Update on effects of cleaning agents on allergy and asthma

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ABSTRACT

Background: Cleaning and disinfecting agents are widely used in modern life, in homes, schools, public places, and workplaces as well as in recreational facilities such as swimming pools. Use has been for sanitizing purposes and to assist in reduction of infection as well as for deodorizing purposes. However, adverse respiratory effects have been associated with use of cleaning products ranging from effects in infancy and early childhood up to adults at home and work.

Methods: This review summarizes recent published literature on the effects of cleaning agents used pre-natally, in childhood and adult life, at home, work, and in swimming pools.

Results: Several studies have indicated that there is an increased risk of developing asthma among adults with frequent exposure to cleaning products at work and in the home. Potential mechanisms include sensitization and respiratory irritant effects. Exposure to irritant chlorine by-products from swimming pools have also been associated with respiratory effects and increased risk of asthma. Potential effects from maternal exposures to cleaning products on infants, and effects on early childhood atopy are less clear.

Conclusions: Exposure to cleaning agents increases relative risks of asthma among workers, and adults using these agents in the home. Risks are also increased with exposure to chlorinated by-products from swimming pools, both in adults and children. Further studies are needed to understand the mechanisms of these associations.

Introduction

Cleaning and disinfecting agents are widely used in modern life, in homes, schools, public places, and workplaces as well as in recreational facilities such as swimming pools. Use has been for sanitizing purposes and to assist in reduction of infection as well as for deodorizing purposes. Products used as part of a hand hygiene program have significantly contributed to reduced transmission of infection in health care but have increased the potential for irritant and contact dermatitis (Kurtz 2016). In addition, these agents can also have other potential unwanted effects. This review will address current knowledge of the effects on allergy and asthma.

Potential effects of cleaning agents on allergy and asthma can range from effects on the unborn baby from maternal exposure, to effects in early childhood, school-age children, and adults. These include possible modulation of TH1/TH2 switching in early childhood resulting in increasing risk of atopy, altered airway epithelial function due to chlorinated compounds from swimming pools, increased airway responsiveness, acute irritant-induced asthma from irritating cleaning chemicals, as well as specific immunologic responses

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to cleaning agents causing allergic rhinitis, conjunctivitis, and asthma.

Pre-natal and early childhood exposures

A Spanish study of 4 prospective birth cohorts, including over 2000 pregnant women (Casas et al. 2013), reported an increased period prevalence of lower respiratory tract infection among the infants up to 12–18 months of age if the mothers had been exposed in pregnancy to sprays (OR = 1.29; 95% confidence interval (CI): 1.04–1.59) or air fresheners (OR = 1.29; 95% CI: 1.03–1.63). Wheezing was increased with spray or solvent use, with similar odds ratios. The associations were seen for sprays and air freshener use in pregnancy even if there was no exposure after birth, but associations were greater when post-natal exposures were included. A Polish study of risk factors for early childhood wheeze and atopic dermatitis (Stelmach et al. 2014) found that more frequent house cleaning was a predictor of atopic dermatitis in the first year of life, odds ratio 1.8 (95% CI: 1.1–2.9), but the mechanism of the association was not clear.

The hygiene hypothesis has suggested that the increased prevalence of allergy and asthma in early childhood may relate to an increase in T-lymphocyte switching from TH1 to TH2 type lymphocytes due to reduced exposure to microorganisms in early childhood, from increased cleanliness in the home, less early childhood exposure to animals and early infection (Strachan 2000). If this hypothesis is correct, it would be expected that increased use of cleaning products in the home during early childhood may result in less exposure to indoor allergens and microorganisms and may be associated with more asthma and allergy. However, the hygiene hypothesis has been questioned and especially the potential role of home cleanliness (Liu 2015; Weber et al. 2015; Ege 2017). Some of the variability in reported studies, illustrated below, might relate to the age of children studied.

Cleaning with bleach was associated with a reduction in surface bacteria, airborne fungal spores, and dust antigens, and also an improvement in asthma quality of life among children with asthma aged 2–17 (Barnes et al. 2008). A Belgian study (Nickmilder et al. 2007), reported that children aged 10–13 living in a home that was cleaned with bleach at least once a week were less likely to have asthma (OR = 0.10; 95% CI: 0.02–0.51), eczema (OR = 0.22; 95% CI: 0.06–0.79), and less risk of being sensitized to indoor aeroallergens (OR = 0.53; 95% CI: 0.27–1.02), especially house dust mite (OR = 0.43; 95% CI: 0.19–0.99). There was no reduction in sensitization to grass pollen, so the apparent benefits in that study may have resulted from reduced exposure to the home allergens and did not suggest a significant effect on T-cell switching. An earlier study (Henderson et al. 2008) showed an association between high domestic chemical exposure in pregnancy and persistent wheezing and reduced FEV_1 and $FEF_{25\%-75\%}$, from birth to age 7 years, but there was no difference in rates of atopy with chemical exposure and the authors concluded the effects may have been from pre-natal respiratory developmental effects or post-natal irritant effects, but were unlikely related to improved hygiene in the home.

In young adults, exposure to household disinfectants has been associated with increased incident asthma (OR = 2.79; 95% CI: 1.14–6.83) (Weinmann et al. 2017). Frequent use of bleach has been reported to increase the risk in women for non-allergic adult-onset asthma (adjusted odds ratio = 3.3; 95% CI: 1.5–7.1) (Matulonga et al. 2016). In addition, a greater progressive decline in both FEV_1 and FVC over a 20 year period has been reported among women in the European Community Respiratory Health Study for those women who undertook cleaning at home or at work at least once a week ($p = 0.004$), compared with women who did not, although there was no difference in decline of FEV_1/FVC ratio (Svanes et al. 2018). No similar pulmonary function effect was seen among men. Doctor-diagnosed asthma was more common among the women cleaning at home or work (9.6% among women not cleaning, 12.3% in women cleaning at home, and 13.7% in women cleaning at work). Rates of doctor-diagnosed asthma among men were lower but also showed a difference for those who cleaned at home: 7% in those who did not clean, or who cleaned at work, and 10.3% among men who cleaned at home (Svanes et al. 2018). Spray cleaners have been associated with increased exhaled nitric oxide and lower FEV_1 (Le Moual et al. 2014), and with asthma in older women (average age 68) (Bedard et al. 2014) as well as with current asthma and poorly-controlled asthma in younger women (Le Moual et al. 2012).

Few studies have assessed short term effects of home cleaning agents among women with asthma and non-asthmatics. In a small prospective study (Bernstein et al. 2009), peak flow readings were associated with increased lower respiratory symptoms in the asthmatics but no differences in serial peak expiratory flow recordings were found with cleaning exposures. In a controlled brief exposure to ammonia at or above irritant thresholds in volunteers with and without asthma who reported sensitivity to household cleaners, there also were no changes in lung function and similar increases in symptoms were reported by both asthmatics and non-asthmatics (Petrova et al. 2008). In a follow-up of the European Community Respiratory Health Survey, use of cleaning sprays at least weekly in the home was associated with the incidence of asthma symptoms and medications (Zock et al. 2007). The incidence of doctor-diagnosed asthma was higher in those who used cleaning sprays at least 4 days a week (Zock et al. 2007).

Occupational exposures among healthcare workers

Healthcare workers (HCW) are over-represented in the workforce among adults with work-related asthma, with 1 study demonstrating that 9% and 37.5% of HCWs assessed had occupational asthma or work-exacerbated asthma, respectively (Knoeller et al. 2013). Moreover, a recent study in a Canadian tertiary clinic that compared 2 time periods (2000–2007 and 2008–2015) reported that cleaning agents as a suspected causative agent for work-related asthma patients increased from 6% to 18% (Gotzev et al. 2016). In a surveillance study assessing 4 states, healthcare was reported as the first or second most prevalent industry for work-related asthma cases between 1993 and 1997 (Pechter et al. 2005). Common cleaning agents that are used by HCWs include quaternary ammonium compounds, glutaraldehyde, bleach, acetic acid, subtilisin, phthalaldehyde, formaldehyde, and chlorhexidine. Cleaning products that contain these agents are often used for cleaning or disinfecting purposes, but may have undesirable respiratory and allergic effects on HCWs. Cleaning products have been shown to remain airborne for several minutes even after cessation of the cleaning task (Bello et al. 2010), which may lead to continued exposure to the individual and others. This was especially found for volatile organic compounds, where background exposure was identified up to 20 minutes following completion of the cleaning task (Bello et al. 2010). The current literature has numerous case reports and studies showing associations between cleaning products and occupational asthma and work-exacerbated asthma through sensitizing or irritant mechanisms.

In a study (Arif and Delclos 2012) that included 3650 HCWs who responded to a questionnaire, the likelihood of developing work-related asthma was 2.64 (95% CI: 0.57–12.14) for those exposed to cleaning products once a week. The odds of developing work-related asthma increased to 5.37 (95% CI: 1.43–20.16) for those exposed to cleaning products at least once a day. Interestingly, this study reported that among HCWs exposed to chloramine for 6 months or longer, there was nearly a fivefold greater likelihood of developing occupational asthma (95% CI: 1.28–18.06). It has been proposed that risk of developing asthma is most significant during disinfection, especially during manual mixing/dilution tasks as the worker may be exposed to peaks of the concentrated cleaning product (Gonzalez et al. 2014). A cross-sectional survey study (Arif et al. 2009) that compared 448 nursing professionals to 3186 other healthcare workers reported a greater frequency of asthma and bronchial hyper-responsiveness among nursing professional who cleaned medical instruments (95% CI: 1.06–2.62) and who were exposed to cleaning disinfectants (95% CI: 1.00–2.94). A recent study (Casey et al. 2017), investigated health effects of surface disinfectant products containing hydrogen peroxide, peracetic acid, and acetic acid. They identified that the prevalence of wheeze and epiphora was significantly higher among HCWs exposed to disinfectant products.

Although studies have revealed strong associations between cleaning products and work-related asthma, it is sometimes difficult to establish temporal causal relations, and even more challenging to identify the respiratory pathophysiological mechanisms underlying patients' asthma. These clinical challenges sometimes accompany specific cleaning agents including, but not limited to, glutaraldehyde, hydrogen peroxide, and peracetic acid. A study (Lipinska-Ojrzanowska et al. 2014) in Poland reported that among 142 hospital cleaners, 59% experienced at least 1 "allergic" symptom (nasal, eye, respiratory, or dermal), including 47.2% of workers with a new onset while cleaning, but none of the

workers had a positive skin prick test or serum IgE antibody test. This may be a reflection of the difficulty demonstrating immunologic hypersensitivity responses to low-molecular weight sensitizers but also indicates the importance of considering possible upper airway irritant mechanisms for asthma-like symptoms in addition to considering sensitizing or irritant lower airway responses. The cleaning agents identified in this study included chloramine, formaldehyde, chlorhexidine, and glutaraldehyde, that are recognized potential sensitizers as well as irritants.

Glutaraldehyde is a common disinfectant used in endoscopy labs to disinfect medical instruments. A surveillance study (Walters et al. 2013) of healthcare workers with occupational asthma reported that the most frequent cleaning agent identified was glutaraldehyde. Another older study (Dimich-Ward et al. 2004) identified that respiratory therapists were at greater risk of developing asthma, wheeze, and episodes of dyspnea upon awakening. They found that sterilization of medical instruments using glutaraldehyde and administration of aerosolized ribavirin was associated with asthma.

A study in France (Dumas et al. 2012) identified that among hospital workers, females were more frequently exposed to cleaning products compared to males on a weekly basis (81% vs. 55%, respectively; $p < 0.001$). The HCWs most frequently identified were cleaners and personal support workers, and some of these HCWs presented with current asthma. Interestingly, this study found no association between exposure to cleaning tasks and asthma for men or women, but specific cleaning products were identified to have an association with current asthma for women. It has been suggested that when environmental and safety measures are appropriately implemented including proper ventilation, the effects of cleaning products on HCWs may be minimized (El-Helaly et al. 2016).

Quaternary ammonium compounds are frequently used as disinfectants and antiseptics. A study in Belgium (Vandenplas et al. 2013) included 44 participants with work-related asthma who were administered a specific inhalation challenge (SIC). Thirty-nine percent of participants had a FEV_1 drop of 20% or greater, and of these, quaternary ammonium compounds were the most frequently identified cleaning agent inducing a positive SIC. This study suggested that quaternary ammonium compounds may represent one of the primary cleaning agents associated with sensitizer-induced occupational asthma.

Other reports have included occupational asthma from a cleaning product containing triclosan (Walters et al. 2017), and asthma that was triggered when a chlorinated cleaning product was mixed with urine but not when the product was used alone, presumably due to the chloramine by-products (Moore et al. 2017).

Risks of asthma among cleaners have been shown to be greater among women and among those with longer exposure and with early life disadvantage, as reviewed recently (Folletti et al. 2017).

A Task Force consensus statement from the European Academy of Allergy, Asthma and Clinical Immunology on asthma among cleaners (Siracusa et al. 2013), and later publications (Tarlo et al. 2018), have provided suggestions as to limiting exposure for these workers.

Effects of swimming pool exposure on allergy and asthma

Swimming in chlorinated pools is a commonly attended activity by both recreational and elite swimmers ranging in age from infancy to adulthood. Research into the effects of lung exposure to chlorine by-products proposes that the increased emergence of allergic diseases in the developed world may relate more to the products that are used to achieve hygiene than the elimination of microbes, as suggested by the hygiene hypothesis (Bernard 2007). As reviewed by Uyan et al. (2009), the "pool chlorine hypothesis" suggests that chlorination products, possibly the world's most ubiquitous cleaning agents, used to sanitize water-based recreational areas are thus implicated in an increased risk of allergy and respiratory disorders.

Chlorine is added to pool water in various forms due to its availability, low cost, biocidal, and deodorant properties. Chemical reactions between chlorine in pool water and organic materials from swimmers create disinfectant by-products (DBPs) which account for the respiratory irritation and odor associated with swimming pools (Uyan et al. 2009). Trichloramine, a common DBP, is a volatile irritant gas. Transfer of this gas from water to the surrounding air is promoted by

the dynamic activities of swimmers (Weng et al. 2011) and is influenced by factors such as ventilation, air recirculation, and water temperature (Uyan et al. 2009). Levels may fluctuate from 0.2 to 0.9 mg/m^3 in indoor pools, depending on occupancy and ventilation, an exposure that is substantially greater when compared to typical air pollutant levels of 0.3 mg/m^3 in non-pool environments (Bernard et al. 2006). Levels also tend to be higher in indoor pool environments than outside swimming pools (Uyan et al. 2009). Trichloramine causes respiratory irritation similar to formaldehyde and chlorine and has been shown to cause epithelial damage in rodents and respiratory tract irritation in lifeguards and other pool attendees (Bernard et al. 2006, 2015).

Data from accidental chlorine exposure has established a harmful role for chlorine DBPs on the respiratory tract. Symptoms ranging from rhinitis, tracheobronchitis, and pneumonitis to pulmonary oedema and bronchiolitis have been reported after acute chlorine exposure. Symptoms tend to remit in most affected individuals, although the development of reactive airways dysfunction syndrome has been reported. In the pediatric population, short term effects may be prolonged and last up to 1 month with increased symptoms in children with respiratory disease (Uyan et al. 2009). A persistence of leukotriene B4, a marker of neutrophilic inflammation, has been demonstrated at several months following exposure despite improvements in symptoms and lung function, suggesting subclinical inflammation (Uyan et al. 2009).

The main mechanism by which non-accidental, lower level exposure to chlorine disinfection by-products (DBPs) may predispose to allergy and respiratory symptoms through swimming relates to their effecting lung epithelium hyperpermeability, conferring vulnerability to allergen sensitization (Bernard et al. 2015). Induction of lung injury and inflammation have also been described in this setting. Font-Ribera et al. (2010) studied respiratory epithelial effects in 48 healthy non-smoking adults who had lung function and biomarkers of airway inflammation, oxidative stress, and epithelial permeability measured before and after a 40-minute swim in a chlorinated pool. Breath levels of trihalomethanes were measured to quantify individual exposure to DBPs. Overall, a slight increase in a marker of epithelial permeability, Clara cell protein 16 (CC16), was found in healthy adults after a swim. No significant changes in inflammatory markers were found or thought to mediate this change. Biomarkers of epithelial permeability have been further studied in school age children (Bernard et al. 2015). A 2015 study of 835 adolescents gathered health information, serum concentrations of CC16, surfactant associated protein D (SP-D), and total and aeroallergen specific IgE (Bernard et al. 2015). The CC16/SP-D ratio was proposed as representing permeability and secretory changes in the epithelium. The study found that a low CC16 and low CC16/SPD index was predicted by early swimming in chlorinated pools and was associated with increased odds for allergic disease including aeroallergen sensitization and rhinitis, supporting the view that early swimming may predispose to atopy and epithelial barrier defects.

Airway inflammation is also postulated to be caused by chlorinated pool attendance. In elite swimmers, several studies have shown increased respiratory symptoms and airway inflammation with chronic chlorine exposure (Uyan et al. 2009). Greater proportions of eosinophils and neutrophils in the sputum of elite swimmers compared to healthy controls, with increase bronchial hyperreactivity have also been demonstrated (Helenius and Haahtela 2000). These effects display attenuation following cessation of the sport. Other work has demonstrated significantly higher exhaled breath condensate leukotriene B4 (LTB4) with fractional exhaled nitric oxide (FeNO) levels similar to age matched individuals in elite swimmers, suggesting that chronic chlorine exposure may lead to the development of a neutrophil-driven inflammation (Uyan et al. 2009). However, in addition to exposure to chlorine, other factors may also be implicated in causing respiratory inflammation in this niche group of individuals. Elite swimmers exhibit low frequency-high tidal volume breathing, engage in long training hours and use increased minute volumes whilst swimming, all mechanisms which may in themselves induce transient epithelial damage and inflammation (Bougault and Boulet 2012).

Beyond experimental studies, researchers have endeavored to answer whether recreational swimming plays a role in the development of asthma and allergies in the pediatric setting. An ecological study looking at geographic swimming pool availability in Europe and childhood asthma showed that the presence of wheeze or ever asthma increased by 0.96%–3.39% with an

increase of 1 indoor chlorinated pool per 100 000 inhabitants for children aged 13–14 years (Nickmilder and Bernard 2007). Similar effects were noted in younger age groups. This group of investigators from Belgium also examined cumulated pool attendance (CPA) with childhood asthma and atopy (Bernard et al. 2006). A comprehensive health questionnaire, exercise induced bronchoconstriction and FeNO testing was conducted in 341 school children aged 10–13 years attending the same school with pool trichloramine levels of 0.3–0.5 mg/m^3. CPA emerged as predictive of doctor-diagnosed asthma and FeNO measurements. However, the probability of developing asthma with increased CPA occurred only in subsets of children with elevated IgE levels >100, particularly in pool attendance at age 6–7 years, suggesting that exposure to pool chlorine may interact with other factors in its association with allergy and asthma.

Exposure of infants to chlorinated pools has come under scrutiny in light of literature suggesting a long-term effect of chlorine exposure. Infants may be particularly susceptible due to attendance to warmer, more polluted pools and their developing lungs (Uyan et al. 2009). In addition, some studies have found that exposure is higher to chloramines in air and water in younger swimmers (Uyan et al. 2009). However, in contrast to previously discussed work that has shown an increased risk of asthma with early age pool attendance in Belgium, follow up of a birth cohort of 2192 children in Germany found that swimming attendance in the first year of life is not associated with atopic disease later in life. Notably, allowable limits for chlorine are lower in Germany than in Belgium (Uyan et al. 2009). An observational study in 430 kindergarten aged children using questionnaire data to assess health, swimming behaviours, and confounders found that attendance at chlorinated pools at any stage prior to age 2 years was associated with an increased risk of bronchiolitis (Voisin et al. 2010). This association was strengthened to an odds ratio of 4.45 and 4.44 for >20 hours cumulative time spent in a chlorinated pool when family history of atopy and day care attendance were excluded. The group suggested an increased risk of asthma and allergies later in childhood in those children who were affected by bronchiolitis and who also had higher cumulative swimming exposure (Voisin et al. 2010).

While an association between pool chlorine exposure and respiratory irritation, epithelial and inflammatory effects has been raised by the literature, meta-analysis data does not support an association with the development of asthma (Valeriani et al. 2017*a*). Seven reports (with 5851 subjects) which looked at the link between exposure to DPBs in indoor swimming pools during childhood and asthma were analyzed. The odds ratio for asthma prevalence in relation to swimming pool attendance was 0.58–2.30, with no significant increase in prevalence to controls (Valeriani et al. 2017*a*, 2017*b*). The finding echoes previous opinion in the literature which suggests that the current evidence of an association between childhood swimming and new-onset asthma is suggestive but not conclusive (Weisel et al. 2009; Valeriani et al. 2017*a*, 2017*b*). Other reviews have found evidence for respiratory effects in elite swimmers more compelling than current data on the effects of low chronic exposure in recreational swimmers (Uyan et al. 2009).

Prospective evaluation and follow-up studies to assess whether a cause–effect relationship exists between recreational swimming and asthma development may be important to inform guidelines that balance caution regarding public health risks with a pragmatic approach to a popular and active pastime. While definitive data is awaited, ongoing regulation of chlorine levels, temperature, and ventilation in indoor swimming pools and an emphasis on personal hygiene in swimmers will be important to decrease the presence of respirable irritants around swimming pools (Uyan et al. 2009).

Conclusions

Several studies have indicated that there is an increased risk of developing asthma among adults with frequent exposure to cleaning products at work and in the home. Risks appear to be greater with sprayed products, likely reflecting greater respiratory exposure. Potential mechanisms include sensitization and potential respiratory irritant effects. Exposure to irritant chlorine by-products from swimming pools have also been associated with respiratory effects and increased risk of asthma. Potential effects from maternal exposures to cleaning products on infants, and effects on early childhood atopy are less clear. There remain several unanswered questions regarding relative risks of specific cleaning chemicals and mechanisms of the observed associations. The relative benefits from a clean indoor environment and reduction of harmful microorganisms need to be taken into consideration and balanced with

the possible risks, as has been suggested for those working with these products.

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