WORK-RELATED ASTHMA AND EXPOSURE TO CLEANING AGENTS IN HEALTHCARE SETTINGS – A REVIEW OF THE LITERATURE

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ABSTRACT
Health workers are exposed to a wide range of chemicals used for cleaning and disinfection. This trend has been largely attributed to the ever-increasing demand for effective cleaning and disinfection in hospital settings in an effort to prevent healthcare-associated infections. This review summarises recent findings on the association between work-related asthma and exposure to cleaning agents in healthcare settings. The review found an increasing body of evidence linking cleaning agents to adverse work-related health effects such as rhinitis, asthma and contact dermatitis. There is, however, little information on the specific cleaning agents and tasks associated with various asthma-related outcomes. In addition, few studies have conducted quantitative exposure assessments for cleaning agents in the healthcare setting. Furthermore, limited information exists regarding exposure-response relationships between the frequency of exposure to specific cleaning agents and asthma–related outcomes. There is a need for larger prospective studies in health workers exposed to cleaning agents using various clinical, physiological and inflammatory markers in order to characterise further the asthma phenotypes and the risk factors (environmental, individual) associated with these outcomes in these workers. A specific focus on and understanding of work-related dermatitis associated with such agents and its relationship to the adverse respiratory outcomes also deserves further study.

Keywords: work-related asthma, cleaning agents, exposure, healthcare setting

INTRODUCTION
Various studies have demonstrated that health workers (HWs) are at increased risk of developing work-related asthma as a result of exposure to various agents that are respiratory sensitisers or irritants. These include cleaning agents, natural rubber latex (NRL), diisocyanates, methacrylates, medications and mildew.[1–4] Exposure to cleaning agents is particularly important in healthcare settings because of the extensive use of various types of cleaning chemicals in order to comply with strict infection-prevention standards intended to prevent healthcare-associated infections.[3,5]

In the past two decades, an increasing number of case reports, epidemiological and surveillance studies have reported an increased risk of asthma, rhinitis and contact dermatitis associated with cleaning-related exposures in healthcare settings.[3,5–8] However, only a limited number of studies have investigated the specific cleaning agents associated with work-related asthma in HWs.

SEARCH STRATEGY
Published studies were identified from several literature sources, including PubMed, Cochrane Library, Embase and Google Scholar, using various key words: allergy, asthma, occupational asthma, work-related asthma, cleaning agents, cleaning products, disinfectants, sterilants, chlorhexidine, ortho-phthalaldehyde, glutaraldehyde. Reference lists from the articles obtained were also analysed for relevant studies. This review is an update of a previous study[9] that was published in 2013. The selection of articles to be included in the review was not restricted to any time period. However, epidemiological studies that investigated work-related asthma associated with cleaning agents in the healthcare setting during the past 15 years (2004–2019) are summarised in Table I below.

WORKING POPULATIONS AT RISK
In the healthcare sector, cleaning is one of the most important tasks and it is performed by many HWs from various occupations. HWs considered to be potentially at increased risk include

nurses, cleaners, endoscopy technicians, dental assistants, medical equipment preparers, physicians and respiratory therapists.[10,11] A previous US study[10] demonstrated that, among nurses, registered nurses had the highest prevalence of reported asthma (10.2%), followed by licensed vocational nurses (8%) and nurse practitioners and nursing assistants (6.9%). The authors did not explain the reason(s) for differences in the prevalence of reported asthma among these groups of nurses in this study[10] and perhaps they were not well understood at the time. Studies among cleaners working in hospitals have reported higher odds (odds ratio (OR) = 2.1; 95% CI: 1.1 to 4.2) of having current asthma.[12]

EXPOSURE CHARACTERISATION FOR CLEANING AGENTS

The assessment of exposure to cleaning agents has been challenging, partly because of the fact that many cleaning agents containing different ingredients are used simultaneously in the healthcare setting. Airborne exposures generated in these settings are commonly a complex mixture of various chemicals with different physicochemical properties requiring different sampling techniques.[13,14] Another challenge is that the type of product used, its frequency and its duration of use usually vary, depending on the specific cleaning task performed.[13,15] Commonly, several cleaning tasks are performed in a single room and may be repeated several times a day. Furthermore, HWs may use cleaning agents differently, resulting in varying amounts of chemical exposures for a single category of HW. As a result, very few studies have conducted quantitative exposure assessments for cleaning agents in the healthcare setting. In a case-control study among Spanish cleaners, airborne exposure levels of both chlorine (median: 0–0.4 ppm) and ammonia (median: 0.6–6.4 ppm) were detectable in domestic cleaning that made use of products containing bleach and ammonia.[16]

There is limited information about assessing environmental exposure to aldehydes such as glutaraldehyde (GTA) and ortho-phthalaldehyde (OPA). In a study of various endoscopy units in an Italian hospital,[17] detectable GTA levels (mean 0.005 ppm) were slightly higher than in the US study[18] of HWs from eight healthcare facilities (range: not detected – 0.005 ppm). However, much higher GTA levels (geometric mean (GM) = 0.025 ppm) were reported in a Canadian study of five hospitals.[19]

Studies that have measured the OPA exposure in air are more evident.[18,20–25] The mean OPA concentration reported in a previous Italian study among HWs in endoscopy units was 0.0015 ppm.[17] A Japanese study reported OPA concentrations in the range of 0.0006–0.002 ppm in an endoscopy unit.[26] The highest concentration (0.002 ppm) was found when a bucket containing OPA was left open without a lid while an endoscope washing machine was operating.[26] A later Japanese study observed higher concentrations of OPA in the manual group (median = 0.0007 ppm) than in the automatic endoscopic washer group (median = 0.0003 ppm).[23] In the US study, the average OPA concentrations were higher (GM = 0.00006 ppm) in the group of workers from the departments using OPA than in the comparison group (GM = 0.00003 ppm) where OPA was not used.[18]

Despite the presence of commercially available passive samplers, the literature search did not find any study that has measured OPA in the air using the passive (diffusive) sampling method. However, studies on passive sampling for formaldehyde and GTA have been reported.[27,28] Previous studies comparing the performance of passive sampling and active (pump) sampling methods for formaldehyde have shown good agreement between the two assessment methods.[27] However, a recent study demonstrated that passive sampling generally overestimated the formaldehyde concentrations when compared to the active method.[29]

Chlorhexidine is one of the most commonly used agents for hand hygiene and patient-care activities such as disinfecting wounds and patients' skin prior to various medical procedures.[30] The most appropriate method of estimating exposure to chlorhexidine is to conduct biological exposure monitoring. Environmental air sampling is considered inappropriate since chlorhexidine has a low likelihood of being aerosolised, given its very much lower vapour pressure. However, only a few studies have used chlorhexidine biomonitoring.[31] Some of these researchers have been able to identify chlorhexidine and its metabolites (*p*-chloroaniline and 1-chloro-4-nitrobenzene) in biological fluids but challenges have arisen in quantifying the concentration of these chemicals.[31–33]

EPIDEMIOLOGY OF ASTHMA RELATED TO CLEANING AGENTS

In the past two decades, few epidemiological studies have investigated the magnitude of asthma among HWs exposed to various cleaning agents. The most recent are summarised in Table I below. The prevalence of new-onset asthma (an asthma attack or taking asthma medication in the past 12 months) among nurses was found to be 4.8% in a prospective population-based European study.[34] A more detailed analysis of HWs from this study[35] reported a slightly higher prevalence (6%) of new-onset asthma (those currently taking asthma medication, having experienced an asthma attack or having been woken up by an attack of shortness of breath in the past 12 months). This is most likely a result of different asthma definitions used. These findings are similar to those of a US-based study among HWs with active professional licences,[1] which demonstrated an overall prevalence of doctor-diagnosed asthma with onset after entry into the healthcare profession to be 6.6%. The highest prevalence was observed among nurses (7.3%) followed by respiratory therapists (5.6%), occupational therapists (4.5%) and doctors (4.2%).

However, a study of the same US population of HWs published two years later reported a much higher prevalence of diagnosed asthma with onset after entry into the healthcare profession (9.8%) among nurses, based on the longest job held.[10] Overall, the prevalence of asthma in HWs exposed to cleaning agents has ranged between 4.4% and 11.2% (current asthma: 4.8–11%; doctor-diagnosed asthma: 9–11.2% and doctor-

TABLE I: RECENT EPIDEMIOLOGICAL STUDIES ON WORK-RELATED ASTHMA ASSOCIATED WITH CLEANING AGENTS IN THE HEALTHCARE SETTING

AUTHOR/ YEAR	POPULATION (N)	PREVALENCE OF ASTHMA PHENOTYPES/ SYMPTOMS	HIGH-RISK ACTIVITIES SIGNIFICANTLY ASSOCIATED WITH ASTHMA OR/RR (95% CI)	CLEANING AGENTS SIGNIFICANTLY ASSOCIATED WITH ASTHMA OR/RR/MR (95% CI)	TOOLS USED FOR ASSESSMENT OF EXPOSURE AND ASTHMA-RELATED OUTCOMES
Dumas et al 2018[30]	Nurses (n = 4 055)	Prevalence not specified. Asthma control was defined by Asthma Control Test (ACT)	Surgical hand/arm hygiene ≥1 time/day: 1.96 (1.52–2.51) <1 time/day: 1.38 (1.06–1.80)	Not specified	Questionnaire
Dumas et al 2017[38]	Nurses (n = 4 102)	Prevalence not specified. Asthma control was defined by ACT	Use of disinfectants for medical instruments: 1.88 (1.38–2.56)	Formaldehyde: 1.33 (1.05–1.68) Enzymatic cleaners: 1.33 (1.12–1.57) Hydrogen peroxide: 1.19 (1.04–1.36) Glutaraldehyde: 1.18 (1.03–1.34) Hypochlorite bleach: 1.18 (1.03–1.36)	Questionnaire Job-task-exposure matrix
Lee et al 2014[39]	Hospital cleaners (n = 183)	Prevalence not specified. Chemical-related symptoms (respiratory, ocular, dermal, neurological and gastrointestinal) in the past 12 months	Sprays: 2.82 (1.16–6.82)	Carpet cleaners: 2.98 (1.28–6.92) Solvents: 2.71 (1.20–6.15) Multi-purpose cleaners: 2.58 (1.13–6.92)	Questionnaire
Gonzalez et al 2014[36]	Health workers (n = 543)	Physician-diagnosed asthma: 11.2% Physician-diagnosed asthma with onset after entry in the healthcare sector (new-onset asthma): 4.4%	Dilution of disinfectants: 4.01 (1.34–12.00) General disinfection tasks: 3.16 (1.17–8.52)	Quaternary ammonium compounds: 7.56 (1.84–31.05)	Questionnaire Workplace observations
Arif and Delclos 2012[40]	Health workers (n = 3650)	WRAS: 3.3% WEA: 1.1% OA: 0.8%	Not specified	Chloramines: 4.81 (1.28–18.06) Cleaners for restrooms and toilets: 4.60 (2.12–9.95) Bleach: 3.72 (1.70–8.12) Ethylene oxide: 2.97 (1.21–7.33) Detergents: 2.84 (1.33–6.08) Formaldehyde: 2.66 (1.03–6.86) Cleaners/abrasives: 2.50 (1.19–5.25) Ammonia: 2.45 (1.28–4.69) Glutaraldehyde/OPA: 2.18 (1.17–4.07)	Questionnaire
Dumas et al 2012[41]	Health workers (n = 724)	Asthma and report of asthma attacks, respiratory symptoms or asthma treatment in the past 12 months: Men: 39.5% Women: 31.6%	General cleaning/ disinfecting tasks: 2.32 (1.11–4.86)	Ammonia: 3.05 (1.19–7.82) Sprays: 2.87 (1.02–8.11) Decalcifiers: 2.32 (1.01–5.31)	Questionnaire Expert assessment *Asthma-specific JEM*
Vizcaya et al 2011[12]	Professional cleaners, including hospital cleaners (n = 917)	Doctor-diagnosed asthma: 9% Asthma attack in the past 12 months or woken by an attack of shortness of breath in past 12 months or currently taking any medicine for asthma: 11% Asthma, with the first asthma attack at the age of 16 years or later: 5%	Hospital cleaners (activities not specified): 2.1 (1.1–4.2)	Carpet cleaners: 2.2 (1.0–5.1) Hydrochloric acid: 1.7 (1.1–2.6); Ammonia: 1.6 (1.0–2.5) Degreasers: 1.6 (1.0–2.4) Multiple purpose products: 1.6 (1.0–2.5) Waxes: 1.6 (1.0–2.6) Air fresheners: 1.5 (1.0–2.4) Perfumed products: 1.5 (1.0–2.4)	Questionnaire
Arif et al 2009[10]	Health workers (n = 3 634)	Doctor-diagnosed asthma with onset after entry into the healthcare profession: 9.8% among nurses BHR-related symptoms: 31.3% among nurses	Building surface cleaning: 1.72 (1.00–2.94) Medical instrument cleaning: 1.67 (1.06–2.62)	Adhesives, glues and/or solvents for patient care: 1.51 (1.08–2.12)	Questionnaire JEM

TABLE I: CONTINUED

AUTHOR/ YEAR	POPULATION (N)	PREVALENCE OF ASTHMA PHENOTYPES/ SYMPTOMS	HIGH-RISK ACTIVITIES SIGNIFICANTLY ASSOCIATED WITH ASTHMA OR/RR (95% CI)	CLEANING AGENTS SIGNIFICANTLY ASSOCIATED WITH ASTHMA OR/RR/MR (95% CI)	TOOLS USED FOR ASSESSMENT OF EXPOSURE AND ASTHMA-RELATED OUTCOMES
Delclos et al 2007[1]	Health workers (n = 3 650)	Doctor-diagnosed asthma with onset after entry into the healthcare profession: Overall: 6.6% Nurses: 7.3% Respiratory therapists: 5.6% Occupational therapists: 4.5% Physicians: 4.2% BHR-related symptoms: overall 27.4%	Medical instrument cleaning: 2.22 (1.34–3.67) Building surface cleaning: 2.02 (1.20–3.40)	Chemical spills: 2.02 (1.28–3.21) Adhesives for patients' care: 1.65 (1.22–2.24)	Questionnaire JEM
Kogevinas et al 2007[34]	General population (n = 6 837)	Asthma attack or taking asthma medication in the past 12 months: 4.8% among nurses	Acute symptomatic inhalational event: 3.33 (1·00–11·13) Nursing (activities not specified): 2.22 (1.25–3.96)		Questionnaire JEM Expert assessment Methacholine challenge test
Mirabelli et al 2007[35]	General population (n = 2 813)	Asthma attack in the past 12 months or woken by an attack of shortness of breath in past 12 months or currently taking any medicine for asthma: 6% among nurses	Not specified	Ammonia and/or bleach: 2.16 (1.03–4.53)	Questionnaire IgE test to common aeroallergens
Delclos et al 2006[42]	Health workers (n = 118)	Self-reported history of asthma: 22.9% Prior physician diagnosis of asthma: 20.3% PC_{20} ≤ 8 mg/mL: 55.1% PC_{20} ≤ 4 mg/mL: 48.3%	Not specified	Not specified	Questionnaire Industrial hygienist interview Methacholine challenge test IgE test to common aeroallergens IgE test to latex

Bronchial hyper-responsiveness (BHR) -related symptoms: combination of eight questions on asthma and allergy symptoms that had exhibited the best combination of sensitivity and specificity when compared to non-specific bronchial challenge testing with methacholine.
WRAS (work-related asthma symptoms): wheezing or whistling *or* shortness of breath at work that gets better when away from work or worsens on return to work.
WEA (work-exacerbated asthma): wheezing *or* whistling *or* shortness of breath at work that gets better when away from work or worsens on return to work *and* physician diagnosis of asthma *and* onset of asthma before entry into healthcare profession.
OA (occupational asthma): wheezing *or* whistling or shortness of breath at work that gets better when away from work or worsens on return to work *and* physician diagnosis of asthma *and* onset of asthma after entry into healthcare profession.
PC_{20}: provocative concentration of methacholine that produced a 20% or greater decrease in forced expired volume in one second (FEV1) from the baseline.
JEM: job-exposure matrix; **IgE**: Immunoglobulin E; **OR**: odds ratio; **RR**: risk ratio; **MR**: mean ratio

diagnosed asthma with onset after entry into the healthcare profession: 4.4–9.8%) (see Table I).[1,10,12,34–36] Little is known about the magnitude of the asthma among HWs in Africa. However, in a recent South African study among dental HWs,[37] the prevalence of atopic asthma was 6.9%, non-atopic asthma 5.9% and work-exacerbated asthma 4%.

PATHOPHYSIOLOGICAL MECHANISMS

Despite the increasing number of studies linking asthma and exposure to cleaning agents, the pathophysiology of asthma associated with cleaning agents is not well characterised. An immunoglobulin E (IgE) -mediated mechanism has been demonstrated for occupational asthma caused by high molecular weight (HMW) agents such as NRL (commonly associated with donning gloves when using cleaning agents) and proteolytic enzymes.[43,44] IgE-mediated immunological mechanisms are also believed to play a major role in occupational asthma induced by some low molecular weight (LMW) agents in non-healthcare settings.[43] However, only a small proportion of individuals with occupational asthma due to most LMW agents have specific IgE in the serum, suggesting that an IgE-independent immunological mechanism (probably involving cell-mediated and mixed Th1 and Th2 responses) may be playing a greater role.[43,45] Furthermore, the mechanism of asthma caused by non-immunological (irritant) mechanisms is also not clearly understood. However, it is believed that irritants (such as common cleaning agents – bleach and ammonia) can destroy bronchial epithelium, in this way exposing nerve endings, and subsequently trigger a neurogenic inflammation characterised by bronchoconstriction, increased mucus secretion and oedema, which are typical features of asthma.[43,46] Oxidative stress resulting from a persistent imbalance between antioxidants and pro-oxidants as well as the dual irritant and adjuvant effects of some of these chemicals (eg formaldehyde and OPA) are also thought to play a role in the pathogenesis of irritant-induced asthma.[3,47–49] It is therefore likely that IgE-independent immunological and irritant mechanisms play a greater role in asthma associated with cleaning agents as most cleaning agents are of LMW.

Experimental studies in mice have shown that some common disinfectants such as GTA and OPA are both dermal and respiratory irritants and sensitisers.[24] Suzukawa et al[50] detected specific IgE to OPA in all three patients who developed anaphylaxis due to OPA. In a recent US study, 5 (4%) HWs had positive skin responses to skin-prick tests (SPTs) with OPA solution but it is of note that none had detectable specific IgE and IgG antibodies in any of the blood samples tested.[18] Furthermore, the clinical history in the case reports of asthma due to OPA and GTA also demonstrated a latency period between first exposure to these agents and the development of symptoms – implying an allergic response associated with these agents.[50,51] Late reactions were also observed in patients that underwent a specific inhalation challenge test to GTA, which alludes to an underlying immunological mechanism.[51]

Nagendran et al also identified four cases of occupational IgE-mediated allergy to chlorhexidine among 53 HWs in a hospital in the United Kingdom.[52] In this study, three of the cases had positive reactions to SPTs, whereas two had positive sIgE tests.[52] Wittczak et al also described three cases of occupational allergy among HWs.[53] While a serum sIgE test to chlorhexidine was positive in all three identified cases, only two had a positive SPT.[53] There have been no African studies that have conducted immunological assessments for chlorhexidine in HWs and their association with occupational asthma.

ASTHMA PHENOTYPES

It is well known that asthma is a heterogeneous disease with diverse clinical, physiological and inflammatory characteristics.[54–56] A number of studies have reported various phenotypes for non-work-related asthma, with significant efforts directed towards characterising the severe asthma phenotypes.[55,56] However, studies that have investigated occupational asthma phenotypes are fairly limited and most of them have characterised only occupational asthma based on its aetiological agent (eg high molecular weight and low molecular weight agents) or according to allergic versus irritant mechanisms.[4,54,57,58] The published literature on asthma phenotypes in HWs exposed to cleaning agents is even more scant.[3]

WORKPLACE ENVIRONMENTAL RISK FACTORS AND CAUSATIVE AGENTS

With the decrease in the incidence of NRL allergy reported in recent studies, cleaning agents have increasingly been considered a major risk factor for WRA among HWs.[3] The extent of exposure to cleaning agents and other asthmagens in the healthcare setting, other than NRL and its association with WRA, is not well characterised. However, few studies in developed countries have attempted to investigate this subject.[35,40] Cross-sectional studies in the United States have reported that, aside from powdered latex-glove usage, occupational exposure to cleaning agents and the use of adhesives/solvents are related to asthma after entry into the healthcare profession.[1,10]

HAZARDOUS WORKPLACE ACTIVITIES

Previous studies in healthcare settings have identified a number of broad categories of chemical exposure associated with cleaning-related activities such as

- medical instrument cleaning and disinfection;
- fixed surfaces cleaning and disinfection;
- floor-finishing tasks (stripping, waxing and buffing);
- patients' skin/wound cleaning and disinfection;
- specimen preparation and hand hygiene.[10,30,38]

Furthermore, accidental chemical exposures and spills are another context for high-risk workplace exposures.[10]

EXPOSURE TO HAZARDOUS AGENTS (ASTHMAGENS)

Over the years, various studies have demonstrated that the development of occupational asthma is related primarily to the level of exposure to a specific workplace agent, and less so to individual factors such as atopy and smoking, which have produced inconsistent results in a number of studies.[59,60] Broad groups of asthmagens in healthcare settings include (Table II):

TABLE II: CLEANING AGENTS ASSOCIATED WITH WORK-RELATED ASTHMA IN HEALTHCARE WORKERS

INSTRUMENT CLEANING/ DISINFECTION	FIXED-SURFACE CLEANERS	ADHESIVE REMOVERS AND HAND CLEANERS/ DISINFECTANTS
Glutaraldehyde Hydrogen peroxide Isopropanol Ortho-phthalaldehyde Peracetic acid/acetic acid Quaternary ammonium compounds Sodium sesquicarbonate Subtilisins (enzymatic cleaners)	Acetic acid/acetic acid anhydride Ammonia/ammonium hydroxide Bleach Butyl paraben, ethyl paraben, methyl paraben Diethanolamine Diethylene-glycol n-butyl ether Hydrochloric acid Isoparaffinic hydrocarbons Phosphoric acid Quaternary ammonium compounds Sodium sulfate Sulfuric acid	Adhesive removers • Acetone • Dipropylene glycol methyl ether • Ethanol • Isoparaffinic hydrocarbons • Isopropanol Stoma care products • Carboxymethyl ether • Hexane-based skin bond • Methylbenzene Hand cleaners/disinfectants • Alcohols • Chlorhexidine • Povidone iodine • Triclosan Other • Methylene chloride • Trichloroethane

Source: Modified from Delclos et al[1]

Figure 1a: Cleaning medical instruments using enzymatic cleaners before high-level disinfection

Figure 1b: Medical instruments in the OPA containers for high-level disinfection

Figure 1c: Changing solution of a high-level disinfectant (OPA)

- fixed-surfaces cleaning products (eg bleach);
- disinfectants and sterilants (eg GTA and OPA);
- hand cleaners (eg chlorhexidine, triclosan);
- aerosolised medications (eg pentamidine);
- methacrylates in dental and surgical cements;
- NRL products;
- micro-organisms and mildew.[1,3]

Most cleaning agents are irritants; however, some have both irritant and sensitising properties. Common irritants encountered in cleaning agents include chlorine (bleach), ammonia, hydrochloric acid, monochloramine, sodium hydroxide, quaternary ammonium compounds (QACs) and monoethanolamine.[6] Some of the known sensitisers in cleaning agents include:

- disinfectants (eg GTA and OPA);
- scents (eg pinene, d-limonene, eugenol);
- QACs;
- preservatives (eg isothiazolinones and formaldehyde); and
- monoethanolamine.[6]

Whereas the chemical products used in the healthcare setting may not always be generalisable across hospitals in different countries, the active ingredients in these cleaning products are often similar across hospitals.

Medical instrument cleaning/disinfecting agents

HWs, especially nursing personnel and endoscopy technicians, are exposed to cleaning agents used for the high-level disinfection of heat-sensitive medical instruments such as endoscopes (see Figure 1a–c). Some of the common agents used for medical instrument disinfection include GTA, OPA, hydrogen peroxide and QACs. GTA has been used for more than 40 years in healthcare settings, not only for the disinfection of medical instruments but also as a fixative for electron microscopy and X-ray films. Several clinical case reports have been reported in the literature linking GTA and various health effects such as occupational asthma[61,62] and allergic contact dermatitis.[63] In 1999, the US Food and Drug Administration (FDA) approved OPA for use as a high-level disinfectant. Subsequently, OPA was considered a safer replacement for GTA and is increasingly being used.[24] However, OPA has recently also been reported to cause occupational asthma[20,64] and anaphylaxis[50,65–67] in various case reports, including patients undergoing instrument procedures. In a Japanese study among HWs responsible for endoscope disinfection, 24% had work-related skin, respiratory or eye symptoms resulting from OPA.[26] Work-related symptoms due to OPA were also reported in another Japanese study among HWs from endoscopy units, with respiratory symptoms being in the majority (16%), followed by skin (10%) and eye (9%) symptoms.[23]

Other cleaning agents used for disinfecting medical instruments include:

- QACs;
- hydrogen peroxide;
- a mixture of hydrogen peroxide and peracetic acid;
- a mixture of hydrogen peroxide, peracetic acid and acetic acid.

Respiratory and ocular symptoms have been reported in individuals exposed to hydrogen peroxide and a mixture of hydrogen peroxide, peracetic acid and acetic.[68,69] In recent years, there has been an increase in the use of enzymatic cleaners for pre-cleaning medical instruments prior to high-level disinfection in healthcare settings.[1,70] Two studies have reported cases of occupational asthma and rhinitis among HWs using enzymatic cleaners.[70,71] Exposure to proteolytic enzymes has long been recognised as a cause of allergic respiratory and skin symptoms, particularly among workers involved in manufacturing detergents.[1,70]

Various epidemiological studies and surveillance systems have also demonstrated an association between various asthma-related outcomes and cleaning agents used for medical instrument disinfection.[10,38,72,73] In a recent study among US

nurses,[38] medical instrument disinfection (OR = 1.88; 95% CI: 1.38–2.56) and exposure to formaldehyde, glutaraldehyde, hypochlorite bleach, hydrogen peroxide and enzymatic cleaners was associated with poor asthma control. Furthermore, a previous US study[10] reported a significantly higher odds of reported asthma among HWs exposed to medical-instrument cleaning agents (OR = 1.67; 95% CI: 1.06–2.62). Of the occupational asthma cases reported to a surveillance system in the United Kingdom 6% were attributable to GTA.[72] Although not specified, it is probable that most, if not all, of these cases were from heathcare settings, where GTA was commonly used.

Fixed-surface cleaning agents

Fixed-surface cleaning is an inherent aspect of the activities performed in the healthcare setting. Cleaners are widely reported to be a high-risk occupation in both industrialised and developing countries.[3,74–76] In a US study,[77] cleaners formed the largest (22%) occupational group in which exposure to cleaning products was associated with WRA, followed by a group of nurses and nurse aides (20%). In this study, the health sector had the highest number (39%) of patients with WRA due to cleaning products.

Bleach, ammonia and hydrochloric acid were reported as the most commonly used agents for fixed-surface cleaning, with airborne chlorine and ammonia being detected during cleaning activities.[78] Another study among cleaners also reported an increased risk of asthma symptoms in workers who used:

- hydrochloric acid (mean ratio (MR) = 1.7; 95% CI: 1.1–2.6);
- degreasers (MR = 1.6; 95% CI: 1.0–2.4);
- air fresheners (MR = 1.5; 95% CI: 1.0–2.4);
- or ammonia (MR = 1.6; 95% CI: 1.0–2.5) in the past year.[12]

A number of studies have demonstrated a positive association between the use of cleaning sprays and asthma or respiratory symptoms.[38,79,80] The use of sprays generates more aerosols and therefore facilitates inhalational exposure.

Surface-cleaning agents comprised the most common group of agents reported (20.5%) among individuals with suspected occupational asthma presenting with acute asthma in South Africa.[81] Kogevinas et al[34] demonstrated a 1.8-fold (RR = 1.80; 95% CI: 1.01–3.18) increased relative risk for asthma with the use of cleaning products. A similar finding was observed among US nurses in a study[10] that showed a significantly higher odds of reported asthma for exposure to fixed-surface cleaning agents and disinfectants (adjusted OR = 1.72; 95% CI: 1.00–2.94). In a population-based European study, nurses who reported using ammonia and/or bleach were found to have a more than two-fold (RR= 2.16; 95% CI: 1.03–4.53) increased risk of developing new-onset asthma.[35] An increased relative risk for asthma (RR = 1.51; 95% CI: 1.36–1.66) has also been reported among cleaners in the Finish healthcare setting.[82]

New asthmagens can be produced when different cleaning agents are mixed together.[6] Chloramines may be released when hypochlorite from bleach is mixed with ammonium salts from cleaning products or body fluids.[6] Chloramines have been reported to cause occupational asthma among pool workers.[83] Recently, increased numbers of occupational asthma cases have been reported among cleaners who used chlorine-based cleaning agents (sodium hypochlorite and sodium dichloroisocyanurate).[73] Interestingly, specific bronchial challenge tests to these cleaning agents were negative and became positive only when challenged with a mixture of urine- and chlorine-based cleaning agents (and therefore producing chloramines).[84] On the other hand, chlorine, a common respiratory irritant, is generated when acid is mixed with bleach.[77] The application of some cleaning agents can also yield high levels of volatile organic compounds (VOC) that can also act as airway irritants.[6,85] This suggests that there is the potential for multiple exposures among workers who are involved in cleaning-related tasks.

Patient skin/wound cleaning and disinfection agents

Chlorhexidine, povidone iodine and alcohols are one of the most commonly used agents for disinfecting wounds and patients' skin prior to various medical procedures. Walk-through surveys performed by occupational hygienists in US hospitals revealed that routine patient-care activities performed by nurses often included the use of adhesives and adhesive removers, particularly in surgical and intensive-care units (ICUs).[1,10] These compounds may contain respiratory irritants such as dimethyl ether, dipropylene glycol methyl ether and isoparaffinic hydrocarbons. Arif et al[10] also found an almost two-fold increased odds of asthma among nursing professionals who were exposed to adhesives, adhesive removers and/or solvents. Furthermore, Pechter et al[86] reported that exposure to solvents accounted for 7% of reported WRA, and various chemicals (including glues and solvents) were associated with asthma among 29% of aides and therapists in the United States.

Hand hygiene (hand-washing/sanitising) agents

Exposure to chemicals contained in hand hygiene products is quite common in hospital settings since HWs are required to wash and disinfect their hands several times per day in order to comply with infection control standards. Alcohols and chlorhexidine are the most commonly used agents for hand hygiene in hospital settings.[30,52,53] Chlorhexidine is a known sensitiser and irritant to both the skin and the airways.[30] There have been a few published reports of asthma and dermatitis due to chlorhexidine, mostly among patients and few occurring in HWs.[52,53,87–89] Povidone iodine is also used commonly for hand-washing;[30] it is a well-known skin irritant but its sensitising properties have not been well characterised.[90] Triclosan, also used as a hand cleaner in the healthcare setting, has been implicated in causating adverse health effects to the skin such as allergic contact dermatitis and contact urticaria as well as occupational asthma.[91–94]

DOSE–RESPONSE RELATIONSHIPS

Little is known about the exposure–response relationship between exposure to specific cleaning agents and asthma-related outcomes. A few studies have only reported exposure-response relationships for broad categories of cleaning-related exposure with limited information on specific cleaning agents.[40] Arif et al demonstrated exposure–response relationships for work-exacerbated asthma in HWs who used disinfectants to disinfect medical instruments and for work-related asthma symptoms in HWs who used cleaning agents for cleaning or disinfecting fixed surfaces.[40] Medina-Ramon et al demonstrated a dose–response relationship between the use of bleach and asthma among domestic cleaners in Spain.[16] Similarly, Zock et al demonstrated dose–response relationships for asthma with the frequency of use of cleaning sprays and also with an increase in the number of the types of spray used.[95] In a recent study by Dumas et al, poor asthma control was positively associated with an increased frequency in hand-hygiene practices among US nurses, with a clear dose–response relationship demonstrated for surgical hand/arm hygiene.[30]

INDIVIDUAL RISK FACTORS

Common individual factors that have been associated with asthma include age, gender, seniority, smoking status and atopy.[1,10] Delclos et al[1] demonstrated that increasing seniority was positively associated with reported asthma. In a study of workers across different industries, atopic individuals had a significantly higher relative risk (RR = 2.9; p-value = 0.019) for new-onset asthma than non-atopics.[34] The study also demonstrated an increased risk of new-onset asthma in participants with a parental history of asthma (RR = 2.1) and in non-smokers (RR = 1.8).

There is inconsistent evidence with regard to the association between smoking and asthma in general and with occupational asthma in particular.[3,54,96] Whereas some studies have demonstrated that smoking at baseline increased the risk of incident asthma in adulthood, no significant association was reported in a follow-up cross-sectional analysis.[97] Furthermore, limited specific information is available on the risk of smoking in relation to asthma among HWs exposed to cleaning agents.[96,98] The study by Zock et al of cleaning workers did not demonstrate any association between smoking and asthma.[98]

Risk factors for non-work-related adult-onset asthma and occupational asthma have also been reviewed in a comparative manner.[54] This review found that while individual factors (eg age, gender, genetics, atopy and obesity) did not differ for these two broad asthma phenotypes, environmental factors appeared to play a very important role in occupational asthma. Recently, Rava et al[99] identified novel genes associated with adult asthma related to occupational exposure to LMW agents/irritants in three large European cohorts (Epidemiological family-based study of the Genetics and Environment of Asthma, Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults and ECRHS.)

Female HWs appear to be more affected than men. In a study of US HWs, females had a higher prevalence of all asthma phenotypes that included WRA symptoms (3.6% vs 1.8%), work-exacerbated asthma (1.3% vs 0.3%) and occupational asthma (1.0% vs 0.1%) than their male counterparts.[40] Similar findings were reported in a large European study[34] that found a slightly higher relative risk of new-onset asthma among women (RR = 1.13) compared to men. It is likely that the gendered distribution of work plays a role. Interestingly, female sex hormones have been implicated in the pathogenesis.[54]

PREVENTION

Several studies have proposed preventive strategies for work-related asthma related to cleaning agents.[3,5,100] However, not enough effort has been directed towards the implementation of the suggested preventive strategies that target relevant stakeholders such as government agencies, manufacturers of cleaning products, suppliers and commercial cleaning companies.[3,5]

Primary prevention is usually the most effective strategy but not always feasible.[101] Some of the primary prevention strategies that have been proposed include *substitution* of certain cleaning agents such as glutaraldehyde, QACs, bleach and ammonia with less hazardous agents.[3,5] One of the challenges of this method has been the difficulties associated with finding the proper alternative cleaning agent(s) and the lack of information regarding the health effects of the newer cleaning agents. This has led to the replacement of a known hazard, such as GTA, with a potentially unknown hazard (eg OPA), that was later demonstrated to cause similar health effects.[24] Quantitative structure-activity software that can predict the sensitisation potential of chemicals may be very useful in making decisions about new cleaning agents to be introduced in workplaces.[102] Avoiding the mixing of cleaning products such as bleach and ammonia has also been strongly advocated.[5,6]

Engineering controls are very important in reducing cleaning-related exposures. Ideally, proper *ventilation* should be maintained in all areas where cleaning agents are used. However, this is fairly rare, since cleaning agents are used almost everywhere. Local exhaust ventilation (LEV) systems should be installed in certain dedicated areas where specific cleaning and disinfection is performed regularly, such as in areas where medical instrument cleaning and disinfection is taking place. A recent US study[18] has proposed specific ventilation standards for areas where OPA is used for the high-level disinfection of medical instruments. Since exposure to cleaning sprays is an important risk factor for work-related asthma,[95] the use of wipes rather than sprays could be very effective in reducing the burden of work-related asthma due to cleaning agents.

Administrative controls such as:

- providing *occupational health and safety* (OHS) education;
- establishing written policies on how to use cleaning agents properly;
- supervising cleaners to ensure that proper *work practices* are followed while working with cleaning agents; and

- exercising preventive maintenance of ventilation systems is also very important in preventing work-related asthma associated with cleaning agents.

However, little is known regarding the effectiveness of the suggested administrative control measures in reducing incidence of WRA related to cleaning agents. An intervention involving collaboration between a cleaners' union and other stakeholders, including OHS technical personnel, in the United States was successful in eliminating the use of the most hazardous cleaning agents, reducing the number of different cleaning agents used, banning the mixing of cleaning agents and enhancing safety training.[103]

It is well known that the use of personal protective equipment (PPE) is the least effective method of controlling work-related hazards. The full support of the employer with the involvement and commitment of employees is required to ensure the proper use of PPE. Its use is usually advised since the most effective means for controlling cleaning-related exposures such as engineering methods are usually absent in most workplaces. Some of the PPE advised for controlling cleaning-related exposures include use of proper respirators with vapour and gas cartridges, eye protection (eg goggles or face shields), fluid-repellent gowns or aprons, proper gloves (eg nitrile gloves) and proper shoes.[18]

Medical surveillance for HWs who work regularly with cleaning agents is also recommended. The aim of this mode of secondary prevention is to detect the disease at an early stage in order to prevent the development of severe adverse health effects. Occupational health practitioners can use medical surveillance information to determine the effectiveness of the available preventive measures. Questionnaire interviews and spirometry are commonly used for medical surveillance in various workplaces. However, the use of immunological tests can be very helpful in the surveillance of HWs using cleaning agents with sensitising properties.[104,105]

CONCLUSION

Cleaning agents have emerged as one of the leading causative agents of WRA among HWs because of their extensive use in the healthcare settings. More efforts need to be directed towards characterising cleaning-related exposure in a more detailed manner so as to obtain more specific information such as cleaning agents and tasks associated with WRA in HWs as well as the frequency and duration of use. Furthermore, future studies need to use more objective measures of assessing exposure for cleaning agents in the healthcare setting. There is a need for larger prospective studies in HWs exposed to cleaning agents using various clinical, physiological and inflammatory markers such as fractional-exhaled nitric oxide (FeNO), serum-specific IgE or SPTs, sputum eosinophils, serum periostin and lung-function testing in order to characterise further the asthma phenotypes in these workers. In addition, more efforts need to be directed towards characterising exposure–response relationships and individual risk factors (eg atopy, gender, smoking) in HWs exposed to cleaning agents. More studies are needed to gain a better understanding of the association between novel genes and adult-onset asthma due to occupational exposure to low-molecular weight agents or irritants in order to develop more specific preventive strategies for WRA associated with cleaning agents in healthcare settings.

DECLARATION OF CONFLICT OF INTEREST
The authors declare no conflict of interest.

This article has been peer reviewed.

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