Brief communication

# Opportunities and obstacles in translating evidence to policy in occupational asthma

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## ARTICLE INFO

## ABSTRACT

*Purpose:* Occupational asthma (OA), a common respiratory disorder in Western countries, is caused by exposures at the workplace. It is part of a broader definition of work-related asthma (WRA) that also includes pre-existing asthma aggravated by substances present in the workplace environment, and it is potentially preventable. The purpose of this paper is to illustrate preventive measures for occupational asthma by case studies.

*Methods:* In three case studies we discuss preventive measures that have been associated with reductions in incidence of occupational asthma from natural rubber latex and from diisocyanates as supported by published literature. We also discuss challenges in relation to asthma from cleaning products in healthcare work.

*Results and conclusions:* Several preventive measures have been associated with reduction in incidence of occupational asthma from natural rubber latex and from diisocyanates, and may provide lessons for prevention of other causes of occupational asthma. Cleaning products remain an unresolved problem at present with respect to asthma risks but potential measures include the use of safer products and safer applications such as avoidance of spray products, use of occupational hygiene methods such as improving local ventilation, and when appropriate, the use of personal protective devices.

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## Introduction

Worldwide, occupational health risk accounts for almost 2% of the burden of disease in terms of disability-adjusted life years [1]. Respiratory hazards can be present at worksites in the form of dust, fumes, gases, or volatile organic compounds. Occupational asthma (OA), a common respiratory disorder in Western countries, is caused by exposures at the workplace. It is part of a broader definition of work-related asthma (WRA) that also includes pre-existing asthma aggravated by substances present in the workplace environment [2]. Most OA results from an immunological response to workplace agents [3]. The prevalence of WRA ranges from 4% to 23%, depending on the case definition [4,5]. Approximately 18% of all adult-onset asthma is attributed to work-related exposures [6] indicating that the burden of OA is substantial on workers' health. This is especially important since many of the workplace exposures, of which more than 400 have been linked to OA [7], are preventable.

Prevention is a hallmark of epidemiology. Epidemiologic studies play a vital role in identifying high-risk populations through surveillance activities, providing evidence for an exposure-response relationship using etiologic studies, and evaluating efficacy, effectiveness, and efficiency through the use of interventions. Results from these studies serve as a basis for developing workplace health-related policies and regulations. Randomized controlled studies provide much stronger evidence in support of primary prevention efforts as they are less prone to selection bias and confounding.

However, these are not common in occupational asthma research [8]. Hence, much evidence on the exposure-response relationship and workplace reduction of exposures in occupational asthma research comes from nonrandomized, clinical, and observational epidemiological studies.

This case study examines how epidemiological evidence helped shape policies to reduce worksite exposure to natural rubber latex and diisocyanates to prevent occupational asthma. Examples are given of epidemiologic studies that collectively provided information that contributed to the introduction of preventive measures. The case study then examines emerging evidence on the association of exposure to cleaning substances with occupational asthma in health care workers.

The three examples presented in this case study carry some different messages. The first example, of natural rubber latex (NRL), shows how the introduction of one policy (universal precautions) can result in a different problem (NRL allergy). This included risks of NRL allergy among workers who adopted the use of NRL glove use when they were at low risk for transmissible disease. The second example, of diisocyanate sensitization, illustrates how new policies may need to address heterogeneity in risk effects and can target different levels of prevention (primary, secondary, and tertiary prevention). The third case example illustrates the need for policies to balance competing risks (infections from health care facilities vs. risks of asthma). The "lessons learned" section relates to *challenges* of translating evidence into policy.

## Case study #1: natural rubber latex-induced asthma

### Background

NRL is manufactured from milky fluid or sap derived from the rubber tree *Hevea brasiliensis*, that is comprised of several different proteins [9,10]. Antioxidants, accelerators, casein, and starch are added to NRL to obtain desired strength, stretch, and durability properties [10,11]. Liquefied NRL is used in the manufacturing of many industrial, medical, and household products, including latex gloves [11]. Occupations that commonly involve exposure to NRL-containing products include health care professionals, hairdressers, food service workers, housekeepers, and workers in latex manufacturing [12].

NRL gloves have been the most widely used form of NRL products, especially in health care [11]. The types and their patterns of use have evolved over the past 20 years, based in part on reports of adverse health effects that led to changes in policies and regulations worldwide. These included more stringent manufacturing quality controls to decrease NRL allergenicity, less use of powdered latex gloves, and the availability of non-NRL glove alternatives.

NRL differs from synthetic rubbers in its ability to release proteins that can cause allergic reactions [9]. Three types of reactions can occur following exposure to a finished NRL product: IgE-mediated allergic reactions (type I), cell-mediated hypersensitivity (type IV), and contact irritation [12,13]. NRL allergy can cross-react with allergies to certain foods, such as bananas, avocados, and kiwis. Effects may be heightened in the presence of certain conditions such as spina bifida or other urogenital abnormalities [13].

The main routes of exposures to NRL are dermal and inhalation. IgE-mediated allergic reactions (Type I) are characterized by specific IgE antibodies in the body to proteins in natural latex [14]. IgE-mediated release of histamine and other mediators can cause urticaria or angioedema, allergic conjunctivitis, allergic rhinitis, asthma, and even anaphylaxis; events that can range from mild to life threatening [12–16].

In the 1980s and early 1990s, overall prevalence of latex sensitization among the general health care worker population was in the 3% to 5% range [17,18], although certain subgroups such as operating room staff had higher rates, closer to 6% to 10%. Vandenplas et al. [19] measured the proportion of latex-sensitized hospital workers who had latex-induced asthma confirmed by specific latex inhalation challenge, corresponding to about 2.5% of the hospital employees [17,19].

In 1992, the United States (U.S.) Occupational Safety and Health Administration (OSHA) passed the Bloodborne Pathogens Standard for the prevention of occupational HIV and hepatitis B transmission from needlesticks and other percutaneous exposures to blood. Central to the standard was a call for greater use of "universal precautions" (now called "standard precautions") and personal protective equipment, leading to a major increase in latex glove use. The usage increased from 800 million pairs in the late 1980s to 4 billion in 1992, and up to 10 billion by 1996, making it difficult for American manufacturers to meet demand [11,20,21]. Gloves produced in other countries increased, resulting in an influx of gloves that at times were poorly produced and more allergenic. During the early 1990s, reports of allergic reactions to NRL increased in the U.S. and worldwide [19,22–25]. The prevalence of sensitization appeared to be increasing, with studies reporting rates of over 10% [17,23,26]. Both the U.S. Food and Drug Administration (FDA) [27] and the National Institute for Occupational Safety and Health (NIOSH) [12] published alerts in 1997 expressing concern about the rise in latex-related allergic reactions, urging health care centers to develop and implement latex control policies, including the use of low-protein powder-free NRL gloves. This concern was echoed by a joint statement by the American Academy of Allergy, Asthma and Immunology and American College of Allergy, Asthma and Immunology [28]. Control recommendations also appeared more or less simultaneously in several countries, including the U.S., Germany, Finland, Italy, and Canada [17,22,29]. By 2000, following the introduction of powder-free/low-protein glove alternatives and other controls, the prevalence of sensitization had decreased from 10% to 4%–7% [30–32].

It is clear that NRL exposure has been a leading cause of OA, especially among health care workers using powdered latex gloves [33,34]. The overall incidence of NRL-induced OA peaked from 10.9 per 100,000 full-time equivalent health care workers in 1991 to 19.7 in 1998 [35]. However, along with the decreases in prevalence of NRL sensitization, this incidence later declined steadily to 3.8 per 100,000 in 2003–2004 [35], a trend confirmed by other studies. In 2001, Liss and Tarlo reported that the number of NRL-induced OA compensation claims among health care workers in Ontario decreased from 7 to 11 in 1991–1994 to 1–2 in 1997–1999 [15]. In 2007, a statewide survey of Texas health care workers reported a near doubling of the risk of new onset NRL-associated asthma in the period 1992 through 2000, but the risk disappeared after the year 2000, presumably due to widespread implementation of latex control policies [34]. Over this time period interventions varied and included nationwide policies and prevention programs, educational campaigns and training sessions, mainly focusing on the substitution with nonpowdered low-protein gloves, nonlatex devices, and institution-based early avoidance measures to prevent progression to severe disease [20,36].

The changes in policies over the 2 decades that involved chief local and government agencies including OSHA, FDA, and NIOSH led to an important publication by NIOSH, called the NIOSH alert: preventing allergic reactions to natural rubber latex in the workplace [12]. This publication offered recommendations to prevent NRL-related reactions in the workplace. These recommendations are currently followed throughout the U.S., consisting mainly of guidelines for better diagnosis of latex allergic reactions, combining clinical history, physical examination, pulmonary function tests where indicated and objective documentation of sensitization to latex, based on blood or skin-based testing. In addition to treatment

of allergic/asthma symptoms with medications, special precautions for reducing allergy symptoms, while maintaining latex-safe areas in facilities were also recommended [12] (Table 1).

Managing NRL allergy centers on exposure control, following the industrial hygiene hierarchical approach of substitution, engineering controls, administrative controls, and use of personal protective equipment, along with worker and employer education. Most important is the elimination or reduction in use of powdered latex gloves [37]. Exposure-control recommendations were aimed at both employers and workers:

- For employers: providing nonlatex gloves to workers where infection potential is less, using only low-protein powder-free latex gloves when necessary, ensuring good housekeeping to remove latex-containing dusts, providing education programs and training material on latex allergy, implementing periodic screening, and evaluating current prevention strategies.
- For workers: using nonlatex gloves in activities not involving contact with infectious agents, appropriate barrier protection and use of power-free gloves with low-protein content, following appropriate work practices such as not using oil-based creams/lotions, washing hands with mild soap after glove use, and good housekeeping practices involving latex dust cleaning (carpets, upholstery, ventilation systems), taking advantage of allergy education and training involving identification of symptoms, avoiding direct contact with latex gloves and products, and consulting a physician when needed.

*Evaluation of preventive measures*

Although never legally mandated, hospitals in the U.S. and other countries began adopting many of these measures as of the mid-1990s, with associated decreases in both the incidence of symptoms associated with NRL allergy worldwide and in compensation claims [15,30,38,39]. Thus, in less than 20 years, the identification and control of latex-related reactions serve as an example of successful translation of evidence into policy, with demonstrable decreases in NRL allergy rates, including asthma.

## Case study #2: isocyanate-induced asthma

*Background*

Diisocyanates have been the most common chemical sensitizers causing OA in many industrialized areas [40–42]. They are low-molecular weight chemicals that are highly reactive due to the presence of two side chains of nitrogen, carbon, and oxygen, -N = C = 0. They are widely used in coatings, including spray paints as used for automotives, sealants for floors as well as adhesives. They are also used to produce flexible or rigid polyurethane foam, including spray foam insulation.

The oldest form of diisocyanates described to cause OA is toluene diisocyanate (TDI), a liquid that is volatile and therefore can be inhaled. Studies before 1980 reported annual incidence of OA among exposed workers up to 5%–8%, with prevalence rates above 10% [43], but rates have significantly fallen in more recent years in many countries such as the U.S., Canada, and European countries [40,44,45]. However, prevalence of OA up to 13.8% of exposed workers has recently been reported from Iran [46]. Other diisocyanates have been developed including the less volatile methylene diphenyl diisocyanate (MDI) which was hoped to have less risk of causing sensitization due to less inhalation. MDI is now the most commonly used diisocyanate in many areas. Despite lower volatility, there still is potential airborne exposure to workers in close proximity since it is heated or sprayed during use, or during activation, and in those settings risks of sensitization appear similar to risks from TDI [47]. This diisocyanate is widely used in adhesives, coatings, and spray foam insulation as well as in production of rigid polyurethane foam. An example of use as an adhesive is in wood products such as medium density fiberboard and in oriented strand board: a layered combination of softwood with resin and MDI. In addition to the risks of sensitization from airborne exposure, it has also been suggested that skin exposure to MDI may cause sensitization and increase risk of developing OA after subsequent inhalation [47,48].

Other less commonly used diisocyanates include hexamethylene diisocyanate, and isophorone diisocyanate that is also volatile and may be found in spray paint. Relative risks of sensitization between various diisocyanates during occupational usage have not been clearly identified due to differences in usage and exposures, but it has been assumed that risks are greatest with TDI, less with MDI, and possibly less with polyisocyanates [49]. However, risks are also partly dependent on the extent of preventive measures as described later.

The mechanism of OA from diisocyanates remains incompletely understood but sensitization does appear to be mediated by immunologic mechanisms, and there are genetic markers that have been associated with OA from diisocyanates [50–53]. Specific IgE antibodies to diisocyanates linked to human albumin have been identified in up to 55% of patients with OA related to diisocyanates [54,55] and have been reported to be very specific for the diagnosis, although having relatively low sensitivity [56]. This suggests an IgE-associated allergic mechanism, at least for a large subset of those with OA from diisocyanates [57]. Support for an IgE-mediated response is also provided by anecdotal case reports of anaphylaxis related to diisocyanates. Lack of identified specific IgE antibodies in the remaining patients with OA from diisocyanates may be due to the lack of an appropriate antigen preparation for the test, or due to other immunologic mechanisms causing sensitization and activation of an inflammatory response. Specific IgG antibodies to diisocyanates linked to human albumin have been identified both in sensitized workers and in asymptomatic exposed workers and appear to be a marker of exposure rather than of OA [56]. However, their presence has also supported the clinical diagnosis of hypersensitivity pneumonitis, mainly from exposure to sprayed MDI [58].

Over the past several years, polyisocyanates have often been substituted for smaller diisocyanate molecules as hardeners in processes such as two-component adhesives and coatings. The assumption is that the combination of diisocyanates in larger molecules would reduce potential antigenicity compared with the equivalent number of reactive groups in smaller diisocyanate molecules, while maintaining the desired chemical activity [49].

*Recommendations*

Preventive measures for diisocyanate-induced OA

- Avoidance/reduction of exposure

These chemicals cannot easily be replaced at present. Less volatile diisocyanates such as MDI have increased in usage and the more volatile TDI has been in relatively reduced usage over the past few decades. Although MDI is often heated or sprayed, the use of this likely results in less inhaled exposure, especially in more open workplace areas. Polyisocyanates, expected to be less antigenic, have also been more widely substituted for the small diisocyanate molecules in recent years [49].

The risk of sensitization to diisocyanates is increased with higher exposures [59,60]. The following local preventive measures

have therefore been advised to reduce respiratory exposure of workers: use of robots where possible in enclosed areas of expected higher exposures; occupational hygiene measures to improve ventilation in other areas of usage, and monitoring of workplace levels of diisocyanates, with legislated exposure limits; enclosure of areas containing diisocyanates such as separately ventilated booths for spray painting; as well as use of respiratory protective devices with appropriate filters such as use of air-supply respirators by workers performing spray painting [61]. Skin protection from exposure has also been advised as it may reduce risks of sensitization to diisocyanates [62].

Exposure limits have been established and continuous air monitoring to keep within allowable air concentrations has been mandated for workplaces using diisocyanates in some jurisdictions such as in the province of Ontario, Canada [63]. In the U.S., although there is no regulatory exposure limit for diisocyanates, a time-weighted average exposure limit of 0.005 ppm is recommended [64].

Occupational hygiene measures are also important in possible prevention of irritant-induced OA. Diisocyanates, in accidental high concentrations, can cause airway irritation and inflammation, resulting in irritant-induced asthma, so worker knowledge as to the appropriate action to take during an accidental spill of diisocyanates may prevent this outcome.

Although genetic factors have been associated with OA from diisocyanates, there are no current sensitive and specific markers that would justify the exclusion of particular individuals from work with diisocyanates. Workers with pre-existing asthma are not known to have an increased risk of becoming sensitized to diisocyanates, but due to the natural variability of asthma it may be more difficult to reach a diagnosis of OA in those workers.

• Secondary preventive measures

Medical surveillance has been advised for workers exposed to diisocyanates to detect sensitized workers relatively early and remove them from further exposure to improve their medical outcome [65]. Components include preplacement assessments with a respiratory questionnaire, and spirometry, and repeat of these at intervals during employment with diisocyanate exposure. An example of this was mandated in Ontario, Canada by the Ministry of Labor in 1983 [63]. It required preplacement performance as well as repeat of the questionnaire at least every 6 months and spirometry at least every year during the employment with diisocyanates. Development of respiratory symptoms or changes in spirometry from baseline would lead to a physician assessment to determine safety for that worker to continue in the same job. In Ontario, the introduction of this program was followed by an initial increase in workers' compensation allowed claims for diisocyanate-induced OA, consistent with increased case-finding ("Hawthorne effect"), followed by a sustained progressive drop in cases [40, 66]. While supportive of a benefit from medical surveillance, it is not possible to identify the specific component associated with benefit and other changes likely contributed to declines in OA rates during this time, such as the primary preventive measures discussed above, and a likely increase in worker knowledge of diisocyanates and asthma as mentioned below.

Although specific serum IgE and IgG antibodies to diisocyanates are not generally included currently in clinical medical surveillance programs for diisocyanates (due to relatively low sensitivity of specific IgE), it has been suggested that specific IgG antibodies could be used as a marker of worker exposure and of the effectiveness of exposure-control measures in a workplace [67].

• Worker education is a primary and secondary preventive measure that is often combined with a medical surveillance

program. Knowledge of the risks of sensitization and of OA may enhance adherence to personal safety measures at work and encourage workers to seek early heath care assessment if respiratory symptoms occur [68].

• Physician education can also play a role in secondary and tertiary prevention. Improved knowledge of work-related asthma may lead to more targeted questioning of patients with respiratory symptoms regarding a work component, resulting in an earlier diagnosis [68].

• Tertiary preventive measures consist of appropriate management of workers who have developed OA from diisocyanates—including appropriate medications, removal from further exposure to diisocyanates, socioeconomic support via workers' compensation, and relocation to a different area in the same workplace or to another workplace (without exposure to diisocyanates) [65].

*Evaluation of preventive measures*

Overall preventive measures (Table 2) have been successful in reducing OA from diisocyanates although it is difficult to determine the relative benefits of each measure. In Ontario, there were progressive declines in rates of workers' compensation claims accepted for diisocyanate-induced OA after 1990, following an initial increase consistent with greater case-finding after the medical surveillance measures were introduced [40,44,61]. There also was an earlier diagnosis after the medical surveillance was introduced (mean of 2 years from onset of symptoms vs. 3 years before the surveillance measures), with milder asthma at the time of diagnosis and a trend to better outcome [61]. However, in Ontario over time, there has also been an earlier diagnosis reached in nondiisocyanate OA claims, suggesting greater awareness by physicians and/or patients of WRA [61,66]. Falls in rates of diisocyanate-induced OA may also relate to the primary preventive measures: during the time when rates have fallen both in Ontario, Canada, and in other countries

**Table 1**
Lessons learned from natural rubber latex

| Preventive measures | Methods |
|---|---|
| **Primary preventive measures** Avoidance/reduction of exposure | • Change from latex gloves to powder free or nonlatex gloves<br>• Control exposure levels by removing latex-containing dusts<br>• Avoiding oil-based creams and lotions to prevent glove deterioration. |
| **Secondary preventive measures** Identifying sentinel events through surveillance | • Government agencies such as the FDA and NIOSH played an important role in sentinel event detection, collection, and dissemination in the form of national alerts that played an important role in raising awareness of NRL allergy in the research and practice communities. This led to more rigorous epidemiological studies that confirmed the risk presented by occupational exposure to NRL. |
| Worker education | • Provide education and training to avoid (primary prevention) and early recognition (secondary prevention) of latex allergy symptoms. |
| Tertiary measures | • Treatment of OA with medications, removal from further exposure, and providing support through workers compensation claims. |

FDA = Food and Drug Administration; NIOSH = National Institute for Occupational Safety and Health; OA = occupational asthma.

**Table 2**
Lessons learned for OA from diisocyanates

| Preventive measures | Methods |
| --- | --- |
| Primary preventive measures | |
| Avoidance/reduction of exposure | Change from diisocyanates to a nonsensitizing product |
| | Reduce usage |
| | Control exposure levels by occupational hygiene means such as containment, use of robots, improved ventilation |
| | Use of protective equipment—to reduce inhaled exposure, gloves, and coveralls to reduce skin exposure |
| Secondary preventive measures | |
| Medical surveillance has been advised for workers exposed to diisocyanates to detect sensitized workers relatively early and remove them from further exposure to improve their medical outcome [26]. | Medical surveillance may include preplacement assessments including a respiratory questionnaire, and spirometry, and repeat of these at intervals during employment with diisocyanate exposure. |
| | Specific serum IgE when such tests are feasible, such as for enzymes, platinum salts, and high molecular weight sensitizers. |
| | It has been suggested that specific IgG antibodies could be used as a marker of worker exposure and of the effectiveness of exposure-control measures for diisocyanates. |
| Worker education | Worker education is a primary and secondary preventive measure often combined with a medical surveillance program. Knowledge of the risks of sensitization and of OA may enhance adherence to personal safety measures at work and encourage workers to seek early heath care assessment if respiratory symptoms occur [29]. |
| Physician education | Physician education can also play a role in secondary and tertiary prevention. Improved knowledge of work-related asthma may lead to appropriate questioning of patients with respiratory symptoms regarding a work component, resulting in an earlier diagnosis. |
| Tertiary measures | Appropriate management of workers who have developed OA from diisocyanates—including appropriate medications, removal from further exposure to diisocyanates and socioeconomic support via workers' compensation and relocation to a different area in the same workplace or to another workplace (without exposure to diisocyanates) |

OA = occupational asthma.

such as UK, and Belgium [45,69], there have been increases in use of MDI and polyisocyanates [49] rather than of TDI, more use of robotics in workplaces, and possibly better worker education and use of protective equipment.

## Case study #3: cleaning and disinfecting in health care

### Background

Cleaning and disinfecting are necessary activities in health care facilities, but they also have the potential to contribute to the onset and exacerbation of asthma and related respiratory symptoms. Unlike the other two topics addressed in this article, this topic involves different agents with multiple mechanisms, and our understanding of these agents and related interventions is still under investigation.

Health care-associated infections (HAIs) pose a serious risk to the health of patients and workers, and are an ongoing challenge worldwide [70—72]. Environmental surfaces can become contaminated with pathogens from the hands of patients, workers, and visitors, these agents can remain or possibly increase in numbers without appropriate cleaning and/or disinfecting [73], and then be transferred to others [74,75]. Cleaning and/or disinfection can reduce the number of infectious agents on environmental surfaces in health care settings and lower the risk of infection [76,77]. Special attention to the cleaning and disinfection of a room previously occupied by an infected patient can reduce HAIs among subsequent occupants [78,79].

Common ingredients of cleaning and disinfecting products such as chlorine bleach, ammonia solutions, peracetic acid, and peroxyacetic acid are irritants that can adversely impact the eyes, skin, and upper and lower airways of exposed workers. Irritant exposures like these have been identified as common causes of OA and work-exacerbated asthma among cleaners [80]. High-level accidental exposures to irritant gases can induce OA without latency, commonly called reactive airways dysfunction syndrome. In addition, chronic exposure to lower levels of irritants may result in asthma as well, although this remains under investigation [81]. With other disinfecting ingredients, sensitizing mechanisms are suspected but often only partially understood. From clinical studies, OA patients have had positive-specific inhalation challenge tests to

agents such as quaternary ammonium compounds (quats), glutaraldehyde, ethanolamines, and ortho-phthalaldehydes, suggesting an immunologic response [82—84] though the exact mechanism is unclear [84—86].

There is a robust literature on the association of asthma with workplace exposure to cleaning and disinfecting products. These articles include case reports [84,87], as well as findings from surveillance [80,88] and epidemiologic studies conducted in general population samples [89] and among cleaning workers [90,91]. The findings from surveillance [92,93] and epidemiologic studies [34,94—98] support the conclusion that asthma and related symptoms are associated with cleaning and disinfecting activities in health care facilities. For example, a study of health care workers in France reported an association of current asthma with exposure to ammonia and to sprays with moderate/high intensity, with exposure based on both expert assessment and a job exposure matrix [97]. Participants with baseline asthma in the longitudinal Nurses' Health Study II in the United States were more likely to change to jobs that had lower exposure to disinfectants [98]. From an investigation of health care workers in Texas, onset of asthma after entering a health care profession was associated with job exposure matrix-assessed exposure to instrument cleaning and surface cleaning products [34,95,96], and work-related asthma symptoms and work-exacerbated asthma were associated with self-reported use of various cleaning and disinfecting products [94].

### Preventive measures

In medical facilities, actions to protect health care workers from the harmful exposure to cleaning and disinfecting products are often judged by whether they compromise the goal of infection prevention and control. As proposed recently by a working group in the United States, an integrated approach is needed, with the dual objective of preventing both HAIs and occupational illnesses in health care settings [99]. This approach is made possible by establishing a committee in which occupational safety and health staff engage directly with infection prevention staff, as well as with representatives of other stakeholders such as affected workers and management. The committee provides a framework for the selection, implementation, and monitoring of preventive practices. Members would meet regularly to assess the cleaning and

**Table 3**
Proposed integrated approach to address cleaning and disinfecting in health care facilities

| Preventive measures | Methods |
| --- | --- |
| **Primary/secondary preventive measures** | |
| Committee to address cleaning and disinfecting issues | • Establish the dual objective to prevent both health care-associated infections and occupational illnesses.<br>• Pursue this objective by setting up a committee with occupational safety and health staff, infection prevention staff, and other stakeholders (such as affected workers and management), to meet regularly and address issues related to cleaning and disinfecting. |
| Worker education | • Train workers in proper use of chemical products, equipment, and personal protective equipment, consistent with their cleaning and disinfecting duties, to minimize exposure (primary prevention).<br>• Educate workers about possible health effects to facilitate early recognition of disease (secondary prevention). |
| Primary preventive measures | • Evaluate with input from stakeholders, and substitute nonhazardous or less hazardous products when possible.<br>• Employ engineering controls when possible, such as diluting concentrated products in an enclosed ventilated system, avoiding use of sprayed products, and using materials like copper that have antibacterial properties in high-touch locations.<br>• Use personal protective equipment such as respirators when appropriate. |

disinfecting needs of the facility, identify the least hazardous chemical products and methods that will accomplish infection prevention goals, actively address employee health issues suspected to be caused by cleaning and disinfecting, and monitor the maintenance of cleaning/disinfecting and exposure-control equipment and the assessment of workplace exposures.

The following are descriptions of additional practices that support primary prevention, except where indicated as secondary prevention (Table 3).

- Substitution of a nonhazardous or less hazardous material is at the top of the hierarchy of controls in occupational environments [100]. Green chemistry holds the promise of cleaning and disinfecting products with fewer adverse health effects. However, the independent organizations that certify green products establish their own criteria, and there are no universally accepted criteria for green cleaners and disinfectants. An example of this are the Green Seal-37 criteria, which specify that industrial and institutional cleaning and disinfecting products should not include asthmagens and other harmful toxins [101]. The Green Seal organization defines an asthmagen as any asthma-causing agent that has fulfilled criteria for a sensitizer (other than enzymes) as determined by the Association of Occupational and Environmental Clinics in the United States [102]. It is unclear how widely green cleaning and disinfecting products are used in medical facilities, and whether they both prevent infections and do not contribute to respiratory problems among staff and patients. There have been instances in which a substitute product that prevents HAIs has an adverse health effect similar to the original product (such as when ortho-phthalaldehydes were used in place of glutaraldehyde) [83,103].

- Engineering controls such as isolation of the source of exposure and local exhaust ventilation are typically unrealistic with cleaning and disinfecting activities that are conducted in numerous dispersed locations throughout the workplace. However, some engineering controls can still be practical and effective in this setting. For example, the dilution of concentrated cleaning and disinfecting products can be automated in enclosed cabinets with exhaust ventilation that prevents worker exposure. Also, technological changes can potentially support infection control and limit exposure to chemical products. Spraying of cleaning products can contribute to aerosol exposures and has been associated with current asthma and related symptoms, both in health care and other settings [97,104]. Replacing spray products with wipes might reduce exposures and prevent some of the adverse respiratory effects. A promising approach is to use materials like copper that have antibacterial properties in locations commonly touched by patients and staff, including door knobs, faucet handles, and patient over-bed tables [105]. These materials would likely reduce the need for chemicals to fight microbial agents. Nonchemical, nontouch approaches to terminal cleaning of vacated patient rooms and clinics, such as with ultraviolet light and hydrogen peroxide systems, hold promise and are still being investigated [106,107].

- Personal protective equipment (PPE) including respirators, gloves, protective clothing, and eye protection, are appropriate for some cleaning and disinfecting activities. Using respirators in a setting where patients and/or others are not protected may cause undo alarm. PPE use is feasible during terminal cleaning of patient or examination rooms in a medical center when patients and others are not present. However, this raises the issue of safe removal of gases, which might be re-circulated through a building's ventilation system, potentially exposing others who would not have PPE.

- Workers involved in cleaning and disinfecting need to be trained in proper use of different chemical products and equipment, and the use of PPE, consistent with their duties, to minimize exposure (primary prevention). Only a few ingredients of cleaning and disinfecting products (such as chlorine, ammonia, and 2-butoxyethanol) have received enough attention to warrant occupational exposure limits. However, manufacturers of cleaning and disinfecting products provide guidelines for proper use that should be communicated to workers. Workers should also be educated about possible health effects like respiratory symptoms to facilitate early recognition of disease (secondary prevention).

*Lessons learned from the case studies*

1) The history of NRL allergy and changes in glove use serve as an excellent example of how epidemiological research, government efforts, and community-based dissemination can effectively translate evidence into policies. Three main lessons emerge (Table 1). First, government agencies (FDA, NIOSH) played an important role in sentinel event detection, collection, and dissemination in the form of national alerts in raising awareness in the research and practice communities. This led to more rigorous epidemiological studies that confirmed the risk presented by occupational exposure to NRL. Second, the prompt elaboration of reasonable exposure-control recommendations led to their adoption by employers, usually on a voluntary basis, and was key to reducing disease incidence. And finally, research went beyond describing the problem and also evaluated the impact, albeit indirectly, of these control measures.

2) Interventions for diisocyanates (Table 2) may also be applicable to other sensitizing causes of OA. Some aspects of this model for other common sensitizing chemicals include the likely benefits of avoiding or minimizing worker skin and airborne exposures to sensitizers by substitution and occupational hygiene measures including use of robots when appropriate, use of protective equipment when avoidance is not possible; and consideration of a medical surveillance program, when possible including tests for immunologic sensitization. Despite lack of clear evidence of the relative values of each of these measures, the approach to this common cause of OA can act as a model for other chemical sensitizers that cause OA and may be cost-effective [108].

3) Cleaning products remain an unresolved problem at present with respect to asthma risks but potential measures include the use of safer products and safer applications such as avoidance of spray products, use of occupational hygiene methods such as improving local ventilation, and when appropriate, the use of personal protective devices (Table 3).

## Conclusions

Workplaces play an important role in creating jobs and driving economy. Therefore, it is no surprise that public policy makers and regulators in the U.S. have to address the concerns of a diverse group of stakeholders including businesses, industries, communities, and workers before coming up with policies acceptable to all the groups. Unfortunately, the process is painstakingly slow. No doubt workplaces are much safer today than 4 decades ago when OSHA was established through an act of Congress. Both fatal and non-fatal injuries and illnesses have declined substantially since 1971, but significant challenges remain. In 2015, the second and the fourth most frequently cited worksite standard violations related to chemical hazard communication and respiratory protection, respectively [109], two standards that are most relevant in reducing the occurrence of OA. Similarly, workplace regulatory exposure limits exists only for 470 chemical substances [110]; currently there are more than 85,000 chemicals listed in the Toxic Substances Control Act Chemical Substance Inventory [111]. Efforts by OSHA to reduce the exposure limits or regulate additional chemical exposures have met with challenges in courts by businesses and industries who argue regulations raise costs and undermine their economic interests. For worksite occupational health and safety programs to be successful, it requires organizational level changes such as removal of occupational hazards by substituting them with safer products, engineering controls like installing ventilation systems, training workers, and providing personal protective equipment if needed [112]. These system level changes are not possible without management support and addressing their concerns related to cost and benefit to their "bottom-line." Epidemiology can help evaluate implementation of these programs, assess the effect of these system level changes on workers' health, and identify savings in direct and indirect cost through cost-benefit and cost-effectiveness analysis. As illustrated in the examples of NRL and isocyanates, evidence based on clinical and epidemiological studies along with successful engagement of stakeholders led various organizations and employers to voluntarily adopt preventive measures to minimize workers exposure levels. A similar approach can be used to advance exposure reduction policy initiatives for cleaning-related chemicals.

### Additional resources regarding cleaning agents

The report from the working group [99] previously mentioned includes additional observations about fulfilling the dual goal of infection and occupational illness prevention in health care, including research that would assist fulfilling this goal. Also, a professional medical organization [113] recently provided suggestions for minimizing harmful exposures to cleaning and disinfecting agents. In terms of practical educational materials that can be used in workplaces, the U.S. government published a fact sheet in 2012 entitled "Protecting Workers Who Use Cleaning Chemicals" [114] that can be accessed online at http://www.cdc.gov/niosh/docs/2012-126/pdfs/2012-126.pdf.

## References

[1] World Health Organization. Global health risks: mortality and burden of disease attributable to selected major risks. Geneva, Switzerland: World Health Organization; 2009vi, 62.

[2] Tarlo SM, Balmes J, Balkissoon R, Beach J, Beckett W, Bernstein D, et al. Diagnosis and management of work-related asthma: American College Of Chest Physicians Consensus Statement. Chest 2008;134(3 Suppl):1S–41S.

[3] Mapp CE, Boschetto P, Maestrelli P, Fabbri LM. Occupational asthma. Am J Respir Crit Care Med 2005;172(3):280–305.

[4] Arif AA, Whitehead LW, Delclos GL, Tortolero SR, Lee ES. Prevalence and risk factors of work related asthma by industry among United States workers: data from the third national health and nutrition examination survey (1988-94). Occup Environ Med 2002;59(8):505–11.

[5] Mazurek JM, White GE. Work-related asthma-22 States, 2012. MMWR Morb Mortal Wkly Rep 2015;64(13):343–6.

[6] Toren K, Blanc PD. Asthma caused by occupational exposures is common—a systematic analysis of estimates of the population-attributable fraction. BMC Pulm Med 2009;9:7.

[7] Bernstein IL, Chan-Yeung M, Malo JL, Bernstein D. Asthma in the workplace, and related conditions. 3rd ed. New York: Taylor & Francis; 2006xxiii, 875.

[8] de Groene GJ, Pal TM, Beach J, Tarlo SM, Spreeuwers D, Frings-Dresen MH, et al. Workplace interventions for treatment of occupational asthma. Cochrane Database Syst Rev 2011;(5):CD006308.

[9] CDC/NIOSH. Latex Allergy A Prevention Guide: CDC/NIOSH. DHHS (NIOSH), Atlanta, Georgia, Publication Number; 1998. p. 98–113. Available at, https://www.cdc.gov/niosh/docs/98-113/ [accessed 6.8.2016].

[10] Canadian Centre for Occupational Health and Safety. Latex Allergy: Canadian Centre for Occupational Health & Safety. 2016. updated September 28, 2016. Available at: https://www.ccohs.ca/oshanswers/diseases/latex.html [accessed 6.8.2016].

[11] Levy DA, Leynadier F. Latex allergy: review of recent advances. Curr Allergy Rep 2001;1(1):32–8.

[12] NIOSH/CDC. NIOSH alert: preventing allergic reactions to natural rubber latex in the workplace. Hosp Technol Ser 1997;16(7):10–3.

[13] Kelly KJ. Allergy Fact Sheet: American Latex Allergy Association; updated 2016. Available at: http://latexallergyresources.org/allergy-fact-sheet. [accessed 9.8.2016].

[14] Asthma and Allergy Foundation of America. Latex Allergy. Asthma and Allergy Foundation of America, Landover, Maryland, USA; 2015. Available at: http://www.aafa.org/page/latex-allergy.aspx [accessed 20.8.2016].

[15] Liss GM, Tarlo SM. Natural rubber latex-related occupational asthma: association with interventions and glove changes over time. Am J Ind Med 2001;40(4):347–53.

[16] CDC. Frequently Asked Questions - Contact Dermatitis and Latex Allergy: CDC. 2013. Available at: http://www.cdc.gov/oralhealth/infectioncontrol/faq/latex.htm [accessed 20.8.2016].

[17] Sussman GL, Beezhold DH, Liss G. Latex allergy: historical perspective. Methods 2002;27(1):3–9.

[18] Turjanmaa K. Incidence of immediate allergy to latex gloves in hospital personnel. Contact Dermatitis 1987;17(5):270–5.

[19] Vandenplas O, Delwiche JP, Evrard G, Aimont P, van der Brempt X, Jamart J, et al. Prevalence of occupational asthma due to latex among hospital personnel. Am J Respir Crit Care Med 1995;151(1):54–60.

[20] Occupational Safety and Health Administration. Latex Allergy. Occupational Safety and Health Administration; 2011. Available at: https://www.osha.gov/Publications/laboratory/OSHAquickfacts-lab-safety-latex-allergy.pdf [accessed 9.8.2016].

[21] Kellett PB. Latex allergy: a review. J Emerg Nurs 1997;23(1):27–34. quiz 34–36.

[22] Larese Filon F, Bochdanovits L, Capuzzo C, Cerchi R, Rui F. Ten years incidence of natural rubber latex sensitization and symptoms in a prospective cohort of health care workers using non-powdered latex gloves 2000-2009. Int Arch Occup Environ Health 2014;87(5):463–9.

[23] Lagier F, Vervloet D, Lhermet I, Poyen D, Charpin D. Prevalence of latex allergy in operating room nurses. J Allergy Clin Immunol 1992;90(3 Pt 1):319–22.

[24] Hadjiliadis D, Khan K, Tarlo SM. Skin test responses to latex in an allergy and asthma clinic. J Allergy Clin Immunol 1995;96(3):431–2.

[25] Hamann CP, Turjanmaa K, Rietschel R, Siew C, Owensby D, Gruninger SE, et al. Natural rubber latex hypersensitivity: incidence and prevalence

of type I allergy in the dental professional. J Am Dent Assoc 1998;129(1):43–54.

[26] Liss GM, Sussman GL, Deal K, Brown S, Cividino M, Siu S, et al. Latex allergy: epidemiological study of 1351 hospital workers. Occup Environ Med 1997;54(5):335–42.

[27] FDA. Natural rubber-containing medical devices; user labeling–FDA. Final rule. Fed Regist 1997;62(189):51021–30.

[28] ACAAI. AAAAI and ACAAI Joint Statement concerning the use of powdered and non-powdered natural rubber latex gloves. Ann Allergy Asthma Immunol 1997;79(6):487.

[29] Allmers H, Schmengler J, John SM. Decreasing incidence of occupational contact urticaria caused by natural rubber latex allergy in German health care workers. J Allergy Clin Immunol 2004;114(2):347–51.

[30] Tarlo SM, Easty A, Eubanks K, Parsons CR, Min F, Juvet S, et al. Outcomes of a natural rubber latex control program in an Ontario teaching hospital. J Allergy Clin Immunol 2001;108(4):628–33.

[31] Bousquet J, Flahault A, Vandenplas O, Ameille J, Duron JJ, Pecquet C, et al. Natural rubber latex allergy among health care workers: a systematic review of the evidence. J Allergy Clin Immunol 2006;118(2):447–54.

[32] Phaswana SM, Naidoo S. The prevalence of latex sensitisation and allergy and associated risk factors among healthcare workers using hypoallergenic latex gloves at King Edward VIII Hospital, KwaZulu-Natal South Africa: a cross-sectional study. BMJ Open 2013;3(12):e002900.

[33] Amr S, Suk WA. Latex allergy and occupational asthma in health care workers: adverse outcomes. Environ Health Perspect 2004;112(3):378–81.

[34] Delclos GL, Gimeno D, Arif AA, Benavides FG, Zock JP. Occupational exposures and asthma in health-care workers: comparison of self-reports with a workplace-specific job exposure matrix. Am J Epidemiol 2009;169(5):581–7.

[35] Vandenplas O, Larbanois A, Vanassche F, Francois S, Jamart J, Vandeweerdt M, et al. Latex-induced occupational asthma: time trend in incidence and relationship with hospital glove policies. Allergy 2009;64(3):415–20.

[36] Meade BJ, Weissman DN, Beezhold DH. Latex allergy: past and present. Int Immunopharmacol 2002;2(2–3):225–38.

[37] Charous BL, Tarlo SM, Charous MA, Kelly K. Natural rubber latex allergy in the occupational setting. Methods 2002;27(1):15–21.

[38] Latza U, Haamann F, Baur X. Effectiveness of a nationwide interdisciplinary preventive programme for latex allergy. Int Arch Occup Environ Health 2005;78(5):394–402.

[39] Turjanmaa K, Kanto M, Kautiainen H, Reunala T, Palosuo T. Long-term outcome of 160 adult patients with natural rubber latex allergy. J Allergy Clin Immunol 2002;110(2 Suppl):S70–4.

[40] Ribeiro M, Tarlo SM, Czyrka A, Vernich L, Luce CE, Liss GM. Diisocyanate and non-diisocyanate sensitizer-induced occupational asthma frequency during 2003 to 2007 in Ontario, Canada. J Occup Environ Med 2014;56(9):1001–7.

[41] Guarnieri G, Cattoni I, Barbetta G, Liviero F, Mason P, Scarpa MC, et al. Features of occupational asthma in Northern Italy from 1987 to 2012. Eur Respir J 2013;42:1901. Available at: http://erj.ersjournals.com/content/42/Suppl_57/P1901.full.pdf+html?sid=1c7cf100-1223-4666-bb1d-5109f639e67d [accessed 17.2.2017].

[42] Bakerly ND, Moore VC, Vellore AD, Jaakkola MS, Robertson AS, Burge PS. Fifteen-year trends in occupational asthma: data from the Shield surveillance scheme. Occup Med (Lond) 2008;58(3):169–74.

[43] Diller WF. Frequency and trends of occupational asthma due to toluene diisocyanate: a critical review. Appl Occup Environ Hyg 2002;17(12):872–7.

[44] Buyantseva LV, Liss GM, Ribeiro M, Manno M, Luce CE, Tarlo SM. Reduction in diisocyanate and non-diisocyanate sensitizer-induced occupational asthma in Ontario. J Occup Environ Med 2011;53(4):420–6.

[45] Walters GI, Kirkham A, McGrath EE, Moore VC, Robertson AS, Burge PS. Twenty years of SHIELD: decreasing incidence of occupational asthma in the West Midlands, UK? Occup Environ Med 2015;72(4):304–10.

[46] Attarchi M, Dehghan F, Yazdanparast T, Mohammadi S, Golchin M, Sadeghi Z, et al. Occupational asthma in a cable manufacturing company. Iran Red Crescent Med J 2014;16(10):e9105.

[47] Petsonk EL, Wang ML, Lewis DM, Siegel PD, Husberg BJ. Asthma-like symptoms in wood product plant workers exposed to methylene diphenyl diisocyanate. Chest 2000;118(4):1183–93.

[48] Wisnewski AV, Xu L, Robinson E, Liu J, Redlich CA, Herrick CA. Immune sensitization to methylene diphenyl diisocyanate (MDI) resulting from skin exposure: albumin as a carrier protein connecting skin exposure to subsequent respiratory responses. J Occup Med Toxicol 2011;6:6.

[49] Wisnewski AV, Redlich C, Mapp C, Bernstein DI. Polyisocyanates and their prepolymers. In: Bernstein IL, Chan-Yeung M, Malo J-L, Bernstein D, editors. Asthma in the Workplace. 3rd edition. New York: Taylor and Frances Group; 2006. p. 481–504.

[50] Yucesoy B, Kaufman KM, Lummus ZL, Weirauch MT, Zhang G, Cartier A, et al. Genome-wide association study identifies novel loci associated with diisocyanate-induced occupational asthma. Toxicol Sci 2015;146(1):192–201.

[51] Yucesoy B, Johnson VJ, Lummus ZL, Kashon ML, Rao M, Bannerman-Thompson H, et al. Genetic variants in the major histocompatibility complex class I and class II genes are associated with diisocyanate-induced Asthma. J Occup Environ Med 2014;56(4):382–7.

[52] Yucesoy B, Johnson VJ, Lummus ZL, Kissling GE, Fluharty K, Gautrin D, et al. Genetic variants in antioxidant genes are associated with diisocyanate-induced asthma. Toxicol Sci 2012;129(1):166–73.

[53] Bernstein DI, Kashon M, Lummus ZL, Johnson VJ, Fluharty K, Gautrin D, et al. CTNNA3 (alpha-catenin) gene variants are associated with diisocyanate asthma: a replication study in a Caucasian worker population. Toxicol Sci 2013;131(1):242–6.

[54] Wisnewski AV, Stowe MH, Cartier A, Liu Q, Liu J, Chen L, et al. Isocyanate vapor-induced antigenicity of human albumin. J Allergy Clin Immunol 2004;113(6):1178–84.

[55] Budnik LT, Preisser AM, Permentier H, Baur X. Is specific IgE antibody analysis feasible for the diagnosis of methylenediphenyl diisocyanate-induced occupational asthma? Int Arch Occup Environ Health 2013;86(4):417–30.

[56] Wisnewski AV. Developments in laboratory diagnostics for isocyanate asthma. Curr Opin Allergy Clin Immunol 2007;7(2):138–45.

[57] North CM, Ezendam J, Hotchkiss JA, Maier C, Aoyama K, Enoch S, et al. Developing a framework for assessing chemical respiratory sensitization: A workshop report. Regul Toxicol Pharmacol 2016;80:295–309.

[58] Vandenplas O, Malo JL, Dugas M, Cartier A, Desjardins A, Levesque J, et al. Hypersensitivity pneumonitis-like reaction among workers exposed to diphenylmethane [correction to piphenylmethane] diisocyanate (MDI). Am Rev Respir Dis 1993;147(2):338–46.

[59] Tarlo SM, Liss GM, Dias C, Banks DE. Assessment of the relationship between isocyanate exposure levels and occupational asthma. Am J Ind Med 1997;32(5):517–21.

[60] Ott MG, Diller WF, Jolly AT. Respiratory effects of toluene diisocyanate in the workplace: a discussion of exposure-response relationships. Crit Rev Toxicol 2003;33(1):1–59.

[61] Tarlo SM, Liss GM. Diisocyanate-induced asthma: diagnosis, prognosis, and effects of medical surveillance measures. Appl Occup Environ Hyg 2002;17(12):902–8.

[62] Bello D, Herrick CA, Smith TJ, Woskie SR, Streicher RP, Cullen MR, et al. Skin exposure to isocyanates: reasons for concern. Environ Health Perspect 2007;115(3):328–35.

[63] Ontario Ministry of Labour. Regulation respecting isocyanates made under the Occupational Health and Safety Act. Ontario Ministry of Labour, Occupational Health and Safety Division, 1983; Waterloo, ON; 1980.

[64] Occupational Safety & Health Administration [OSHA]. Hexamethylene Diisocyanate: Exposure Limits and Health Effects n.d. Available at: https://www.osha.gov/dts/chemicalsampling/data/CH_245198.html. [accessed 17.2.2017].

[65] de Groene GJ, Pal TM, Beach J, Tarlo SM, Spreeuwers D, Frings-Dresen MH, et al. Workplace interventions for treatment of occupational asthma: a Cochrane systematic review. Occup Environ Med 2012;69(5):373–4.

[66] Tarlo SM, Liss GM, Yeung KS. Changes in rates and severity of compensation claims for asthma due to diisocyanates: a possible effect of medical surveillance measures. Occup Environ Med 2002;59(1):58–62.

[67] Lushniak BD, Reh CM, Bernstein DI, Gallagher JS. Indirect assessment of 4,4'-diphenylmethane diisocyanate (MDI) exposure by evaluation of specific humoral immune responses to MDI conjugated to human serum albumin. Am J Ind Med 1998;33(5):471–7.

[68] Santos MS, Jung H, Peyrovi J, Lou W, Liss GM, Tarlo SM. Occupational asthma and work-exacerbated asthma: factors associated with time to diagnostic steps. Chest 2007;131(6):1768–75.

[69] Vandenplas O, Lantin AC, D'Alpaos V, Larbanois A, Hoet P, Vandeweerdt M, et al. Time trends in occupational asthma in Belgium. Respir Med 2011;105(9):1364–72.

[70] Klevens RM, Edwards JR, Richards Jr CL, Horan TC, Gaynes RP, Pollock DA, et al. Estimating health care-associated infections and deaths in U.S. hospitals, 2002. Public Health Rep 2007;122(2):160–6.

[71] Haagsma JA, Tariq L, Heederik DJ, Havelaar AH. Infectious disease risks associated with occupational exposure: a systematic review of the literature. Occup Environ Med 2012;69(2):140–6.

[72] Nayak AP, Hettick JM, Siegel PD, Anderson SE, Long CM, Green BJ, et al. Toluene diisocyanate (TDI) disposition and co-localization of immune cells in hair follicles. Toxicol Sci 2014;140(2):327–37.

[73] Kramer A, Schwebke I, Kampf G. How long do nosocomial pathogens persist on inanimate surfaces? A systematic review. BMC Infect Dis 2006;6:130.

[74] Morgan DJ, Rogawski E, Thom KA, Johnson JK, Perencevich EN, Shardell M, et al. Transfer of multidrug-resistant bacteria to healthcare workers' gloves and gowns after patient contact increases with environmental contamination. Crit Care Med 2012;40(4):1045–51.

[75] Bhalla A, Pultz NJ, Gries DM, Ray AJ, Eckstein EC, Aron DC, et al. Acquisition of nosocomial pathogens on hands after contact with environmental surfaces near hospitalized patients. Infect Control Hosp Epidemiol 2004;25(2):164–7.

[76] Dancer SJ. Importance of the environment in meticillin-resistant staphylococcus aureus acquisition: the case for hospital cleaning. Lancet Infect Dis 2008;8(2):101–13.

[77] Hayden MK, Bonten MJ, Blom DW, Lyle EA, van de Vijver DA, Weinstein RA. Reduction in acquisition of vancomycin-resistant enterococcus after enforcement of routine environmental cleaning measures. Clin Infect Dis 2006;42(11):1552–60.

[78] Eckstein BC, Adams DA, Eckstein EC, Rao A, Sethi AK, Yadavalli GK, et al. Reduction of clostridium difficile and vancomycin-resistant enterococcus contamination of environmental surfaces after an intervention to improve cleaning methods. BMC Infect Dis 2007;7:61.

[79] Hacek DM, Ogle AM, Fisher A, Robicsek A, Peterson LR. Significant impact of terminal room cleaning with bleach on reducing nosocomial clostridium difficile. Am J Infect Control 2010;38(5):350–3.

[80] Rosenman KD, Reilly MJ, Schill DP, Valiante D, Flattery J, Harrison R, et al. Cleaning products and work-related asthma. J Occup Environ Med 2003;45(5):556–63.

[81] Dumas O, Le Moual N. Do chronic workplace irritant exposures cause asthma? Curr Opin Allergy Clin Immunol 2016;16(2):75–85.

[82] Vandenplas O, D'Alpaos V, Evrard G, Jamart J, Thimpont J, Huaux F, et al. Asthma related to cleaning agents: a clinical insight. BMJ Open 2013;3(9):e003568.

[83] Robitaille C, Boulet LP. Occupational asthma after exposure to orthoph-thalaldehyde (OPA). Occup Environ Med 2015;72(5):381.

[84] Purohit A, Kopferschmitt-Kubler MC, Moreau C, Popin E, Blaumeiser M, Pauli G. Quaternary ammonium compounds and occupational asthma. Int Arch Occup Environ Health 2000;73(6):423–7.

[85] Bernstein JA, Stauder T, Bernstein DI, Bernstein IL. A combined respiratory and cutaneous hypersensitivity syndrome induced by work exposure to quaternary amines. J Allergy Clin Immunol 1994;94(2):257–9.

[86] Nielsen GD, Larsen ST, Olsen O, Løvik M, Poulsen LK, Glue C, et al. Do indoor chemicals promote development of airway allergy? Indoor Air 2007;17(3):236–55.

[87] Burge PS, Richardson MN. Occupational asthma due to indirect exposure to lauryl dimethyl benzyl ammonium chloride used in a floor cleaner. Thorax 1994;49(8):842–3.

[88] Orriols R, Isidro I, Abu-Shams K, Costa R, Boldu J, Rego G, et al. Reported occupational respiratory diseases in three Spanish regions. Am J Ind Med 2010;53(9):922–30.

[89] Kogevinas M, Zock JP, Jarvis D, Kromhout H, Lillienberg L, Plana E, et al. Exposure to substances in the workplace and new-onset asthma: an international prospective population-based study (ECRHS-II). Lancet 2007;370(9584):336–41.

[90] Obadia M, Liss GM, Lou W, Purdham J, Tarlo SM. Relationships between asthma and work exposures among non-domestic cleaners in Ontario. Am J Ind Med 2009;52(9):716–23.

[91] Vizcaya D, Mirabelli MC, Anto JM, Orriols R, Burgos F, Arjona L, et al. A workforce-based study of occupational exposures and asthma symptoms in cleaning workers. Occup Environ Med 2011;68(12):914–9.

[92] Pechter E, Davis LK, Tumpowsky C, Flattery J, Harrison R, Reinisch F, et al. Work-related asthma among health care workers: surveillance data from California, Massachusetts, Michigan, and New Jersey, 1993-1997. Am J Ind Med 2005;47(3):265–75.

[93] Walters GI, Moore VC, McGrath EE, Burge PS, Henneberger PK. Agents and trends in health care workers' occupational asthma. Occup Med 2013;63(7):513–6.

[94] Arif AA, Delclos GL. Association between cleaning-related chemicals and work-related asthma and asthma symptoms among healthcare professionals. Occup Environ Med 2012;69(1):35–40.

[95] Arif AA, Delclos GL, Serra C. Occupational exposures and asthma among nursing professionals. Occup Environ Med 2009;66(4):274–8.

[96] Delclos GL, Gimeno D, Arif AA, Burau KD, Carson A, Lusk C, et al. Occupational risk factors and asthma among health care professionals. Am J Respir Crit Care Med 2007;175(7):667–75.

[97] Dumas O, Donnay C, Heederik DJ, Hery M, Choudat D, Kauffmann F, et al. Occupational exposure to cleaning products and asthma in hospital workers. Occup Environ Med 2012;69(12):883–9.

[98] Dumas O, Varraso R, Zock JP, Henneberger PK, Speizer FE, Wiley AS, et al. Asthma history, job type and job changes among US nurses. Occup Environ Med 2015;72(7):482–8.

[99] Quinn MM, Henneberger PK, Braun B, Delclos GL, Fagan K, Huang V, et al. Cleaning and disinfecting environmental surfaces in health care: toward an integrated framework for infection and occupational illness prevention. Am J Infect Control 2015;43(5):424–34.

[100] Office of Technology Assessment. Preventing Illness and Injury in the Workplace. Washington, DC: US Congress, Office of Technology Assessment; 1985.

[101] Green Seal Inc.. GS-37 Green Seal™ standard for cleaning products for industrial and institutional use (Edition 7.2). Washington, DC: Green Seal Inc; 2015. Available at: http://www.greenseal.org/Portals/0/Documents/GS-37_Ed7–2_Cleaning_Products_for_Industrial_and_Institutional_Use.pdf [accessed 30.9.2016].

[102] Rosenman KD, Beckett WS. Web based listing of agents associated with new onset work-related asthma. Respir Med 2015;109(5):625–31.

[103] Fujita H, Ogawa M, Endo Y. A case of occupational bronchial asthma and contact dermatitis caused by ortho-phthalaldehyde exposure in a medical worker. J Occup Health 2006;48(6):413–6.

[104] Zock JP, Kogevinas M, Sunyer J, Almar E, Muniozguren N, Payo F, et al. Asthma risk, cleaning activities and use of specific cleaning products among Spanish indoor cleaners. Scand J Work Environ Health 2001;27(1):76–81.

[105] Karpanen TJ, Casey AL, Lambert PA, Cookson BD, Nightingale P, Miruszenko L, et al. The Antimicrobial efficacy of copper alloy furnishing in the clinical environment: a crossover study. Infect Control Hosp Epidemiol 2012;33(1):3–9.

[106] Weber DJ, Kanamori H, Rutala WA. 'No touch' technologies for environmental decontamination: focus on ultraviolet devices and hydrogen peroxide systems. Curr Opin Infect Dis 2016;29(4):424–31.

[107] Weber DJ, Rutala WA, Anderson DJ, Chen LF, Sickbert-Bennett EE, Boyce JM. Effectiveness of ultraviolet devices and hydrogen peroxide systems for terminal room decontamination: Focus on clinical trials. Am J Infect Control 2016;44(5):e77–84.

[108] Wild DM, Redlich CA, Paltiel AD. Surveillance for isocyanate asthma: a model based cost effectiveness analysis. Occup Environ Med 2005;62(11):743–9.

[109] Occupational Safety, Health Administration [OSHA]. Commonly Used Statistics. Available at: https://www.osha.gov/oshstats/commonstats.html. [accessed 17.2.2017].

[110] Occupational Safety, Health Administration [OSHA]. Chemical Management and Permissible Exposure Limits (PELs). Available at: https://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=FEDERAL_REGISTER&p_id=24773. [accessed 17.2.2017].

[111] US Environmental Protection Agency [EPA]. Toxic Substance Control Act (TCSA) Chemical Substance Inventory. Available at: https://www.epa.gov/tsca-inventory. [accessed 17.2.2017].

[112] U.S. Department of Health and Human Services PHSCenters for Disease Control and PreventionNational Institute for Occupational Safety and HealthDHHS (NIOSH). Research Compendium: The NIOSH Total Worker Health Program: Seminal Research Papers 2012. Washington, DC: National Institute of Occupational Safety and Health; 2012.

[113] Siracusa A, De Blay F, Folletti I, Moscato G, Olivieri M, Quirce S, et al. Asthma and exposure to cleaning products—a European Academy of Allergy and Clinical Immunology task force consensus statement. Allergy 2013;68(12):1532–45.

[114] OSHA, NIOSH. Protecting workers who use cleaning chemicals Washington, DC. 2012. Available at: http://www.cdc.gov/niosh/docs/2012-126/pdfs/2012-126.pdf [accessed 5.10.2016].