleaning materials and the mode of exposure during SIC were selected based on the subjects' interview, the Material Safety Data Sheets, and, most often, an analysis of the job exposure by WCB's hygienists. The cleaning agents were diluted in cold or heated water, brushed on a cardboard and/or sprayed according to the collected information.

The duration of exposure to the cleaning products was gradually increased (i.e. 1 min, 4 min, 10 min, 15 min, 30 min, and 60 min) until a ≥20% fall in FEV_1 occurred or a cumulative exposure of two hours was completed. Spirometry was obtained at baseline and serially after exposure for a total of at least six hours. A SIC was considered positive when a sustained ≥20% fall in FEV_1 was recorded. The level of AHR to histamine was determined at the end of the control day (i.e. baseline value), seven hours after the end of each active challenge when the FEV_1 was within 10% of baseline value, and 24 hours after the last active challenge.[25] AHR was expressed as the provocative concentration of histamine causing a 20% fall in FEV_1 (PC_{20}).[22] Since March 2006, sputum cell counts were assessed at the end of the control day and seven hours after the end of active challenges (i.e. after the assessment of AHR and administration of an inhaled bronchodilator). Sputum was induced through the inhalation of increasing concentrations (3%, 4%, and 5%) of hypertonic saline and processed as previously described.[26]

Those subjects who did not demonstrate a ≥20% fall in FEV_1 during the first active test day underwent a repeated challenge for a maximum of 2-3 hours on the next day. Further challenges were proposed when there was a >3-fold decrease in the post-challenge PC_{20} value or a >3% increase in sputum eosinophils as compared to the control day.[25, 26]

Data analysis

The following information was collected from the medical charts: 1) demographic, clinical, and occupational characteristics of the subjects; and 2) baseline functional data, histamine PC_{20} value on the control day and after the last active challenge, as well as the corresponding sputum cell counts when available. Changes in AHR were considered

significant when there was a >3-fold decrease in post-challenge histamine PC_{20} compared to baseline value.[25] An increase in sputum eosinophils of more than two percentage points compared with the control day value was regarded as clinically relevant.[25, 27]

Quantitative data are presented as median and 25^{th} and 75^{th} interquartile range. Comparisons between subgroups of subjects were made using the chi-squared test, Fisher exact test, or Wilcoxon rank-sum test as appropriate. The Wilcoxon signed-rank test was used for comparing variables before and after SIC in the same subjects. All statistical tests were two-tailed; a p-value <0.05 was considered significant. Statistical analysis was performed using the IBM SPSS Statistics 19.0 software (SPSS Inc, Chicago, Ill).

RESULTS

Baseline characteristics

During the reviewed period, 44 of 713 (6%) subjects were challenged with cleaning agents and/or disinfectants. The main demographic, occupational, and clinical characteristics of the subjects are presented in Table 1. A ≥20% decrease in FEV_1 was recorded during SIC in 17 (39%) of the subjects, 24% showing an isolated immediate reaction, 18% an isolated late reaction, 29% dual reactions, and 30% atypical reactions. The median (interquartile range) duration of exposure to cleaning agents that elicited an asthmatic reaction was 120 (32-150) minutes. The cleaning products that induced a positive FEV_1 response contained quaternary ammonium compounds (QAC) (mainly, benzalkonium and didecyldimethylammonium chlorides) in 10 (59%) subjects, glutaraldehyde in three instances, both agents in one instance, and ethanolamines in two subjects (Table 1). No known sensitizing agent was identified in one subject.

The subjects who developed an asthmatic response to cleaning agents and/or disinfectants did not differ from those who did not for most of the demographic and clinical characteristics. The pattern of the work-related respiratory symptoms was similar in both groups (Table 1), although wheezing at work was slightly more frequently reported by subjects with a positive SIC (82% vs. 52%, p=0.056). The subjects with a positive SIC tended to experience a lower level of asthma control. The proportion of these subjects who required the use of an inhaled short-acting $beta_2$-agonist at least once a day was significantly higher (41%) as compared to those with a negative SIC (4%; p=0.002), although the daily dose of inhaled corticosteroids were similar in both groups. In addition, baseline spirometry revealed more often significant airway obstruction in subjects who showed a positive SIC (29%) than in those who did not (4%, p=0.016).

Non-specific airway hyperresponsiveness

At baseline, the subjects with a positive SIC to cleaning products showed a significantly lower median histamine PC_{20} value than those with a negative SIC (p=0.004) (Table 2). A post-challenge histamine PC_{20} value was available in 12 of the 17 subjects who showed a positive SIC and in 25 of 27 subjects with a negative SIC. The post-challenge PC_{20} value was not measured because the FEV_1 24 hours after the end of exposure was still ≥20% lower than the pre-challenge value in four subjects with a positive SIC or because the subjects refused to complete the test in the other instances. Positive SICs were associated with a significant decrease in the median post-challenge PC_{20} value, whereas no change was documented in subjects with a negative SIC. Five of the 12 (42%) subjects with a positive SIC demonstrated a >3-fold decrease in post-challenge PC_{20} value, while none of those with a negative SIC did so.

Sputum cell counts

Among the subjects who were investigated from 2006 onwards, a suitable sputum sample was obtained seven hours after the end of the last active challenge in 13 of 15 positive SICs and in seven of 11 negative SICs (Table 2). At baseline, the subjects with a positive SIC showed a slightly higher sputum eosinophil percentage than those with a negative SIC (p=0.046). Positive SICs were associated with a significant post-challenge increase in sputum eosinophils, while eosinophil counts did not significantly change in negative SICs. Eight (62%) of the 13 subjects with a positive SIC showed a >2% increase in post-challenge eosinophils, while none of the subjects with a negative SIC did so. In subjects with a positive SIC, there was an increase in the absolute number of sputum neutrophils after the last active challenge while the percentage of neutrophils was not significantly different at baseline and on the last challenge day.

Overall, positive SICs were associated with either a >3-fold decrease in post-challenge PC_{20} value in three subjects, a >2% increase in sputum eosinophils in six subjects, or both of these outcomes in two subjects.

DISCUSSION

This study showed that challenge exposure to the cleaning agents and/or disinfectants used at work induced an asthmatic reaction in 39% of the subjects who experienced asthma symptoms upon exposure to these products. In addition, the results of the SICs provided evidence supporting a specific hypersensitivity mechanism rather than a nonspecific bronchoconstriction due to an irritant effect. Indeed, eleven (65%) of the 17 positive SICs induced by cleaning agents were associated with a significant increase in post-challenge AHR, an increase in sputum eosinophils, or both of these outcomes. Noticeably, among the subjects who developed a positive bronchial response to QACs, a post-challenge increase in sputum eosinophils and/or in the level of AHR was documented in nine of ten instances.

To the best of our knowledge, this is the first study reporting the changes in lung function parameters and markers of airway inflammation in subjects challenged with the cleaning materials suspected of causing work-related asthma symptoms. Available evidence indicates that cleaning materials can both exacerbate asthma (i.e. work-exacerbated asthma) and induce the development of asthma (i.e. occupational asthma) through either immunological or irritant mechanisms.[12, 16, 19, 28] Median-Ramon et al. investigated the daily changes in peak expiratory flow (PEF) in 43 female domestic cleaners with a recent history of asthma and/or chronic bronchitis.[20] There was no significant association between the changes in PEF and cleaning exposures, with the exception of a decrease in PEF at night that was related to the use of ammonia. Nevertheless, analysis of PEF data using the Occupational Asthma System (OASYS) program identified a work-related pattern in 30% of the subjects, but the specific exposures associated with these changes were not described. By contrast, Bernstein et al. reported an increase in lower respiratory tract symptoms during cleaning activities in asthmatic homemakers compared with non-asthmatics in the absence of significant changes in PEF.[21] Our findings in subjects with a positive SIC are consistent with previous studies which reported that an increase in AHR and sputum eosinophils occurs specifically – though inconstantly – in sensitized individuals who develop asthmatic reactions

induced by common inhalant allergens as well as high-molecular-weight and low-molecular-weight occupational agents.[29] Only one subject developed a ≥20% fall in FEV_1 on exposure to a degreasing spray that apparently did not contain a known sensitizing agent. This subject who reported pre-existing asthma, also failed to demonstrate a post-challenge increase in AHR or sputum eosinophils, suggesting that the bronchial response resulted from an irritant effect consistent with the concept of "work-exacerbated asthma".[30]

Noticeably, 13 subjects with a negative SIC showed AHR to histamine neither at baseline nor after challenge exposure to the cleaning agents (Table 2), although nine of them were treated with an inhaled corticosteroid. These findings are consistent with those reported by Chiry et al. who found that a high proportion (57%) of subjects referred to tertiary centres for work-related asthma symptoms failed to demonstrate any functional evidence of asthma, although they experienced respiratory symptoms that were similar to those diagnosed as having OA or work-exacerbated asthma, except for a lower prevalence of wheezing.[31] A recent population-based questionnaire survey of health care workers exposed to cleaning materials also found that a high proportion (64%) of the subjects who experienced work-related asthma symptoms had not been given a diagnosis of asthma.[12]

There is little information on the specific agents involved in the various phenotypes of asthma related to cleaning exposure. Most epidemiological studies have linked asthma with exposure to irritant cleaning materials, mainly bleach,[9, 11, 12, 17, 28] ammonia,[9, 11, 12, 20, 28] and cleaning/degreasing sprays.[9, 11, 12, 20] On the other hand, occasional case reports have described OA presumably due to specific sensitization to disinfectants, such as chloramine-T, glutaraldehyde, QACs, and isothiazolinone, surfactants, ethanolamines used in wax-removing compounds, and detergent enzymes.[1, 2] Among the cases of asthma related to cleaning products identified by the US Sentinel Event Notification Systems for Occupational Risks (SENSOR), 62% were considered as "OA with a latency period", but only 14% of these cases were related to an identified respiratory sensitizer.[16] A recent Finnish report described 20 cases of OA diagnosed in professional cleaning workers using SIC

during the period 1994-2004.[32] The majority (70%) of these cases were caused by moulds and non-cleaning chemicals (e.g. isocyanates) that were present at the workplace, whereas only six cases of OA were attributed to cleaning agents, including ethanolamines and chloramine-T. Our study focusing on the role of cleaning products and/or disinfectants indicates that QACs are the most frequent agent causing OA in workers exposed to such materials in various occupations. Very few cases of OA due to QACs have been reported in the literature,[33, 34] although these compounds are widely used in cleaning products.[14, 15] QACs are non-volatile, but it is likely that inhalation exposure may occur during spray application of the products.[14, 15] The immunological mechanisms involved in the development of specific airway hypersensitivity to QACs is unknown as it is the case for most low-molecular-weight occupational agents.[29]

The major limitation of this study results from the lack of quantitative exposure assessment during the SICs. The agents that induced the observed asthmatic reactions could not be formally identified since the subjects were challenged with the commercial products they used at work, which most often contained a mixture of various potentially sensitizing and irritant compounds. The causal agents could only be inferred from their known asthmagenic potential. The asthma hazard index of QACs (0.81 to 0.95), glutaraldehyde (0.82), and ethanolamines (0.64 to 0.86) derived from a quantitative structure activity relationship model is above the cut-off value of 0.5, which predicts the potential for inducing OA with a sensitivity of 86% and a specificity of 99% (Seed MJ, personal communication; *http://www.coeh.man.ac.uk/research/asthma/*; last accessed 28 January 2012) [35].

The subjects described in this report may not accurately represent the whole population of workers with asthma related to cleaning activities. The data were derived from the single specialized centre of the French-speaking part of Belgium (~1.7 million active workers) where all SICs were performed during the period from 1992 to 2011. Nevertheless, the subjects evaluated in this study may represent only a subset of cleaning workers whom symptoms are severe enough for seeking specialized medical advice or claim compensation. It is also likely

that domestic cleaners were largely underrepresented in our series since most private home cleaners are employed in the informal sector and are not eligible for compensation. In addition, the study focused on individuals who experienced asthma symptoms that were directly related to cleaning products and/or disinfectants; those with symptoms related to workplace agents other than cleaning products were not included in this study.

CONCLUSION

This study based on SICs indicates that a substantial proportion of subjects who experience asthma symptoms related to cleaning materials actually suffer from sensitizer-induced OA, predominantly caused by QACs. The findings of this study may help to improve the diagnosis, management and prevention of cleaning-related asthma, although further investigation is required to identify the underlying pathophysiological mechanisms.

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Contributorship statement:

OV, JT, JCR, and FH: Conception of the study, interpretation of data, and reviewing of the manuscript; VD, GE, and JJ: Data collection, analysis of data, and reviewing of the manuscript. OV supervised specific inhalation challenges, drafted the initial version of the manuscript, and acts as guarantor of the final content of the manuscript.

Data sharing statement:

Extra data is available by emailing olivier.vandenplas@uclouvain.be

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Table 1. Demographic, occupational, and clinical characteristics of the subjects

	Positive SIC (n=17)	Negative SIC (n=27)	p-value
Gender (female)	13 (76)	23 (85)	0.466
Age, yr*	47 (39-49)	47 (35-53)	0.942
Referral by WCB	13 (76)	20 (74)	0.858
Job/industry :			
Professional cleaners:	9	15	
Healthcare facilities	2	5	
Various industries	3	4	
Private houses	1	3	
Public buildings	2	2	
Kitchens	1	1	
Healthcare workers	7	9	
Food workers	1	2	
Pharmaceutical workers	0	1	
Exposure to respiratory sensitizers:	16 (94)	16 (59)	0.033
QAC	10	6	
QAC and glutaraldehyde	1	3	
Glutaraldehyde	3	7	
Ethanolamines	2	0	
No identified sensitizer	1	11	
Current and ex-smokers	6 (35)	8 (30)	0.694
Atopy †	7 (41)	13 (48)	0.651
Asthma pre-existing to exposure	2 (12)	2 (7)	0.624
Duration of exposure before onset of asthma, mo*	12 (5-153)	53 (31-165)	0.114
Duration of asthma before SIC, mo*	25 (7-59)	25 (10-55)	0.980
Delay since last work exposure, mo*	10 (0.3-16)	8 (0.1-24)	0.808
Work-related respiratory symptoms:			
Wheezing	14 (82)	14 (52)	0.056
Breathlessness	14 (82)	20 (74)	0.716
Cough	11 (65)	21 (78)	0.343
Chest tightness	11 (65)	18 (67)	0.893
Sputum	4 (24)	8 (30)	0.740
Work-related rhinitis	8 (47)	16 (59)	0.429
Work-related dermatitis:	5 (29)	5 (19)	0.401
Inhaled corticosteroid:			0.160
No. with Inhaled corticosteroid	13 (76)	15 (56)	0.129
Low dose ‡	3 (18)	5 (19)	
Medium dose ‡	5 (29)	5 (19)	0.494
High dose ‡	5 (29)	5 (19)	
Short-acting beta$_2$-agonist ≥ once a day	7 (41)	1 (4)	0.002
Baseline FEV_1,% predicted*	92 (73-101)	100 (88-109)	0.049
Baseline FEV_1/FVC, %*	71 (63-77)	80 (73-83)	0.002
Baseline airway obstruction ¥	5 (29)	1 (4)	0.016

Legend: Data are presented as n (% of available data) unless otherwise specified. FEV_1: forced expiratory volume in one-second; FVC: forced vital capacity; PC_{20}: provocative concentration of histamine causing a 20% fall in FEV_1; QAC: quaternary ammonium compound; SIC: specific inhalation challenge; WCB: workers' compensation board.

*: Median value with 25th-75th interquartile range in parentheses;

†: Atopy defined by a positive skin-prick test to at least one common inhalant allergen;

‡: Low dose: equal or less than 500 µg beclomethasone dipropionate equivalent per day; medium dose: more than 500 µg but equal or less than 1000 µg per day; and high dose: more than 1000 µg per day.

¥: Airway obstruction defined by an FEV_1 <80% predicted value and an FEV_1/FVC ratio <70%.

Table 2. Changes in non-specific airway responsiveness and sputum cells during inhalation challenges with cleaning agents

	Positive SIC			Negative SIC		
	Baseline	**Post-challenge**	**p-value**	**Baseline**	**Post-challenge**	**p-value**
AHR to histamine:	(n=17)	(n=12)		(n=27)	(n=25)	
PC_{20}, mg/ml	1.4 (0.2-4.22)	0.5 (0.4-3.0)†	0.019	13.0 (1.4-32.0)	16.9 (2.6-32.0)	0.267
PC_{20} >16 mg/ml*	2 (12)	0		13 (48)	13 (52)	
>3-fold decrease in PC_{20}*		5 (42)			0	
Sputum cell counts:‡	(n=13)	(n=13)		(n=7)	(n=7)	
Total cell count, 10^6/ml	0.54 (0.34-0.97)	1.15 (0.53-2.17)	0.041	0.34 (0.26-1.89)	0.65 (0.38-1.81)	0.735
Eosinophils, 10^6 cells/ml	0.02 (0.01-0.04)	0.12 (0.02-0.39)	0.006	0 (0-0.01)	0.01 (0.01-0.010)	0.345
Eosinophils, %	1.8 (0.8-7.2)	10.0 (4.1-15.9)	0.009	0.2 (0-2.5)	0.8 (0.2-1.5)	0.786
Increase in eosinophils >2%*		8 (62)			0	
Neutrophils, 10^6 cells/ml	0.40 (0.17-0.70)	0.71 (0.38-1.62)	0.009	0.19 (0.16-1.70)	0.34 (0.25-1.52)	0.866
Neutrophils,%	57.3 (42.4-72.5)	69.5 (56.9-83.0)	0.152	60.3 (55.7-83.0)	70.3 (52.5-84.0)	0.866

Legend: Data are presented as median value with 25^{th}-75^{th} interquartile range in parentheses unless otherwise specified. AHR: airway hyperresponsiveness; PC_{20}: provocative concentration of histamine causing a 20% fall in FEV_1; SIC: specific inhalation challenge.

*: Data expressed as n (% of available data);

†: Histamine PC_{20} was measured at seven hours after the end of exposure in six subjects and 24 hours post-exposure in six subjects with positive SIC;

‡: Data available in subjects who performed an SIC from 2006 onwards.

REFERENCES

1. Zock JP, Vizcaya D, Le Moual N. Update on asthma and cleaners. *Curr Opin Allergy Clin Immunol* 2010;10:114-20.
2. Quirce S, Barranco P. Cleaning agents and asthma. *J Investig Allergol Clin Immunol* 2010;20:542-50; quiz 2p following 50.
3. Zock JP, Kogevinas M, Sunyer J, et al. Asthma risk, cleaning activities and use of specific cleaning products among Spanish indoor cleaners. *Scand J Work Environ Health* 2001;27:76-81.
4. Medina-Ramon M, Zock JP, Kogevinas M, et al. Asthma symptoms in women employed in domestic cleaning: a community based study. *Thorax* 2003;58:950-4.
5. Arif AA, Delclos GL, Whitehead LW, et al. Occupational exposures associated with work-related asthma and work-related wheezing among U.S. workers. *Am J Ind Med* 2003;44:368-76.
6. Karjalainen A, Martikainen R, Karjalainen J, et al. Excess incidence of asthma among Finnish cleaners employed in different industries. *Eur Respir J* 2002;19:90-5.
7. Kogevinas M, Zock JP, Jarvis D, et al. Exposure to substances in the workplace and new-onset asthma: an international prospective population-based study (ECRHS-II). *Lancet* 2007;370:336-41.
8. Ghosh RE, Cullinan P, Fishwick D, et al. Asthma and occupation in the 1958 birth cohort. *Thorax* 2013;68:365-71.
9. Mirabelli MC, Zock JP, Plana E, et al. Occupational risk factors for asthma among nurses and related healthcare professionals in an international study. *Occup Environ Med* 2007;64:474-9.
10. Delclos GL, Gimeno D, Arif AA, et al. Occupational risk factors and asthma among health care professionals. *Am J Respir Crit Care Med* 2007;175:667-75.
11. Vizcaya D, Mirabelli MC, Anto JM, et al. A workforce-based study of occupational exposures and asthma symptoms in cleaning workers. *Occup Environ Med* 2011;68:914-9.

12. Arif AA, Delclos GL. Association between cleaning-related chemicals and work-related asthma and asthma symptoms among healthcare professionals. *Occup Environ Med* 2012;69:35-40.
13. Obadia M, Liss GM, Lou W, et al. Relationships between asthma and work exposures among non-domestic cleaners in Ontario. *Am J Ind Med* 2009;52:716-23.
14. Wolkoff P, Schneider T, Kildeso J, et al. Risk in cleaning: chemical and physical exposure. *Sci Total Environ* 1998;215:135-56.
15. Bello A, Quinn MM, Perry MJ, et al. Characterization of occupational exposures to cleaning products used for common cleaning tasks--a pilot study of hospital cleaners. *Environ Health* 2009;8:11.
16. Rosenman KD, Reilly MJ, Schill DP, et al. Cleaning products and work-related asthma. *J Occup Environ Med* 2003;45:556-63.
17. Medina-Ramon M, Zock JP, Kogevinas M, et al. Asthma, chronic bronchitis, and exposure to irritant agents in occupational domestic cleaning: a nested case-control study. *Occup Environ Med* 2005;62:598-606.
18. Orriols R, Costa R, Albanell M, et al. Reported occupational respiratory diseases in Catalonia. *Occup Environ Med* 2006;63:255-60.
19. Vizcaya D, Mirabelli MC, Orriols R, et al. Functional and biological characteristics of asthma in cleaning workers. *Respir Med* 2013;107:673-83.
20. Medina-Ramon M, Zock JP, Kogevinas M, et al. Short-term respiratory effects of cleaning exposures in female domestic cleaners. *Eur Respir J* 2006;27:1196-203.
21. Bernstein JA, Brandt D, Rezvani M, et al. Evaluation of cleaning activities on respiratory symptoms in asthmatic female homemakers. *Ann Allergy Asthma Immunol* 2009;102:41-6.
22. Sterk PJ, Fabbri LM, Quanjer PH, et al. Airway responsiveness. Standardized challenge testing with pharmacological, physical and sensitizing stimuli in adults. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal.

Official Statement of the European Respiratory Society. *Eur Respir J Suppl* 1993;16:53-83.

23. Vandenplas O, Malo JL. Inhalation challenges with agents causing occupational asthma. *Eur Respir J* 1997;10:2612-29.
24. Pepys J, Hutchcroft BJ. Bronchial provocation tests in etiologic diagnosis and analysis of asthma. *Am Rev Respir Dis* 1975;112:829-59.
25. Vandenplas O, Delwiche JP, Jamart J, et al. Increase in non-specific bronchial hyperresponsiveness as an early marker of bronchial response to occupational agents during specific inhalation challenges. *Thorax* 1996;51:472-8.
26. Vandenplas O, D'Alpaos V, Heymans J, et al. Sputum eosinophilia: an early marker of bronchial response to occupational agents. *Allergy* 2009;64:754-61.
27. Girard F, Chaboillez S, Cartier A, et al. An effective strategy for diagnosing occupational asthma: use of induced sputum. *Am J Respir Crit Care Med* 2004;170:845-50.
28. de Fatima Macaira E, Algranti E, Medina Coeli Mendonca E, et al. Rhinitis and asthma symptoms in non-domestic cleaners from the Sao Paulo metropolitan area, Brazil. *Occup Environ Med* 2007;64:446-53.
29. Maestrelli P, Boschetto P, Fabbri LM, et al. Mechanisms of occupational asthma. *J Allergy Clin Immunol* 2009;123:531-42; quiz 43-4.
30. Nicholson PJ, Cullinan P, Taylor AJ, et al. Evidence based guidelines for the prevention, identification, and management of occupational asthma. *Occup Environ Med* 2005;62:290-9.
31. Chiry S, Boulet LP, Lepage J, et al. Frequency of work-related respiratory symptoms in workers without asthma. *Am J Ind Med* 2009;52:447-54.
32. Makela R, Kauppi P, Suuronen K, et al. Occupational asthma in professional cleaning work: a clinical study. *Occup Med (Lond)* 2011;61:121-6.
33. Burge PS, Richardson MN. Occupational asthma due to indirect exposure to lauryl dimethyl benzyl ammonium chloride used in a floor cleaner. *Thorax* 1994;49:842-3.

34. Purohit A, Kopferschmitt-Kubler MC, Moreau C, et al. Quaternary ammonium compounds and occupational asthma. *Int Arch Occup Environ Health* 2000;73:423-7.

35. Seed M, Agius R. Further validation of computer-based prediction of chemical asthma hazard. *Occup Med (Lond)* 2010;60:115-20.

ASTHMA RELATED TO CLEANING AGENTS: A CLINICAL INSIGHT

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ASTHMA RELATED TO CLEANING AGENTS: A CLINICAL INSIGHT

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List of abbreviations

AHR: Non-specific airway hyperresponsiveness

FEV_1: Forced expiratory volume in one second

OA: Occupational asthma

PC_{20}: Provocative concentration of histamine causing a 20% fall in FEV_1

PEF: Peak expiratory flow

QAC: Quaternary ammonium compound

SIC: Specific inhalation challenge

WCB: Workers' Compensation Board

ARTICLE SUMMARY

Article focus

- There is accumulating evidence of an increased risk of asthma among cleaning workers, although the agents and mechanisms involved in the development of cleaning-related asthma remain largely uncertain.
- We undertook a retrospective case series analysis of all subjects who completed a specific inhalation challenge with cleaning/disinfecting materials over the period 1992-2011 in order to assess the pattern of bronchial responses induced by these agents and to evaluate the mechanisms involved in cleaning-related asthma.

Key messages

- The asthmatic reactions induced by challenge exposures to cleaning agents were associated with a significant increase in post-challenge nonspecific airway hyperresponsiveness to histamine and/or an increase in sputum eosinophils
- This study based on specific inhalation challenges indicates that a substantial proportion of subjects who experience asthma symptoms related to cleaning materials may actually suffer from sensitizer-induced OA, predominantly caused by quaternary ammonium compounds.

Strengths and limitations

- This is the first report describing the pattern of functional and sputum cell changes induced by cleaning/disinfecting materials. The findings provide further insight into the mechanisms of cleaning-related asthma and may have practical implications for the diagnosis and management of this condition.
- The major limitations of this study result from the lack of quantitative exposure assessment during the challenge tests and the selection of the studied population. The subjects described in this report may not accurately represent the whole population of workers with asthma related to cleaning activities; they may represent only a subset of

cleaning workers whom symptoms are severe enough for seeking specialized medical advice and they did not include subjects with acute irritant-induced asthma.

ABSTRACT

Objective: To determine the agents causing asthmatic reactions during specific inhalation challenges (SICs) in workers with cleaning-related asthma symptoms and to assess the pattern of bronchial responses in order to identify the mechanisms involved in cleaning-related asthma.

Design: A retrospective case series analysis.

Setting: The study included all subjects who completed a SIC procedure with the cleaning/disinfecting products suspected of causing work-related asthma over the period 1992-211 in a tertiary centre, which is the single specialized centre of the French-speaking part of Belgium where all subjects with work-related asthma are referred for SIC.

Results: The review identified 44 subjects who completed an SIC with cleaning/disinfecting agents. Challenge exposure to the suspected cleaning agents elicited a ≥20% fall in FEV_1 in 17 (39%) subjects. The cleaning products that induced a positive SIC contained quaternary ammonium compounds (n=10), glutaraldehyde (n=3), both of these agents (n=1), and ethanolamines (n=2). Positive SICs were associated with a significant decrease in the median (interquartile range) value of the provocative concentration of histamine causing a 20% fall in FEV_1 (PC_{20}) from 1.4 (0.2-4.2) mg/ml at baseline to 0.5 (0.4-3.0) mg/ml after the challenge and a significant increase in sputum eosinophils from 1.8 (0.8-7.2)% at baseline to 10.0 (4.1-15.9)% 7 hours after the challenge exposure while these parameters did not significantly change in subjects with a negative SIC. Overall, 11 of 17 subjects with positive SICs showed a >3-fold decrease in post-challenge histamine PC_{20} value, a >2% increase in sputum eosinophils, or both of these outcomes.

Conclusions: These data indicate that a substantial proportion of workers who experience asthma symptoms related to cleaning materials show a pattern of bronchial reaction consistent with sensitizer-induced occupational asthma. The results also suggest that quaternary ammonium compounds are the principal cause of sensitizer-induced OA among cleaners.

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INTRODUCTION

In recent years, there has been a growing concern about the potential role of exposure to cleaning products in the initiation and aggravation of asthma.[1, 2] Epidemiological surveys have consistently documented increased prevalence[3-5] and incidence[6-8] rates of asthma in workers exposed to cleaning materials and/or disinfectants, especially in domestic cleaners[3, 4] and healthcare workers[9-12]. In addition, some studies have reported an increased risk of work-related asthma symptoms in exposed workers.[5, 12, 13]

However, there is still limited knowledge on the specific exposures and pathophysiological mechanisms involved in cleaning-related asthma.[1, 2] Cleaning materials typically contain a wide variety of ingredients, some of which are respiratory irritants, such as chlorine-releasing agents and ammonia, while others are potential airway sensitizers.[14, 15] Asthma in cleaners has been mostly associated with the irritant effects of cleaning products, which may exacerbate asthma and, at high exposure levels, cause acute irritant-induced asthma (or "reactive airways dysfunction syndrome").[10, 16-19] Nevertheless, occasional case reports have described occupational asthma (OA) due to specific airway hypersensitivty to components of detergents or disinfectants,[2] Overall the determinants of cleaning-related-asthma symptoms remain largely uncertain since most available studies have relied on self-reported symptoms or physician-based diagnosis. Only two studies have investigated the effects of cleaning exposures on peak expiratory flow (PEF) variability with inconsistent results.[20, 21]

Therefore, the data of subjects who completed specific inhalation challenges (SICs) with the cleaning agents and/or disinfectants suspected of causing their work-related asthma symptoms were reviewed in order: 1) to determine the prevalence and causes of asthmatic reactions induced by these agents; and 2) to compare the clinical features as well as the changes in nonspecific airway hyperresponsiveness (AHR) and sputum cell counts in subjects with positive or negative responses to SIC.

METHODS

This study was a retrospective analysis of the charts of all subjects investigated through a SIC in our tertiary centre during the period of 1992-2011 for asthma symptoms related to cleaning products and/or disinfectants. The study was approved by the *Comité d'éthique médicale* of the *Centre Hopitalier Universitaire de Mont-Godinne*; approval number 84/2012.

Subjects

In our centre, SICs with the occupational agent(s) suspected of causing work-related symptoms are routinely performed to diagnose OA provided that the baseline FEV_1 is equal to or above 60% of the predicted value.[22] The subjects are referred either by their attending physicians or by the Belgian Workers' Compensation Board (WCB). All French-speaking workers submitting a claim for work-related asthma to the WCB are referred to our centre in order to perform a SIC procedure.

The subjects who completed a SIC procedure with cleaning agents and/or disinfectants were identified from a database of 713 subjects who underwent a SIC for possible work-related asthma from 1992 up to 2011. Professional cleaners who had been challenged with latex gloves (n=23) or non-cleaning chemicals present at the workplace (n=3) were excluded from this analysis.

Specific inhalation challenges

SICs were completed according to a standardized protocol, which remained unchanged throughout the studied period.[23]. On the first test day, a "control" challenge was performed by exposing the subjects to a paint diluent containing a mixture of alkyl esters, ketones, and aromatic hydrocarbons nebulised in a five-cubic-meter challenge room for 30 min in order to ensure that fluctuations in FEV_1 were ≤12%. On the following day(s), the subjects were challenged with the cleaning product(s) suspected of causing their asthma symptoms at work. Exposure to these products was generated through a "realistic" approach aimed at

reproducing as close as possible the conditions of exposure at the workplace.[24] The tested cleaning materials and the mode of exposure during SIC were selected based on the subjects' interview, the Material Safety Data Sheets, and, most often, an analysis of the job exposure by WCB's hygienists. The cleaning agents were diluted in cold or heated water, brushed on a cardboard and/or sprayed according to the collected information.

The duration of exposure to the cleaning products was gradually increased (i.e. 1 min, 4 min, 10 min, 15 min, 30 min, and 60 min) on the same day until a ≥20% fall in FEV_1 occurred or a cumulative exposure of two hours was completed. Spirometry was obtained at baseline and serially after exposure for a total of at least six hours. A SIC was considered positive when a sustained ≥20% fall in FEV_1 was recorded. The level of AHR to histamine was determined at the end of the control day (i.e. baseline value), seven hours after the end of each active challenge when the FEV_1 was within 10% of baseline value, and 24 hours after the last active challenge.[25] AHR was expressed as the provocative concentration of histamine causing a 20% fall in FEV_1 (PC_{20}).[22] Since March 2006, sputum cell counts were assessed at the end of the control day and seven hours after the end of active challenges (i.e. after the assessment of AHR and administration of an inhaled bronchodilator). Sputum was induced through the inhalation of increasing concentrations (3%, 4%, and 5%) of hypertonic saline and processed as previously described.[26]

Those subjects who did not demonstrate a ≥20% fall in FEV_1 during the first active test day underwent a repeated challenge for a maximum of 2-3 hours on the next day. Further challenges were proposed when there was a >3-fold decrease in the post-challenge PC_{20} value or a >3% increase in sputum eosinophils as compared to the control day.[25, 26]

Data analysis

The following information was collected from the medical charts: 1) demographic, clinical, and occupational characteristics of the subjects; and 2) baseline functional data, histamine PC_{20} value on the control day and after the last active challenge, as well as the

corresponding sputum cell counts when available. Changes in AHR were considered significant when there was a >3-fold decrease in post-challenge histamine PC_{20} compared to baseline value.[25] An increase in sputum eosinophils of more than two percentage points compared with the control day value was regarded as clinically relevant.[25, 27]

Quantitative data are presented as median and 25^{th} and 75^{th} interquartile range. Comparisons between subgroups of subjects were made using the chi-squared test, Fisher exact test, or Wilcoxon rank-sum test as appropriate. The Wilcoxon signed-rank test was used for comparing variables before and after SIC in the same subjects. All statistical tests were two-tailed; a p-value <0.05 was considered significant. Statistical analysis was performed using the IBM SPSS Statistics 19.0 software (SPSS Inc, Chicago, Ill).

RESULTS

Baseline characteristics

During the reviewed period, 44 of 713 (6%) subjects were challenged with cleaning agents and/or disinfectants. The main demographic, occupational, and clinical characteristics of the subjects are presented in Table 1. A ≥20% decrease in FEV_1 was recorded during SIC in 17 (39%) of the subjects, 24% showing an isolated immediate reaction, 18% an isolated late reaction, 29% dual reactions, and 30% atypical reactions. The proportion of subjects referred for possible OA due to cleaning agents among all subjects evaluated through an SIC procedure in our centre increased from 3.2% (10 of 316) during the period 1992-2001 to 8.6% (34 of 397, p=0.003) from 2002 to 2011. The vast majority of the subjects with a positive SIC (16 of 17) had been evaluated during the last decade (2002-2011).

The median (interquartile range) duration of exposure to cleaning agents that elicited an asthmatic reaction was 120 (32-150) minutes. The cleaning products that induced a positive FEV_1 response contained quaternary ammonium compounds (QAC) (mainly, benzalkonium and didecyldimethylammonium chlorides) in 10 (59%) subjects, glutaraldehyde in three instances, both agents in one instance, and ethanolamines in two subjects (Table 1). No known sensitizing agent was identified in one subject who had been challenged with a cleaning product that contained sodium octylsulfate, nitrilotriacetic acid, and potassium hydroxide.

The subjects who developed an asthmatic response to cleaning agents and/or disinfectants did not differ from those who did not for most of the demographic and clinical characteristics. The pattern of the work-related respiratory symptoms was similar in both groups (Table 1), although wheezing at work was slightly more frequently reported by subjects with a positive SIC (82% vs. 52%, p=0.056). The subjects with a positive SIC tended to experience a lower level of asthma control. The proportion of these subjects who required the use of an inhaled short-acting $beta_2$-agonist at least once a day was significantly higher (41%) as compared to

those with a negative SIC (4%; p=0.002), although the daily dose of inhaled corticosteroids were similar in both groups. In addition, baseline spirometry revealed more often significant airway obstruction in subjects who showed a positive SIC (29%) than in those who did not (4%, p=0.016).

Non-specific airway hyperresponsiveness

At baseline, the subjects with a positive SIC to cleaning products showed a significantly lower median histamine PC_{20} value than those with a negative SIC (p=0.004) (Table 2). Among the 27 subjects with a negative SIC, 13 (48%) failed to demonstrate significant airway hyperresponsiveness (i.e. histamine PC_{20} value >16 mg/ml) at the pre-challenge assessment. These subjects differed from the 14 subjects with a histamine PC_{20} value ≤16 mg/ml only by a longer duration of work-related asthma symptoms before the SIC (47 [21-70] months vs. 19 [6-41] months, p=0.036).

A post-challenge histamine PC_{20} value was available in 12 of the 17 subjects who showed a positive SIC and in 25 of 27 subjects with a negative SIC. The post-challenge PC_{20} value was not measured because the FEV_1 24 hours after the end of exposure was still ≥20% lower than the pre-challenge value in four subjects with a positive SIC or because the subjects refused to complete the test in the other instances. Positive SICs were associated with a significant decrease in the median post-challenge PC_{20} value, whereas no change was documented in subjects with a negative SIC. Five of the 12 (42%) subjects with a positive SIC demonstrated a >3-fold decrease in post-challenge PC_{20} value, while none of those with a negative SIC did so.

Sputum cell counts

Among the subjects who were investigated from 2006 onwards, a suitable sputum sample was obtained seven hours after the end of the last active challenge in 13 of 15 positive SICs and in seven of 11 negative SICs (Table 2). At baseline, the subjects with a positive SIC

showed a slightly higher sputum eosinophil percentage than those with a negative SIC (p=0.046). Positive SICs were associated with a significant post-challenge increase in sputum eosinophils, while eosinophil counts did not significantly change in negative SICs. Eight (62%) of the 13 subjects with a positive SIC showed a >2% increase in post-challenge eosinophils, while none of the subjects with a negative SIC did so. In subjects with a positive SIC, there was an increase in the absolute number of sputum neutrophils after the last active challenge while the percentage of neutrophils was not significantly different at baseline and on the last challenge day.

Overall, positive SICs were associated with either a >3-fold decrease in post-challenge PC_{20} value in three subjects, a >2% increase in sputum eosinophils in six subjects, or both of these outcomes in two subjects.

Table 1. Demographic, occupational, and clinical characteristics of the subjects

	Positive SIC (n=17)	Negative SIC (n=27)	p-value
Gender (female)	13 (76)	23 (85)	0.466
Age, yr*	47 (39-49)	47 (35-53)	0.942
Referral by WCB	13 (76)	20 (74)	0.858
Job/industry :			
Professional cleaners:	9	15	
Healthcare facilities	2	5	
Various industries	3	4	
Private houses	1	3	
Public buildings	2	2	
Kitchens	1	1	
Healthcare workers	7	9	
Food workers	1	2	
Pharmaceutical workers	0	1	
Exposure to respiratory sensitizers:	16 (94)	16 (59)	0.033
QAC	10	6	
QAC and glutaraldehyde	1	3	
Glutaraldehyde	3	7	
Ethanolamines	2	0	
No identified sensitizer	1	11	
Current and ex-smokers	6 (35)	8 (30)	0.694
Atopy †	7 (41)	13 (48)	0.651
Asthma pre-existing to exposure	2 (12)	2 (7)	0.624
Duration of exposure before onset of asthma, mo*	12 (5-153)	53 (31-165)	0.114
Duration of asthma before SIC, mo*	25 (7-59)	25 (10-55)	0.980
Delay since last work exposure, mo*	10 (0.3-16)	8 (0.1-24)	0.808

Work-related respiratory symptoms:			
Wheezing	14 (82)	14 (52)	0.056
Breathlessness	14 (82)	20 (74)	0.716
Cough	11 (65)	21 (78)	0.343
Chest tightness	11 (65)	18 (67)	0.893
Sputum	4 (24)	8 (30)	0.740
Work-related rhinitis	8 (47)	16 (59)	0.429
Work-related dermatitis:	5 (29)	5 (19)	0.401
Inhaled corticosteroid:			
No. with Inhaled corticosteroid	13 (76)	15 (56)	0.160
Low dose ‡	3 (18)	5 (19)	
Medium dose ‡	5 (29)	5 (19)	0.494
High dose ‡	5 (29)	5 (19)	
Short-acting beta$_2$-agonist ≥ once a day	7 (41)	1 (4)	0.002
Baseline FEV$_1$,% predicted*	92 (73-101)	100 (88-109)	0.049
Baseline FEV$_1$/FVC, %*	71 (63-77)	80 (73-83)	0.002
Baseline airway obstruction ¥	5 (29)	1 (4)	0.016

Legend: Data are presented as n (% of available data) unless otherwise specified. FEV$_1$: forced expiratory volume in one-second; FVC: forced vital capacity; PC$_{20}$: provocative concentration of histamine causing a 20% fall in FEV$_1$; QAC: quaternary ammonium compound; SIC: specific inhalation challenge; WCB: workers' compensation board.

*: Median value with 25th-75th interquartile range in parentheses;

†: Atopy defined by a positive skin-prick test to at least one common inhalant allergen;

‡: Low dose: equal or less than 500 µg beclomethasone dipropionate equivalent per day; medium dose: more than 500 µg but equal or less than 1000 µg per day; and high dose: more than 1000 µg per day.

¥: Airway obstruction defined by an FEV$_1$ <80% predicted value and an FEV$_1$/FVC ratio <70%.

Table 2. Changes in non-specific airway responsiveness and sputum cells during inhalation challenges with cleaning agents

	Positive SIC			Negative SIC		
	Baseline	**Post-challenge**	**p-value**	**Baseline**	**Post-challenge**	**p-value**
AHR to histamine:	(n=17)	(n=12)		(n=27)	(n=25)	
PC_{20}, mg/ml	1.4 (0.2-4.22)	0.5 (0.4-3.0)†	0.019	13.0 (1.4-32.0)	16.9 (2.6-32.0)	0.267
PC_{20} >16 mg/ml*	2 (12)	0		13 (48)	13 (52)	
>3-fold decrease in PC_{20}*		5 (42)			0	
Sputum cell counts:‡	(n=13)	(n=13)		(n=7)	(n=7)	
Total cell count, 10^6/ml	0.54 (0.34-0.97)	1.15 (0.53-2.17)	0.041	0.34 (0.26-1.89)	0.65 (0.38-1.81)	0.735
Eosinophils, 10^6 cells/ml	0.02 (0.01-0.04)	0.12 (0.02-0.39)	0.006	0 (0-0.01)	0.01 (0.01-0.010)	0.345
Eosinophils, %	1.8 (0.8-7.2)	10.0 (4.1-15.9)	0.009	0.2 (0-2.5)	0.8 (0.2-1.5)	0.786
Increase in eosinophils >2%*		8 (62)			0	
Neutrophils, 10^6 cells/ml	0.40 (0.17-0.70)	0.71 (0.38-1.62)	0.009	0.19 (0.16-1.70)	0.34 (0.25-1.52)	0.866
Neutrophils,%	57.3 (42.4-72.5)	69.5 (56.9-83.0)	0.152	60.3 (55.7-83.0)	70.3 (52.5-84.0)	0.866

Legend: Data are presented as median value with 25^{th}-75^{th} interquartile range in parentheses unless otherwise specified. AHR: airway hyperresponsiveness; PC_{20}: provocative concentration of histamine causing a 20% fall in FEV_1; SIC: specific inhalation challenge.

*: Data expressed as n (% of available data);

†: Histamine PC_{20} was measured at seven hours after the end of exposure in six subjects and 24 hours post-exposure in six subjects with positive SIC;

‡: Data available in subjects who performed an SIC from 2006 onwards.

DISCUSSION

This study showed that challenge exposure to the cleaning agents and/or disinfectants used at work induced an asthmatic reaction in 39% of the subjects who experienced asthma symptoms upon exposure to these products. In addition, the results of the SICs provided evidence supporting a specific hypersensitivity mechanism rather than a nonspecific bronchoconstriction due to an irritant effect. Indeed, eleven (65%) of the 17 positive SICs induced by cleaning agents were associated with a significant increase in post-challenge AHR, an increase in sputum eosinophils, or both of these outcomes. Noticeably, among the subjects who developed a positive bronchial response to QACs, a post-challenge increase in sputum eosinophils and/or in the level of AHR was documented in nine of ten instances.

To the best of our knowledge, this is the first study reporting the changes in lung function parameters and markers of airway inflammation in subjects challenged with the cleaning materials suspected of causing work-related asthma symptoms. Available evidence indicates that cleaning materials can both exacerbate asthma (i.e. work-exacerbated asthma) and induce the development of asthma (i.e. occupational asthma) through either immunological or irritant mechanisms.[12, 16, 19, 28] Medina-Ramon et al. investigated the daily changes in peak expiratory flow (PEF) in 43 female domestic cleaners with a recent history of asthma and/or chronic bronchitis.[20] There was no significant association between the changes in PEF and cleaning exposures, with the exception of a decrease in PEF at night that was related to the use of ammonia. Nevertheless, analysis of PEF data using the Occupational Asthma System (OASYS) program identified a work-related pattern in 30% of the subjects, but the specific exposures associated with these changes were not described. By contrast, Bernstein et al. reported an increase in lower respiratory tract symptoms during cleaning activities in asthmatic homemakers compared with non-asthmatics in the absence of significant changes in PEF.[21] Our findings in subjects with a positive SIC are consistent with previous studies which reported that an increase in AHR and sputum eosinophils occurs specifically – though inconstantly – in sensitized individuals who develop asthmatic reactions

induced by common inhalant allergens as well as high-molecular-weight and low-molecular-weight occupational agents.[29] Only one subject developed a ≥20% fall in FEV_1 on exposure to a degreasing spray that apparently did not contain a known sensitizing agent. This subject who reported pre-existing asthma, also failed to demonstrate a post-challenge increase in AHR or sputum eosinophils, suggesting that the bronchial response resulted from an irritant effect consistent with the concept of "work-exacerbated asthma".[30]

Noticeably, 13 subjects with a negative SIC showed AHR to histamine neither at baseline nor after challenge exposure to the cleaning agents (Table 2), although nine of them were treated with an inhaled corticosteroid. These findings are consistent with those reported by Chiry et al. who found that a high proportion (57%) of subjects referred to tertiary centres for work-related asthma symptoms failed to demonstrate any functional evidence of asthma, although they experienced respiratory symptoms that were similar to those diagnosed as having OA or work-exacerbated asthma, except for a lower prevalence of wheezing.[31] A recent population-based questionnaire survey of health care workers exposed to cleaning materials also found that a high proportion (64%) of the subjects who experienced work-related asthma symptoms had not been given a diagnosis of asthma.[12]

There is little information on the specific agents involved in the various phenotypes of asthma related to cleaning exposure. Most epidemiological studies have linked asthma with exposure to irritant cleaning materials, mainly bleach,[9, 11, 12, 17, 28] ammonia,[9, 11, 12, 20, 28] and cleaning/degreasing sprays.[9, 11, 12, 20] On the other hand, occasional case reports have described OA presumably due to specific sensitization to disinfectants, such as chloramine-T, glutaraldehyde, QACs, and isothiazolinone, surfactants, ethanolamines used in wax-removing compounds, and detergent enzymes.[1, 2] Among the cases of asthma related to cleaning products identified by the US Sentinel Event Notification Systems for Occupational Risks (SENSOR), 62% were considered as "OA with a latency period", but only 14% of these cases were related to an identified respiratory sensitizer.[16] A recent Finnish report described 20 cases of OA diagnosed in professional cleaning workers using SIC

during the period 1994-2004.[32] The majority (70%) of these cases were caused by moulds and non-cleaning chemicals (e.g. isocyanates) that were present at the workplace, whereas only six cases of OA were attributed to cleaning agents, including ethanolamines and chloramine-T. Our study focusing on the role of cleaning products and/or disinfectants indicates that QACs are the most frequent agent causing OA in workers exposed to such materials in various occupations. Very few cases of OA due to QACs have been reported in the literature,[33, 34] although these compounds are widely used in cleaning products.[14, 15] QACs are non-volatile, but it is likely that inhalation exposure may occur during spray application of the products.[14, 15] The immunological mechanisms involved in the development of specific airway hypersensitivity to QACs is unknown as it is the case for most low-molecular-weight occupational agents.[29]

The major limitation of this study results from the lack of quantitative exposure assessment during the SICs. The agents that induced the observed asthmatic reactions could not be formally identified since the subjects were challenged with the commercial products they used at work, which most often contained a mixture of various potentially sensitizing and irritant compounds. The causal agents could only be inferred from their known asthmagenic potential. The asthma hazard index of QACs (0.81 to 0.95), glutaraldehyde (0.82), and ethanolamines (0.64 to 0.86) derived from a quantitative structure activity relationship model is above the cut-off value of 0.5, which predicts the potential for inducing OA with a sensitivity of 86% and a specificity of 99% (Seed MJ, personal communication; *http://www.coeh.man.ac.uk/research/asthma/*; last accessed 28 January 2012) [35].

The subjects described in this report may not accurately represent the whole population of workers with asthma related to cleaning activities. The data were derived from the single specialized centre of the French-speaking part of Belgium (~1.7 million active workers) where all SICs were performed during the period from 1992 to 2011. However, the subjects evaluated in this study may represent only a subset of cleaning workers whom symptoms are severe enough for seeking specialized medical advice or claim compensation. It is likely that

domestic cleaners were largely underrepresented in our series since most private home cleaners are employed in the informal sector and are not eligible for compensation. Failure to refer workers with possible cleaning-related asthma to our tertiary centre may also result from under-recognition of the condition by health care providers and reluctance by workers to seek medical advice for work-related symptoms because of concerns about adverse professional and financial consequences, as already outlined for work-related asthma in general.[36, 37] However, facilities for performing objective assessment of work-related asthma are easily available in Belgium, SIC procedures are paid by the WCB, and those workers who qualify for compensation are entitled to receive several types of financial awards, which are better than those obtained from the national health insurance. Noteworthy, the study focused on individuals who experienced work-related asthma symptoms that were directly related to cleaning products and/or disinfectants; those with symptoms related to workplace agents other than cleaning products were not included in this study.

This study did not allow for estimating the incidence of OA among workers exposed to cleaning/disinfecting materials. Indeed, the number of workers exposed to these agents in the French-speaking part of Belgium could not be accurately determined since the subjects with cleaning-related asthma were employed in a wide spectrum of occupations and industrial sectors. Despite their inherent limitations, the data yield some suggestion as to a a recent increase in OA caused by cleaning/disinfecting materials, since most cases in our series were evaluated during the last ten years of the study period.

CONCLUSION

This study based on SICs indicates that a substantial proportion of subjects who experience asthma symptoms related to cleaning materials actually suffer from sensitizer-induced OA, predominantly caused by QACs. The findings of this study may help to improve the diagnosis, management and prevention of cleaning-related asthma, although further investigation is required to identify the underlying pathophysiological mechanisms.

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Contributorship statement:

OV, JT, JCR, and FH: Conception of the study, interpretation of data, and reviewing of the manuscript; VD, GE, and JJ: Data collection, analysis of data, and reviewing of the manuscript. OV supervised specific inhalation challenges, drafted the initial version of the manuscript, and acts as guarantor of the final content of the manuscript.

Data sharing statement:

Extra data is available by emailing olivier.vandenplas@uclouvain.be

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Competing interests: None to declare.

REFERENCES

1. Zock JP, Vizcaya D, Le Moual N. Update on asthma and cleaners. *Curr Opin Allergy Clin Immunol* 2010;10:114-20.
2. Quirce S, Barranco P. Cleaning agents and asthma. *J Investig Allergol Clin Immunol* 2010;20:542-50; quiz 2p following 50.
3. Zock JP, Kogevinas M, Sunyer J, et al. Asthma risk, cleaning activities and use of specific cleaning products among Spanish indoor cleaners. *Scand J Work Environ Health* 2001;27:76-81.
4. Medina-Ramon M, Zock JP, Kogevinas M, et al. Asthma symptoms in women employed in domestic cleaning: a community based study. *Thorax* 2003;58:950-4.
5. Arif AA, Delclos GL, Whitehead LW, et al. Occupational exposures associated with work-related asthma and work-related wheezing among U.S. workers. *Am J Ind Med* 2003;44:368-76.
6. Karjalainen A, Martikainen R, Karjalainen J, et al. Excess incidence of asthma among Finnish cleaners employed in different industries. *Eur Respir J* 2002;19:90-5.
7. Kogevinas M, Zock JP, Jarvis D, et al. Exposure to substances in the workplace and new-onset asthma: an international prospective population-based study (ECRHS-II). *Lancet* 2007;370:336-41.
8. Ghosh RE, Cullinan P, Fishwick D, et al. Asthma and occupation in the 1958 birth cohort. *Thorax* 2013;68:365-71.
9. Mirabelli MC, Zock JP, Plana E, et al. Occupational risk factors for asthma among nurses and related healthcare professionals in an international study. *Occup Environ Med* 2007;64:474-9.
10. Delclos GL, Gimeno D, Arif AA, et al. Occupational risk factors and asthma among health care professionals. *Am J Respir Crit Care Med* 2007;175:667-75.

11. Vizcaya D, Mirabelli MC, Anto JM, et al. A workforce-based study of occupational exposures and asthma symptoms in cleaning workers. *Occup Environ Med* 2011;68:914-9.
12. Arif AA, Delclos GL. Association between cleaning-related chemicals and work-related asthma and asthma symptoms among healthcare professionals. *Occup Environ Med* 2012;69:35-40.
13. Obadia M, Liss GM, Lou W, et al. Relationships between asthma and work exposures among non-domestic cleaners in Ontario. *Am J Ind Med* 2009;52:716-23.
14. Wolkoff P, Schneider T, Kildeso J, et al. Risk in cleaning: chemical and physical exposure. *Sci Total Environ* 1998;215:135-56.
15. Bello A, Quinn MM, Perry MJ, et al. Characterization of occupational exposures to cleaning products used for common cleaning tasks--a pilot study of hospital cleaners. *Environ Health* 2009;8:11.
16. Rosenman KD, Reilly MJ, Schill DP, et al. Cleaning products and work-related asthma. *J Occup Environ Med* 2003;45:556-63.
17. Medina-Ramon M, Zock JP, Kogevinas M, et al. Asthma, chronic bronchitis, and exposure to irritant agents in occupational domestic cleaning: a nested case-control study. *Occup Environ Med* 2005;62:598-606.
18. Orriols R, Costa R, Albanell M, et al. Reported occupational respiratory diseases in Catalonia. *Occup Environ Med* 2006;63:255-60.
19. Vizcaya D, Mirabelli MC, Orriols R, et al. Functional and biological characteristics of asthma in cleaning workers. *Respir Med* 2013;107:673-83.
20. Medina-Ramon M, Zock JP, Kogevinas M, et al. Short-term respiratory effects of cleaning exposures in female domestic cleaners. *Eur Respir J* 2006;27:1196-203.
21. Bernstein JA, Brandt D, Rezvani M, et al. Evaluation of cleaning activities on respiratory symptoms in asthmatic female homemakers. *Ann Allergy Asthma Immunol* 2009;102:41-6.

22. Sterk PJ, Fabbri LM, Quanjer PH, et al. Airway responsiveness. Standardized challenge testing with pharmacological, physical and sensitizing stimuli in adults. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J Suppl* 1993;16:53-83.

23. Vandenplas O, Malo JL. Inhalation challenges with agents causing occupational asthma. *Eur Respir J* 1997;10:2612-29.

24. Pepys J, Hutchcroft BJ. Bronchial provocation tests in etiologic diagnosis and analysis of asthma. *Am Rev Respir Dis* 1975;112:829-59.

25. Vandenplas O, Delwiche JP, Jamart J, et al. Increase in non-specific bronchial hyperresponsiveness as an early marker of bronchial response to occupational agents during specific inhalation challenges. *Thorax* 1996;51:472-8.

26. Vandenplas O, D'Alpaos V, Heymans J, et al. Sputum eosinophilia: an early marker of bronchial response to occupational agents. *Allergy* 2009;64:754-61.

27. Girard F, Chaboillez S, Cartier A, et al. An effective strategy for diagnosing occupational asthma: use of induced sputum. *Am J Respir Crit Care Med* 2004;170:845-50.

28. de Fatima Macaira E, Algranti E, Medina Coeli Mendonca E, et al. Rhinitis and asthma symptoms in non-domestic cleaners from the Sao Paulo metropolitan area, Brazil. *Occup Environ Med* 2007;64:446-53.

29. Maestrelli P, Boschetto P, Fabbri LM, et al. Mechanisms of occupational asthma. *J Allergy Clin Immunol* 2009;123:531-42; quiz 43-4.

30. Nicholson PJ, Cullinan P, Taylor AJ, et al. Evidence based guidelines for the prevention, identification, and management of occupational asthma. *Occup Environ Med* 2005;62:290-9.

31. Chiry S, Boulet LP, Lepage J, et al. Frequency of work-related respiratory symptoms in workers without asthma. *Am J Ind Med* 2009;52:447-54.

32. Makela R, Kauppi P, Suuronen K, et al. Occupational asthma in professional cleaning work: a clinical study. *Occup Med (Lond)* 2011;61:121-6.

33. Burge PS, Richardson MN. Occupational asthma due to indirect exposure to lauryl dimethyl benzyl ammonium chloride used in a floor cleaner. *Thorax* 1994;49:842-3.
34. Purohit A, Kopferschmitt-Kubler MC, Moreau C, et al. Quaternary ammonium compounds and occupational asthma. *Int Arch Occup Environ Health* 2000;73:423-7.
35. Seed M, Agius R. Further validation of computer-based prediction of chemical asthma hazard. *Occup Med (Lond)* 2010;60:115-20.
36. Fishwick D, Bradshaw L, Davies J, et al. Are we failing workers with symptoms suggestive of occupational asthma? *Prim Care Respir J* 2007;16:304-10.
37. Santos MS, Jung H, Peyrovi J, et al. Occupational asthma and work-exacerbated asthma: factors associated with time to diagnostic steps. *Chest* 2007;131:1768-75.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	5
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-8
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	8-9
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	11-12
Outcome data	15*	Report numbers of outcome events or summary measures	11-12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14-15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	12-15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

ASTHMA RELATED TO CLEANING AGENTS: A CLINICAL INSIGHT

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Running head: Cleaners' asthma

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Keywords: Asthma; bronchoprovocation tests; cleaning, quaternary ammonium compounds; occupational disease.

Word count body of manuscript: 3,167 words

List of abbreviations

AHR: Non-specific airway hyperresponsiveness

FEV_1: Forced expiratory volume in one second

OA: Occupational asthma

PC_{20}: Provocative concentration of histamine causing a 20% fall in FEV_1

PEF: Peak expiratory flow

QAC: Quaternary ammonium compound

SIC: Specific inhalation challenge

WCB: Workers' Compensation Board

ARTICLE SUMMARY

Article focus

- There is accumulating evidence of an increased risk of asthma among cleaning workers, although the agents and mechanisms involved in the development of cleaning-related asthma remain largely uncertain.
- We undertook a retrospective case series analysis of all subjects who completed a specific inhalation challenge with cleaning/disinfecting materials over the period 1992-2011 in order to assess the pattern of bronchial responses induced by these agents and to evaluate the mechanisms involved in cleaning-related asthma.

Key messages

- The asthmatic reactions induced by challenge exposures to cleaning agents were associated with a significant increase in post-challenge nonspecific airway hyperresponsiveness to histamine and/or an increase in sputum eosinophils
- This study based on specific inhalation challenges indicates that a substantial proportion of subjects who experience asthma symptoms related to cleaning materials may actually suffer from sensitizer-induced OA, predominantly caused by quaternary ammonium compounds.

Strengths and limitations

- This is the first report describing the pattern of functional and sputum cell changes induced by cleaning/disinfecting materials. The findings provide further insight into the mechanisms of cleaning-related asthma and may have practical implications for the diagnosis and management of this condition.
- The major limitations of this study result from the lack of quantitative exposure assessment during the challenge tests and the selection of the studied population. The subjects described in this report may not accurately represent the whole population of workers with asthma related to cleaning activities; they may represent only a subset of

cleaning workers whom symptoms are severe enough for seeking specialized medical advice and they did not include subjects with acute irritant-induced asthma.

ABSTRACT

Objective: To determine the agents causing asthmatic reactions during specific inhalation challenges (SICs) in workers with cleaning-related asthma symptoms and to assess the pattern of bronchial responses in order to identify the mechanisms involved in cleaning-related asthma.

Design: A retrospective case series analysis.

Setting: The study included all subjects who completed a SIC procedure with the cleaning/disinfecting products suspected of causing work-related asthma over the period 1992-211 in a tertiary centre, which is the single specialized centre of the French-speaking part of Belgium where all subjects with work-related asthma are referred for SIC.

Results: The review identified 44 subjects who completed an SIC with cleaning/disinfecting agents. Challenge exposure to the suspected cleaning agents elicited a ≥20% fall in FEV_1 in 17 (39%) subjects. The cleaning products that induced a positive SIC contained quaternary ammonium compounds (n=10), glutaraldehyde (n=3), both of these agents (n=1), and ethanolamines (n=2). Positive SICs were associated with a significant decrease in the median (interquartile range) value of the provocative concentration of histamine causing a 20% fall in FEV_1 (PC_{20}) from 1.4 (0.2-4.2) mg/ml at baseline to 0.5 (0.4-3.0) mg/ml after the challenge and a significant increase in sputum eosinophils from 1.8 (0.8-7.2)% at baseline to 10.0 (4.1-15.9)% 7 hours after the challenge exposure while these parameters did not significantly change in subjects with a negative SIC. Overall, 11 of 17 subjects with positive SICs showed a >3-fold decrease in post-challenge histamine PC_{20} value, a >2% increase in sputum eosinophils, or both of these outcomes.

Conclusions: These data indicate that a substantial proportion of workers who experience asthma symptoms related to cleaning materials show a pattern of bronchial reaction consistent with sensitizer-induced occupational asthma. The results also suggest that quaternary ammonium compounds are the principal cause of sensitizer-induced OA among cleaners.

Abstract word count: 294 words

INTRODUCTION

In recent years, there has been a growing concern about the potential role of exposure to cleaning products in the initiation and aggravation of asthma.[1, 2] Epidemiological surveys have consistently documented increased prevalence[3-5] and incidence[6-8] rates of asthma in workers exposed to cleaning materials and/or disinfectants, especially in domestic cleaners[3, 4] and healthcare workers[9-12]. In addition, some studies have reported an increased risk of work-related asthma symptoms in exposed workers.[5, 12, 13]

However, there is still limited knowledge on the specific exposures and pathophysiological mechanisms involved in cleaning-related asthma.[1, 2] Cleaning materials typically contain a wide variety of ingredients, some of which are respiratory irritants, such as chlorine-releasing agents and ammonia, while others are potential airway sensitizers.[14, 15] Asthma in cleaners has been mostly associated with the irritant effects of cleaning products, which may exacerbate asthma and, at high exposure levels, cause acute irritant-induced asthma (or "reactive airways dysfunction syndrome").[10, 16-19] Nevertheless, occasional case reports have described occupational asthma (OA) due to specific airway hypersensitivty to components of detergents or disinfectants,[2] Overall the determinants of cleaning-related-asthma symptoms remain largely uncertain since most available studies have relied on self-reported symptoms or physician-based diagnosis. Only two studies have investigated the effects of cleaning exposures on peak expiratory flow (PEF) variability with inconsistent results.[20, 21]

Therefore, the data of subjects who completed specific inhalation challenges (SICs) with the cleaning agents and/or disinfectants suspected of causing their work-related asthma symptoms were reviewed in order: 1) to determine the prevalence and causes of asthmatic reactions induced by these agents; and 2) to compare the clinical features as well as the changes in nonspecific airway hyperresponsiveness (AHR) and sputum cell counts in subjects with positive or negative responses to SIC.

METHODS

This study was a retrospective analysis of the charts of all subjects investigated through a SIC in our tertiary centre during the period of 1992-2011 for asthma symptoms related to cleaning products and/or disinfectants. The study was approved by the *Comité d'éthique médicale* of the *Centre Hopitalier Universitaire de Mont-Godinne*; approval number 84/2012.

Subjects

In our centre, SICs with the occupational agent(s) suspected of causing work-related symptoms are routinely performed to diagnose OA provided that the baseline FEV_1 is equal to or above 60% of the predicted value.[22] The subjects are referred either by their attending physicians or by the Belgian Workers' Compensation Board (WCB). All French-speaking workers submitting a claim for work-related asthma to the WCB are referred to our centre in order to perform a SIC procedure.

The subjects who completed a SIC procedure with cleaning agents and/or disinfectants were identified from a database of 713 subjects who underwent a SIC for possible work-related asthma from 1992 up to 2011. Professional cleaners who had been challenged with latex gloves (n=23) or non-cleaning chemicals present at the workplace (n=3) were excluded from this analysis.

Specific inhalation challenges

SICs were completed according to a standardized protocol, which remained unchanged throughout the studied period.[23]. On the first test day, a "control" challenge was performed by exposing the subjects to a paint diluent containing a mixture of alkyl esters, ketones, and aromatic hydrocarbons nebulised in a five-cubic-meter challenge room for 30 min in order to ensure that fluctuations in FEV_1 were ≤12%. On the following day(s), the subjects were challenged with the cleaning product(s) suspected of causing their asthma symptoms at work. Exposure to these products was generated through a "realistic" approach aimed at

reproducing as close as possible the conditions of exposure at the workplace.[24] The tested cleaning materials and the mode of exposure during SIC were selected based on the subjects' interview, the Material Safety Data Sheets, and, most often, an analysis of the job exposure by WCB's hygienists. The cleaning agents were diluted in cold or heated water, brushed on a cardboard and/or sprayed according to the collected information.

The duration of exposure to the cleaning products was gradually increased (i.e. 1 min, 4 min, 10 min, 15 min, 30 min, and 60 min) on the same day until a ≥20% fall in FEV_1 occurred or a cumulative exposure of two hours was completed. Spirometry was obtained at baseline and serially after exposure for a total of at least six hours. A SIC was considered positive when a sustained ≥20% fall in FEV_1 was recorded. The level of AHR to histamine was determined at the end of the control day (i.e. baseline value), seven hours after the end of each active challenge when the FEV_1 was within 10% of baseline value, and 24 hours after the last active challenge.[25] AHR was expressed as the provocative concentration of histamine causing a 20% fall in FEV_1 (PC_{20}).[22] Since March 2006, sputum cell counts were assessed at the end of the control day and seven hours after the end of active challenges (i.e. after the assessment of AHR and administration of an inhaled bronchodilator). Sputum was induced through the inhalation of increasing concentrations (3%, 4%, and 5%) of hypertonic saline and processed as previously described.[26]

Those subjects who did not demonstrate a ≥20% fall in FEV_1 during the first active test day underwent a repeated challenge for a maximum of 2-3 hours on the next day. Further challenges were proposed when there was a >3-fold decrease in the post-challenge PC_{20} value or a >3% increase in sputum eosinophils as compared to the control day.[25, 26]

Data analysis

The following information was collected from the medical charts: 1) demographic, clinical, and occupational characteristics of the subjects; and 2) baseline functional data, histamine PC_{20} value on the control day and after the last active challenge, as well as the

corresponding sputum cell counts when available. Changes in AHR were considered significant when there was a >3-fold decrease in post-challenge histamine PC_{20} compared to baseline value.[25] An increase in sputum eosinophils of more than two percentage points compared with the control day value was regarded as clinically relevant.[25, 27]

Quantitative data are presented as median and 25^{th} and 75^{th} interquartile range. Comparisons between subgroups of subjects were made using the chi-squared test, Fisher exact test, or Wilcoxon rank-sum test as appropriate. The Wilcoxon signed-rank test was used for comparing variables before and after SIC in the same subjects. All statistical tests were two-tailed; a p-value <0.05 was considered significant. Statistical analysis was performed using the IBM SPSS Statistics 19.0 software (SPSS Inc, Chicago, Ill).

RESULTS

Baseline characteristics

During the reviewed period, 44 of 713 (6%) subjects were challenged with cleaning agents and/or disinfectants. The main demographic, occupational, and clinical characteristics of the subjects are presented in Table 1. A ≥20% decrease in FEV_1 was recorded during SIC in 17 (39%) of the subjects, 24% showing an isolated immediate reaction, 18% an isolated late reaction, 29% dual reactions, and 30% atypical reactions. The proportion of subjects referred for possible OA due to cleaning agents among all subjects evaluated through an SIC procedure in our centre increased from 3.2% (10 of 316) during the period 1992-2001 to 8.6% (34 of 397, p=0.003) from 2002 to 2011. The vast majority of the subjects with a positive SIC (16 of 17) had been evaluated during the last decade (2002-2011).

The median (interquartile range) duration of exposure to cleaning agents that elicited an asthmatic reaction was 120 (32-150) minutes. The cleaning products that induced a positive FEV_1 response contained quaternary ammonium compounds (QAC) (mainly, benzalkonium and didecyldimethylammonium chlorides) in 10 (59%) subjects, glutaraldehyde in three instances, both agents in one instance, and ethanolamines in two subjects (Table 1). No known sensitizing agent was identified in one subject who had been challenged with a cleaning product that contained sodium octylsulfate, nitrilotriacetic acid, and potassium hydroxide.

The subjects who developed an asthmatic response to cleaning agents and/or disinfectants did not differ from those who did not for most of the demographic and clinical characteristics. The pattern of the work-related respiratory symptoms was similar in both groups (Table 1), although wheezing at work was slightly more frequently reported by subjects with a positive SIC (82% vs. 52%, p=0.056). The subjects with a positive SIC tended to experience a lower level of asthma control. The proportion of these subjects who required the use of an inhaled short-acting $beta_2$-agonist at least once a day was significantly higher (41%) as compared to

those with a negative SIC (4%; p=0.002), although the daily dose of inhaled corticosteroids were similar in both groups. In addition, baseline spirometry revealed more often significant airway obstruction in subjects who showed a positive SIC (29%) than in those who did not (4%, p=0.016).

Non-specific airway hyperresponsiveness

At baseline, the subjects with a positive SIC to cleaning products showed a significantly lower median histamine PC_{20} value than those with a negative SIC (p=0.004) (Table 2). Among the 27 subjects with a negative SIC, 13 (48%) failed to demonstrate significant airway hyperresponsiveness (i.e. histamine PC_{20} value >16 mg/ml) at the pre-challenge assessment. These subjects differed from the 14 subjects with a histamine PC_{20} value ≤16 mg/ml only by a longer duration of work-related asthma symptoms before the SIC (47 [21-70] months vs. 19 [6-41] months, p=0.036).

A post-challenge histamine PC_{20} value was available in 12 of the 17 subjects who showed a positive SIC and in 25 of 27 subjects with a negative SIC. The post-challenge PC_{20} value was not measured because the FEV_1 24 hours after the end of exposure was still ≥20% lower than the pre-challenge value in four subjects with a positive SIC or because the subjects refused to complete the test in the other instances. Positive SICs were associated with a significant decrease in the median post-challenge PC_{20} value, whereas no change was documented in subjects with a negative SIC. Five of the 12 (42%) subjects with a positive SIC demonstrated a >3-fold decrease in post-challenge PC_{20} value, while none of those with a negative SIC did so.

Sputum cell counts

Among the subjects who were investigated from 2006 onwards, a suitable sputum sample was obtained seven hours after the end of the last active challenge in 13 of 15 positive SICs and in seven of 11 negative SICs (Table 2). At baseline, the subjects with a positive SIC

showed a slightly higher sputum eosinophil percentage than those with a negative SIC (p=0.046). Positive SICs were associated with a significant post-challenge increase in sputum eosinophils, while eosinophil counts did not significantly change in negative SICs. Eight (62%) of the 13 subjects with a positive SIC showed a >2% increase in post-challenge eosinophils, while none of the subjects with a negative SIC did so. In subjects with a positive SIC, there was an increase in the absolute number of sputum neutrophils after the last active challenge while the percentage of neutrophils was not significantly different at baseline and on the last challenge day.

Overall, positive SICs were associated with either a >3-fold decrease in post-challenge PC_{20} value in three subjects, a >2% increase in sputum eosinophils in six subjects, or both of these outcomes in two subjects.

Table 1. Demographic, occupational, and clinical characteristics of the subjects

	Positive SIC (n=17)	Negative SIC (n=27)	p-value
Gender (female)	13 (76)	23 (85)	0.466
Age, yr*	47 (39-49)	47 (35-53)	0.942
Referral by WCB	13 (76)	20 (74)	0.858
Job/industry :			
Professional cleaners:	9	15	
Healthcare facilities	2	5	
Various industries	3	4	
Private houses	1	3	
Public buildings	2	2	
Kitchens	1	1	
Healthcare workers	7	9	
Food workers	1	2	
Pharmaceutical workers	0	1	
Exposure to respiratory sensitizers:	16 (94)	16 (59)	0.033
QAC	10	6	
QAC and glutaraldehyde	1	3	
Glutaraldehyde	3	7	
Ethanolamines	2	0	
No identified sensitizer	1	11	
Current and ex-smokers	6 (35)	8 (30)	0.694
Atopy †	7 (41)	13 (48)	0.651
Asthma pre-existing to exposure	2 (12)	2 (7)	0.624
Duration of exposure before onset of asthma, mo*	12 (5-153)	53 (31-165)	0.114
Duration of asthma before SIC, mo*	25 (7-59)	25 (10-55)	0.980
Delay since last work exposure, mo*	10 (0.3-16)	8 (0.1-24)	0.808

Work-related respiratory symptoms:			
Wheezing	14 (82)	14 (52)	0.056
Breathlessness	14 (82)	20 (74)	0.716
Cough	11 (65)	21 (78)	0.343
Chest tightness	11 (65)	18 (67)	0.893
Sputum	4 (24)	8 (30)	0.740
Work-related rhinitis	8 (47)	16 (59)	0.429
Work-related dermatitis:	5 (29)	5 (19)	0.401
Inhaled corticosteroid:			
No. with Inhaled corticosteroid	13 (76)	15 (56)	0.160
Low dose ‡	3 (18)	5 (19)	
Medium dose ‡	5 (29)	5 (19)	0.494
High dose ‡	5 (29)	5 (19)	
Short-acting beta$_2$-agonist ≥ once a day	7 (41)	1 (4)	0.002
Baseline FEV$_1$,% predicted*	92 (73-101)	100 (88-109)	0.049
Baseline FEV$_1$/FVC, %*	71 (63-77)	80 (73-83)	0.002
Baseline airway obstruction ¥	5 (29)	1 (4)	0.016

Legend: Data are presented as n (% of available data) unless otherwise specified. FEV$_1$: forced expiratory volume in one-second; FVC: forced vital capacity; PC$_{20}$: provocative concentration of histamine causing a 20% fall in FEV$_1$; QAC: quaternary ammonium compound; SIC: specific inhalation challenge; WCB: workers' compensation board.

*: Median value with 25th-75th interquartile range in parentheses;

†: Atopy defined by a positive skin-prick test to at least one common inhalant allergen;

‡: Low dose: equal or less than 500 µg beclomethasone dipropionate equivalent per day; medium dose: more than 500 µg but equal or less than 1000 µg per day; and high dose: more than 1000 µg per day.

¥: Airway obstruction defined by an FEV$_1$ <80% predicted value and an FEV$_1$/FVC ratio <70%.

Table 2. Changes in non-specific airway responsiveness and sputum cells during inhalation challenges with cleaning agents

	Positive SIC			Negative SIC		
	Baseline	**Post-challenge**	**p-value**	**Baseline**	**Post-challenge**	**p-value**
AHR to histamine:	(n=17)	(n=12)		(n=27)	(n=25)	
PC_{20}, mg/ml	1.4 (0.2-4.22)	0.5 (0.4-3.0)†	0.019	13.0 (1.4-32.0)	16.9 (2.6-32.0)	0.267
PC_{20} >16 mg/ml*	2 (12)	0		13 (48)	13 (52)	
>3-fold decrease in PC_{20}*		5 (42)			0	
Sputum cell counts:‡	(n=13)	(n=13)		(n=7)	(n=7)	
Total cell count, 10^6/ml	0.54 (0.34-0.97)	1.15 (0.53-2.17)	0.041	0.34 (0.26-1.89)	0.65 (0.38-1.81)	0.735
Eosinophils, 10^6 cells/ml	0.02 (0.01-0.04)	0.12 (0.02-0.39)	0.006	0 (0-0.01)	0.01 (0.01-0.010)	0.345
Eosinophils, %	1.8 (0.8-7.2)	10.0 (4.1-15.9)	0.009	0.2 (0-2.5)	0.8 (0.2-1.5)	0.786
Increase in eosinophils >2%*		8 (62)			0	
Neutrophils, 10^6 cells/ml	0.40 (0.17-0.70)	0.71 (0.38-1.62)	0.009	0.19 (0.16-1.70)	0.34 (0.25-1.52)	0.866
Neutrophils,%	57.3 (42.4-72.5)	69.5 (56.9-83.0)	0.152	60.3 (55.7-83.0)	70.3 (52.5-84.0)	0.866

Legend: Data are presented as median value with 25^{th}-75^{th} interquartile range in parentheses unless otherwise specified. AHR: airway hyperresponsiveness; PC_{20}: provocative concentration of histamine causing a 20% fall in FEV_1; SIC: specific inhalation challenge.
*: Data expressed as n (% of available data);
†: Histamine PC_{20} was measured at seven hours after the end of exposure in six subjects and 24 hours post-exposure in six subjects with positive SIC;
‡: Data available in subjects who performed an SIC from 2006 onwards.

DISCUSSION

This study showed that challenge exposure to the cleaning agents and/or disinfectants used at work induced an asthmatic reaction in 39% of the subjects who experienced asthma symptoms upon exposure to these products. In addition, the results of the SICs provided evidence supporting a specific hypersensitivity mechanism rather than a nonspecific bronchoconstriction due to an irritant effect. Indeed, eleven (65%) of the 17 positive SICs induced by cleaning agents were associated with a significant increase in post-challenge AHR, an increase in sputum eosinophils, or both of these outcomes. Noticeably, among the subjects who developed a positive bronchial response to QACs, a post-challenge increase in sputum eosinophils and/or in the level of AHR was documented in nine of ten instances.

To the best of our knowledge, this is the first study reporting the changes in lung function parameters and markers of airway inflammation in subjects challenged with the cleaning materials suspected of causing work-related asthma symptoms. Available evidence indicates that cleaning materials can both exacerbate asthma (i.e. work-exacerbated asthma) and induce the development of asthma (i.e. occupational asthma) through either immunological or irritant mechanisms.[12, 16, 19, 28] Medina-Ramon et al. investigated the daily changes in peak expiratory flow (PEF) in 43 female domestic cleaners with a recent history of asthma and/or chronic bronchitis.[20] There was no significant association between the changes in PEF and cleaning exposures, with the exception of a decrease in PEF at night that was related to the use of ammonia. Nevertheless, analysis of PEF data using the Occupational Asthma System (OASYS) program identified a work-related pattern in 30% of the subjects, but the specific exposures associated with these changes were not described. By contrast, Bernstein et al. reported an increase in lower respiratory tract symptoms during cleaning activities in asthmatic homemakers compared with non-asthmatics in the absence of significant changes in PEF.[21] Our findings in subjects with a positive SIC are consistent with previous studies which reported that an increase in AHR and sputum eosinophils occurs specifically – though inconstantly – in sensitized individuals who develop asthmatic reactions

induced by common inhalant allergens as well as high-molecular-weight and low-molecular-weight occupational agents.[29] Only one subject developed a ≥20% fall in FEV_1 on exposure to a degreasing spray that apparently did not contain a known sensitizing agent. This subject who reported pre-existing asthma, also failed to demonstrate a post-challenge increase in AHR or sputum eosinophils, suggesting that the bronchial response resulted from an irritant effect consistent with the concept of "work-exacerbated asthma".[30]

Noticeably, 13 subjects with a negative SIC showed AHR to histamine neither at baseline nor after challenge exposure to the cleaning agents (Table 2), although nine of them were treated with an inhaled corticosteroid. These findings are consistent with those reported by Chiry et al. who found that a high proportion (57%) of subjects referred to tertiary centres for work-related asthma symptoms failed to demonstrate any functional evidence of asthma, although they experienced respiratory symptoms that were similar to those diagnosed as having OA or work-exacerbated asthma, except for a lower prevalence of wheezing.[31] A recent population-based questionnaire survey of health care workers exposed to cleaning materials also found that a high proportion (64%) of the subjects who experienced work-related asthma symptoms had not been given a diagnosis of asthma.[12]

There is little information on the specific agents involved in the various phenotypes of asthma related to cleaning exposure. Most epidemiological studies have linked asthma with exposure to irritant cleaning materials, mainly bleach,[9, 11, 12, 17, 28] ammonia,[9, 11, 12, 20, 28] and cleaning/degreasing sprays.[9, 11, 12, 20] On the other hand, occasional case reports have described OA presumably due to specific sensitization to disinfectants, such as chloramine-T, glutaraldehyde, QACs, and isothiazolinone, surfactants, ethanolamines used in wax-removing compounds, and detergent enzymes.[1, 2] Among the cases of asthma related to cleaning products identified by the US Sentinel Event Notification Systems for Occupational Risks (SENSOR), 62% were considered as "OA with a latency period", but only 14% of these cases were related to an identified respiratory sensitizer.[16] A recent Finnish report described 20 cases of OA diagnosed in professional cleaning workers using SIC

during the period 1994-2004.[32] The majority (70%) of these cases were caused by moulds and non-cleaning chemicals (e.g. isocyanates) that were present at the workplace, whereas only six cases of OA were attributed to cleaning agents, including ethanolamines and chloramine-T. Our study focusing on the role of cleaning products and/or disinfectants indicates that QACs are the most frequent agent causing OA in workers exposed to such materials in various occupations. Very few cases of OA due to QACs have been reported in the literature,[33, 34] although these compounds are widely used in cleaning products.[14, 15] QACs are non-volatile, but it is likely that inhalation exposure may occur during spray application of the products.[14, 15] The immunological mechanisms involved in the development of specific airway hypersensitivity to QACs is unknown as it is the case for most low-molecular-weight occupational agents.[29]

The major limitation of this study results from the lack of quantitative exposure assessment during the SICs. The agents that induced the observed asthmatic reactions could not be formally identified since the subjects were challenged with the commercial products they used at work, which most often contained a mixture of various potentially sensitizing and irritant compounds. The causal agents could only be inferred from their known asthmagenic potential. The asthma hazard index of QACs (0.81 to 0.95), glutaraldehyde (0.82), and ethanolamines (0.64 to 0.86) derived from a quantitative structure activity relationship model is above the cut-off value of 0.5, which predicts the potential for inducing OA with a sensitivity of 86% and a specificity of 99% (Seed MJ, personal communication; *http://www.coeh.man.ac.uk/research/asthma/*; last accessed 28 January 2012) [35].

The subjects described in this report may not accurately represent the whole population of workers with asthma related to cleaning activities. The data were derived from the single specialized centre of the French-speaking part of Belgium (~1.7 million active workers) where all SICs were performed during the period from 1992 to 2011. However, the subjects evaluated in this study may represent only a subset of cleaning workers whom symptoms are severe enough for seeking specialized medical advice or claim compensation. It is likely that

domestic cleaners were largely underrepresented in our series since most private home cleaners are employed in the informal sector and are not eligible for compensation. Failure to refer workers with possible cleaning-related asthma to our tertiary centre may also result from under-recognition of the condition by health care providers and reluctance by workers to seek medical advice for work-related symptoms because of concerns about adverse professional and financial consequences, as already outlined for work-related asthma in general.[36, 37] However, facilities for performing objective assessment of work-related asthma are easily available in Belgium, SIC procedures are paid by the WCB, and those workers who qualify for compensation are entitled to receive several types of financial awards, which are better than those obtained from the national health insurance. Noteworthy, the study focused on individuals who experienced work-related asthma symptoms that were directly related to cleaning products and/or disinfectants; those with symptoms related to workplace agents other than cleaning products were not included in this study.

This study did not allow for estimating the incidence of OA among workers exposed to cleaning/disinfecting materials. Indeed, the number of workers exposed to these agents in the French-speaking part of Belgium could not be accurately determined since the subjects with cleaning-related asthma were employed in a wide spectrum of occupations and industrial sectors. Despite their inherent limitations, the data yield some suggestion as to a a recent increase in OA caused by cleaning/disinfecting materials, since most cases in our series were evaluated during the last ten years of the study period.

CONCLUSION

This study based on SICs indicates that a substantial proportion of subjects who experience asthma symptoms related to cleaning materials actually suffer from sensitizer-induced OA, predominantly caused by QACs. The findings of this study may help to improve the diagnosis, management and prevention of cleaning-related asthma, although further investigation is required to identify the underlying pathophysiological mechanisms.

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OV, JT, JCR, and FH: Conception of the study, interpretation of data, and reviewing of the manuscript; VD, GE, and JJ: Data collection, analysis of data, and reviewing of the manuscript. OV supervised specific inhalation challenges, drafted the initial version of the manuscript, and acts as guarantor of the final content of the manuscript.

Data sharing statement:

Extra data is available by emailing olivier.vandenplas@uclouvain.be

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REFERENCES

1. Zock JP, Vizcaya D, Le Moual N. Update on asthma and cleaners. *Curr Opin Allergy Clin Immunol* 2010;10:114-20.
2. Quirce S, Barranco P. Cleaning agents and asthma. *J Investig Allergol Clin Immunol* 2010;20:542-50; quiz 2p following 50.
3. Zock JP, Kogevinas M, Sunyer J, et al. Asthma risk, cleaning activities and use of specific cleaning products among Spanish indoor cleaners. *Scand J Work Environ Health* 2001;27:76-81.
4. Medina-Ramon M, Zock JP, Kogevinas M, et al. Asthma symptoms in women employed in domestic cleaning: a community based study. *Thorax* 2003;58:950-4.
5. Arif AA, Delclos GL, Whitehead LW, et al. Occupational exposures associated with work-related asthma and work-related wheezing among U.S. workers. *Am J Ind Med* 2003;44:368-76.
6. Karjalainen A, Martikainen R, Karjalainen J, et al. Excess incidence of asthma among Finnish cleaners employed in different industries. *Eur Respir J* 2002;19:90-5.
7. Kogevinas M, Zock JP, Jarvis D, et al. Exposure to substances in the workplace and new-onset asthma: an international prospective population-based study (ECRHS-II). *Lancet* 2007;370:336-41.
8. Ghosh RE, Cullinan P, Fishwick D, et al. Asthma and occupation in the 1958 birth cohort. *Thorax* 2013;68:365-71.
9. Mirabelli MC, Zock JP, Plana E, et al. Occupational risk factors for asthma among nurses and related healthcare professionals in an international study. *Occup Environ Med* 2007;64:474-9.
10. Delclos GL, Gimeno D, Arif AA, et al. Occupational risk factors and asthma among health care professionals. *Am J Respir Crit Care Med* 2007;175:667-75.

11. Vizcaya D, Mirabelli MC, Anto JM, et al. A workforce-based study of occupational exposures and asthma symptoms in cleaning workers. *Occup Environ Med* 2011;68:914-9.
12. Arif AA, Delclos GL. Association between cleaning-related chemicals and work-related asthma and asthma symptoms among healthcare professionals. *Occup Environ Med* 2012;69:35-40.
13. Obadia M, Liss GM, Lou W, et al. Relationships between asthma and work exposures among non-domestic cleaners in Ontario. *Am J Ind Med* 2009;52:716-23.
14. Wolkoff P, Schneider T, Kildeso J, et al. Risk in cleaning: chemical and physical exposure. *Sci Total Environ* 1998;215:135-56.
15. Bello A, Quinn MM, Perry MJ, et al. Characterization of occupational exposures to cleaning products used for common cleaning tasks--a pilot study of hospital cleaners. *Environ Health* 2009;8:11.
16. Rosenman KD, Reilly MJ, Schill DP, et al. Cleaning products and work-related asthma. *J Occup Environ Med* 2003;45:556-63.
17. Medina-Ramon M, Zock JP, Kogevinas M, et al. Asthma, chronic bronchitis, and exposure to irritant agents in occupational domestic cleaning: a nested case-control study. *Occup Environ Med* 2005;62:598-606.
18. Orriols R, Costa R, Albanell M, et al. Reported occupational respiratory diseases in Catalonia. *Occup Environ Med* 2006;63:255-60.
19. Vizcaya D, Mirabelli MC, Orriols R, et al. Functional and biological characteristics of asthma in cleaning workers. *Respir Med* 2013;107:673-83.
20. Medina-Ramon M, Zock JP, Kogevinas M, et al. Short-term respiratory effects of cleaning exposures in female domestic cleaners. *Eur Respir J* 2006;27:1196-203.
21. Bernstein JA, Brandt D, Rezvani M, et al. Evaluation of cleaning activities on respiratory symptoms in asthmatic female homemakers. *Ann Allergy Asthma Immunol* 2009;102:41-6.

22. Sterk PJ, Fabbri LM, Quanjer PH, et al. Airway responsiveness. Standardized challenge testing with pharmacological, physical and sensitizing stimuli in adults. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J Suppl* 1993;16:53-83.

23. Vandenplas O, Malo JL. Inhalation challenges with agents causing occupational asthma. *Eur Respir J* 1997;10:2612-29.

24. Pepys J, Hutchcroft BJ. Bronchial provocation tests in etiologic diagnosis and analysis of asthma. *Am Rev Respir Dis* 1975;112:829-59.

25. Vandenplas O, Delwiche JP, Jamart J, et al. Increase in non-specific bronchial hyperresponsiveness as an early marker of bronchial response to occupational agents during specific inhalation challenges. *Thorax* 1996;51:472-8.

26. Vandenplas O, D'Alpaos V, Heymans J, et al. Sputum eosinophilia: an early marker of bronchial response to occupational agents. *Allergy* 2009;64:754-61.

27. Girard F, Chaboillez S, Cartier A, et al. An effective strategy for diagnosing occupational asthma: use of induced sputum. *Am J Respir Crit Care Med* 2004;170:845-50.

28. de Fatima Macaira E, Algranti E, Medina Coeli Mendonca E, et al. Rhinitis and asthma symptoms in non-domestic cleaners from the Sao Paulo metropolitan area, Brazil. *Occup Environ Med* 2007;64:446-53.

29. Maestrelli P, Boschetto P, Fabbri LM, et al. Mechanisms of occupational asthma. *J Allergy Clin Immunol* 2009;123:531-42; quiz 43-4.

30. Nicholson PJ, Cullinan P, Taylor AJ, et al. Evidence based guidelines for the prevention, identification, and management of occupational asthma. *Occup Environ Med* 2005;62:290-9.

31. Chiry S, Boulet LP, Lepage J, et al. Frequency of work-related respiratory symptoms in workers without asthma. *Am J Ind Med* 2009;52:447-54.

32. Makela R, Kauppi P, Suuronen K, et al. Occupational asthma in professional cleaning work: a clinical study. *Occup Med (Lond)* 2011;61:121-6.

33. Burge PS, Richardson MN. Occupational asthma due to indirect exposure to lauryl dimethyl benzyl ammonium chloride used in a floor cleaner. *Thorax* 1994;49:842-3.

34. Purohit A, Kopferschmitt-Kubler MC, Moreau C, et al. Quaternary ammonium compounds and occupational asthma. *Int Arch Occup Environ Health* 2000;73:423-7.

35. Seed M, Agius R. Further validation of computer-based prediction of chemical asthma hazard. *Occup Med (Lond)* 2010;60:115-20.

36. Fishwick D, Bradshaw L, Davies J, et al. Are we failing workers with symptoms suggestive of occupational asthma? *Prim Care Respir J* 2007;16:304-10.

37. Santos MS, Jung H, Peyrovi J, et al. Occupational asthma and work-exacerbated asthma: factors associated with time to diagnostic steps. *Chest* 2007;131:1768-75.