PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	ASTHMA RELATED TO CLEANING AGENTS: A CLINICAL INSIGHT
AUTHORS	Vandenplas, Olivier; D'Alpaos, Vinciane; Evrard, Geneviève; JAMART, Jacques; Thimpont, Joël; Huaux, François; Renauld, Jean-Christophe

VERSION 1 - REVIEW

REVIEWER	Catherine Lemiere Professor of Medicine Hôpital du Sacré-Coeur de Montréal Université de MOntréal Montreal (Qc) Canada. I do not have any competing interest in relation to this review.
REVIEW RETURNED	29-Jul-2013

GENERAL COMMENTS	This is a retrospective and descriptive study that reports and characterizes 44 cases referred for possible occupational asthma (OA) to cleaning agents in a Belgium tertiary center. The authors report the results of specific inhalation challenges, measure of airway responsiveness and sputum cell count analysis in 44 subjects exposed to cleaning agents. The diagnosis of OA to cleaning agents was made in 17 subjects (39%). The sensitizers identified were quaternary ammonium compounds, glutaraldehyde, and ethanolamine. Major comments: There is a large body of literature regarding the excess incidence of asthma in cleaners. Although this paper focused on a selected population that does not represent the general population as underlined by the authors, it has the merit to show that cleaning agent such as quaternary ammonium compounds, glutaraldehyde, and ethanolamine can induce asthma through an immunological mechanism. This paper is important for several reasons: 1. It underlines the importance of performing a thorough investigation in subjects with work-related asthma symptoms exposed to cleaning agents since removal from exposure will be important to consider in those subjects. 2. It identifies sensitizers capable of inducing asthma. Clinicians should be aware of those agents when investigating a case of asthma in cleaners. Minor comments: In the SIC negative tests 13 subjects did not have evidence of asthma whereas they seem to be still at work. It would be interesting to describe the characteristics of those subjects in a separate table to see whether they were exposed to the same type of agents and have different clinical characteristics than the subjects with asthma.

	The authors mention that they did not identify a sensitizer in one subject with OA. It would be important to report the substance to which the subject was exposed during SIC unless the SIC was performed at the workplace. This should be clarified.

REVIEWER	Susan M Tarlo, MB BS, FRCP(C), Professor of Medicine, University of Toronto, No competing interests
REVIEW RETURNED	30-Jul-2013

GENERAL COMMENTS	This is a useful retrospective review of specific challenges, performed in a specialized center over a 20 year period, for diagnosis of occupational asthma among workers with suspected occupational asthma from exposure to cleaning products. It indicates the relative frequency of positive responses and the agents identified, and suggests the mechanism is likely to be sensitization to these agents in the subjects described with positive challenges. The numbers are relatively small (44 over this 20 year period), and as the authors pint out, may not accurately represent all workers with asthma from cleaning products since they are derived only from those referred to the tertiary center for these tests. It would be helpful to the reader if the authors could give some estimate of the numbers of workers with exposure at work to cleaning products in the same linguistic and geographic region during the same time period. The authors discuss some possible reasons why others may not have been referred for these tests. Could there also be other reasons such as under-recognition of the possible role of these products in asthma? Were there any trends in the numbers seen in the more recent years? It would be helpful to have further information as to the control challenge exposure - specifically what were the chemicals in the "paint diluent" (page 7 line 21)? It would also be helpful to clarify whether the progressive exposures detailed on page 8 lines 5-7 were all on the first active challenge day or were spread over several days. Page 12 line 16 has a typographic error, should read "Medina-Ramon".

VERSION 1 – AUTHOR RESPONSE

Reviewer: Catherine Lemiere

This is a retrospective and descriptive study that reports and characterizes 44 cases referred for possible occupational asthma (OA) to cleaning agents in a Belgium tertiary center. The authors report the results of specific inhalation challenges, measure of airway responsiveness and sputum cell count analysis in 44 subjects exposed to cleaning agents. The diagnosis of OA to cleaning agents was made in 17 subjects (39%). The sensitizers identified were quaternary ammonium compounds, glutaraldehyde, and ethanolamine.

Major comments:
There is a large body of literature regarding the excess incidence of asthma in cleaners. Although this paper focused on a selected population that does not represent the general population as underlined by the authors, it has the merit to show that cleaning agent such as quaternary ammonium compounds, glutaraldehyde, and ethanolamine can induce asthma through an immunological

mechanism.
This paper is important for several reasons: 1. It underlines the importance of performing a thorough investigation in subjects with work-related asthma symptoms exposed to cleaning agents since removal from exposure will be important to consider in those subjects. 2. It identifies sensitizers capable of inducing asthma. Clinicians should be aware of those agents when investigating a case of asthma in cleaners.

Reviewer's comment:
In the SIC negative tests 13 subjects did not have evidence of asthma whereas they seem to be still at work. It would be interesting to describe the characteristics of those subjects in a separate table to see whether they were exposed to the same type of agents and have different clinical characteristics than the subjects with asthma.
Answer:
The 13 subjects with a negative SIC who failed to demonstrate significant airway hyperresponsiveness (i.e. histamine PC20 value >16 mg/ml) at the pre-challenge assessment differed from the 14 subjects with a histamine PC20 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). This information has been added to the manuscript (page 11, lines 8-12). Since this was the only significant difference between the two subgroups of subjects, a detailed table has not been added to the manuscript.

Reviewer's comment:
The authors mention that they did not identify a sensitizer in one subject with OA. It would be important to report the substance to which the subject was exposed during SIC unless the SIC was performed at the workplace. This should be clarified.
Answer:
The subject with a positive SIC response and no known sensitizing agent was actually challenged with a cleaning product that contained sodium octylsulfate [CAS No. 142-31-4], nitrilotriacetic acid [CAS No. 139-13-9], and potassium hydroxide [CAS No. 1310-58-3]. This information has been added to the revised version of the manuscript (Page 10, last lines of the 2nd paragraph).

Reviewer: Susan M Tarlo,

This is a useful retrospective review of specific challenges, performed in a specialized center over a 20 year period, for diagnosis of occupational asthma among workers with suspected occupational asthma from exposure to cleaning products. It indicates the relative frequency of positive responses and the agents identified, and suggests the mechanism is likely to be sensitization to these agents in the subjects described with positive challenges.

Reviewer's comment:
The numbers are relatively small (44 over this 20 year period), and as the authors pint out, may not accurately represent all workers with asthma from cleaning products since they are derived only from those referred to the tertiary center for these tests. It would be helpful to the reader if the authors could give some estimate of the numbers of workers with exposure at work to cleaning products in the same linguistic and geographic region during the same time period.
Answer:
Unfortunately, our data did not allow for estimating the incidence of OA among workers exposed to

cleaning/disinfecting materials. The number of workers exposed to these agents in the French-speaking part of Belgium could not be quantified since the subjects with cleaning-related asthma were employed in a wide range of occupations and industrial sectors (Discussion section, last paragraph, page 18, lines 14-18).

Reviewer's comment:
The authors discuss some possible reasons why others may not have been referred for these tests. Could there also be other reasons such as under-recognition of the possible role of these products in asthma?
Answer:
Failure to refer workers with possible cleaning-related asthma to our tertiary center 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. 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 (Discussion section, page 18, lines 2-10).

Reviewer's comment:
Were there any trends in the numbers seen in the more recent years?
Answer:
The proportion of subjects referred for possible OA due to cleaning agents among all subjects evaluated through an SIC procedure in our center 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 (16/17) had been evaluated during the last decade (2002-2011). These data suggest a trend toward an increase in the number of OA caused by cleaning/disinfecting materials in recent years. This information is now included and discussed in the manuscript (Baseline characteristics, page 10, 1st paragraph, lines 7-11 and Discussion section, last paragraph, page 18, lines 18-20).

Reviewer's comment:
It would be helpful to have further information as to the control challenge exposure - specifically what were the chemicals in the "paint diluent" (page 7 line 21)?
Answer:
The paint diluents used as "control" substance contained a mixture of alkyl esters, ketones, and aromatic hydrocarbons (page 7, lines 21-22).

Reviewer's comment:
It would also be helpful to clarify whether the progressive exposures detailed on page 8 lines 5-7 were all on the first active challenge day or were spread over several days.
Answer:
It is now clearly mentioned that 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 (page 8, line 7).

Reviewer's comment:
Page 12 line 16 has a typographic error, should read "Medina-Ramon".
Answer:
The typographic error has been corrected (page 15, line 16).